FORMULATION AND EVALUATION OF MODIFIED RELEASE EUDRAGIT® MATRICES CONTAINING DICLOFENAC SODIUM

by

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To my family

Summary

The aim of the present study was to formulate oral modified release matrices of diclofenac sodium, using the Eudragit® polymers. In addition to the formulation processes, numerous variables had to be investigated, which included dissolution variables, formulation variables, and processing variables.

The application of the tabletting technique as well as the use of Eudragit® polymers to modify the release of diclofenac sodium is motivated at the outset. A comprehensive review of modified drug release, the use of the tabletting methodologies and the application of Eudragit® polymers are presented. In-process quality control tests as well as the mechanisms and interpretation of the dissolution process are outlined. Diclofenac sodium, a potent nonsteroidal anti-inflammatory drug, was used in the present study, hence a brief review of this drug is also presented.

The direct compression as well as the wet granulation tabletting methods were investigated. The major limitation of the direct compression method was found to be the lack of suitable flow properties of the powder blend. The wet granulation technique however, was successfully employed to prepare various diclofenac sodium Eudragit® matrix tablets. All tablets were prepared to contain 100 mg diclofenac sodium. The optimisation process was shown to be an integral procedure in influencing the matrix characteristics. In addition, it was shown that drug release was significantly influenced by different types and concentrations of Eudragit® polymers.

A specific formulation was selected to investigate the integrity of the matrices produced by the wet granulation technique. The drug release profile of a commercially available modified release preparation containing diclofenac sodium viz. Veltex® 100 CR (reference standard) was also obtained. A comparison of the drug release profiles of Veltex® 100 CR capsules and the selected formulation showed them to be markedly dissimilar. Hence, a strong motivation is provided for rationalising the selection of the particular formulation in the present study, that was shown to release diclofenac sodium optimally. The selected formulation was prepared using a combination of the Eudragit® RL and Eudragit® RS polymers.

In vitro dissolution studies on the selected as well as various other formulations demonstrated the wet granulation method to be both predictable and reproducible. However, absolute drug release independency of dissolution methods, media and agitation rates was unattainable. Furthermore, drug release was shown to be pH dependent.

The selected formula was subjected to certain formulation and processing variables. An increase in the concentrations of lactose and starch was shown to increase drug release. Different types of diluents were also shown to influence drug release from the tablets. The method of incorporation of the lubricant, magnesium stearate, was investigated. Compression studies demonstrated the susceptibility of the tablets to changes in drug release behaviour and morphological characteristics as the hardness was varied.

X-ray diffraction studies demonstrated that the processes of granulation and compression did not promote any atomic rearrangement of the drug and Eudragit® polymers. Scanning electron microscopy was useful in investigating the integrity and surface morphology of newly formulated as well as stored samples, while energy dispersive x-ray microprobe analysis adequately revealed the elemental composition of the tablets.

The selected formulation was shown to be stable at room temperature ($21 \pm 1°C$) and low temperature ($5 \pm 1°C$), while storage at 37°C with 80% relative humidity and 40°C demonstrated significantly decreased drug release behaviour during short term (3 months) stability testing. Tablet hardness evaluated during the stability testing showed that there were virtually no differences in tablet hardness between the room temperature and low temperature samples, while tablets stored at 37°C with 80% relative humidity and 40°C hardened considerably. However, tablet potencies and the moisture content of the samples were not significantly influenced during the storage period.

In addition to usual observations and mathematical manipulation, some of the data generated from this study were also evaluated statistically.

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Chapter One

Motivation for and Aim of the Study

1.1 MOTIVATION FOR THE FORMULATION OF MODIFIED RELEASE EUDRAGIT® MATRICES CONTAINING DICLOFENAC SODIUM

1.1.1 *INTRODUCTION*

With the current worldwide decline in the number of new drug entities reaching the market place, there has been a resurgence of interest in the development of novel drug delivery systems for the currently available pharmaceutical agents (McGinity *et al.*, 1983). These delivery systems aim to optimise the use of drugs through appropriate formulation (Szylkarski *et al.*, 1991).

The development of oral modified release systems has been a challenge to formulation scientists due to their inability to restrain or localise the system at targeted areas in the gastrointestinal tract (Khan, 1995). Although the intensity of a pharmacological effect is related to the drug concentration at the site of action, which is often also related to the drug plasma concentration, an ideal situation prevails when the concentration in the body is continuously between the minimal effective and maximal safe values. However, when the drug has a relatively short elimination half-life, it becomes impossible to maintain the concentration within the therapeutic range, without the need for frequent dosing (Nishihata *et al.*, 1985). The rapid attainment of 'steady-state' levels and the minimization of the 'peaks' and 'troughs' in the plasma concentration-time profile are important therapeutic goals (Wilson and Washington, 1985).

The fluctuation in drug concentrations afforded by conventional dosage forms does not promote sufficient influence on the mechanisms of disease; consequently this leads to the

excessive and inappropriate use of drugs. The purpose of modified release delivery systems is therefore essentially to improve and rationalise the administration of therapeutic agents. The specification is not the total dose given but the rate and duration of drug release. Of the various solid oral dosage forms able to control the rate of drug delivery, the simplest form consists of a drug dispersed in a polymer to form a matrix (Bidah and Vergnaud, 1991).

1.1.2 *MODIFYING THE RELEASE OF DICLOFENAC SODIUM*

Inflammatory and associated rheumatic disorders are treated mainly with nonsteroidal anti-inflammatory drugs (NSAIDs). The choice of the appropriate NSAID ultimately depends on therapeutic efficacy, tolerability and safety under clinical conditions (Scholer *et al.*, 1986). Diclofenac sodium is a NSAID that has been extensively studied since the early 1970s. It has been shown to have significant anti-inflammatory and analgesic effects, a high therapeutic index and excellent tolerability (Zuckner, 1988). When administered orally, the drug has a mean elimination half-life of 1.5 hours (Small, 1989). However, the short half-life of the drug requires frequent dosing to maintain optimal steady-state plasma levels.

Research has indicated that diclofenac sodium may be unique among the NSAIDs in its pharmacological effect on the arachidonic acid cascade by possessing three potential mechanisms of action:

- it inhibits the cyclo-oxygenase pathway with a subsequent reduction in prostaglandin and thromboxane production;
- it inhibits the lipoxygenase pathway to decrease leukotriene production; and
- it inhibits the release of arachidonic acid and stimulates its uptake (Skoutakis *et al.*, 1988).

An oral modified release preparation of diclofenac sodium would therefore be useful to:

- maintain the therapeutic blood level for a longer period of time in order to provide a constant pharmacological action and reduce undesirable adverse effects;
- reduce the total amount of drug required, by the elimination of too high drug

concentrations; and

- decrease the dosing frequency, thereby improving patient acceptance and compliance (Krówczyński, 1987).

The feasibility of producing an oral modified release diclofenac sodium preparation stems from the fact that it could reduce adverse effects and improve patient compliance. A modified release preparation of diclofenac sodium would therefore contribute towards optimising drug therapy.

1.1.3 *EUDRAGIT® POLYMERS*

The rapid progress in the field of polymer chemistry has been an important prerequisite in the formulation and development of modified release dosage forms. One such group of synthetic polymers is the methacrylate resins, trade-named Eudragit® (Rak *et al.*, 1993).

Pharmaceutically, Eudragit® acrylic resins have been used to formulate oral modified release delivery systems by incorporating them into direct compression tablet formulations (McGinity *et al.*, 1983), by coating small particles, tablets (Ghebre-Sellasie *et al.*, 1987) and drug coated 'non-pareil seeds' (Chetty, 1990; Govender, 1992), and in the preparation of microspheres (Perumal, 1996). Thus, the incorporation of drug into a polymer matrix to form a monolithic device can expand the application of these polymers (Jenquin *et al.*, 1990).

The following salient characteristics motivated the selection of Eudragit® RL and Eudragit® RS polymers in the present investigation:

- they are biocompatible, non-degradable polymers;
- they are insoluble over the entire pH range of the digestive tract;
- they have the ability to swell in aqueous media;
- they exhibit a distinct pH independent permeability for water and water-soluble substances (Efentakis *et al.*, 1990);
- they are characterised by high stability with respect to environmental factors during storage (Govender, 1992);

- they are indifferent to endogenous digestive secretions and enzymes;
- they exhibit a fairly large degree of purity; and
- they are soluble in relatively non-toxic solvents (Perumal, 1996).

The characteristics highlighted above adequately supported the use of the Eudragit® RL and Eudragit® RS polymers as matrix forming agents in the present study.

1.1.4 *TABLETS AND TABLETTING*

The concept of modified drug release has attracted much interest, and numerous oral modified release drug delivery systems are commercially available. These systems release the drug constantly during its passage through the gastrointestinal tract, thereby giving a relatively smooth plasma concentration profile over an extended period (Källstrand and Ekman, 1983). Compressed tablets are the most widely used in the design of these delivery systems, as they are: convenient, easy to use, portable and they deliver a precise dose with a high degree of accuracy (Bandelin, 1989).

Granulations are designed to improve the tabletting properties, including fluidity, compressibility and compactibility of a blend of ingredients (Riepma *et al.*, 1993). Wet granulation is a versatile process, and its application in tablet formulation is unlimited. This fact, together with the need for a reliable, cost effective method to manufacture a modified release delivery system, prompted the investigation of this technique in conjunction with the tabletting technology as a means of preparing a suitable dosage form.

1.1.5 *MATRICES*

Amongst the various modified release techniques, the matrix system appears to be an attractive and interesting approach from an economic as well as from the process development point of view (Efentakis *et al.*, 1990). This is due to the technological simplicity used in the development of matrix systems as opposed to other modified release

systems developed to achieve oral modified release (Bogentoft, 1982). Furthermore, because they do not have a polymer coating that could suddenly crack, there is no danger of an abrupt release of large amounts of drug (Sanders, 1985). Matrix systems may also have the advantage of generally being simpler to manufacture, and therefore more cost effective (Verrall and Yarsley, 1988).

1.2 AIM OF THE STUDY

The primary aim of the study was to formulate and characterise an oral modified release matrix preparation containing diclofenac sodium. To achieve this aim, the processing and formulation variables of the tabletting technique were optimised in order to develop a suitable formulation.

The direct compression as well as the wet granulation techniques were investigated. The latter was regarded as the more suitable technique, and was employed in subsequent investigations. In addition, the influence of Eudragit® concentrations and different types of Eudragit® polymers on the *in vitro* drug release characteristics were investigated. Worldwide, an Official or Compendial method has not been specified by any regulatory organisation to evaluate drug release from any modified release diclofenac sodium preparation. Thus, drug release behaviour from the matrices was evaluated using the Compendial rotating paddle and rotating basket dissolution methods (USP XXIII, 1995) in view of their proven reliability, reproducibility and stringent regulatory requirements.

To establish the integrity of the tablet matrices, fundamental investigations were conducted on a selected optimised formulation. These investigations encompassed:

- the reproducibility of the manufacturing process;
- the influence of different dissolution methods, media and agitation rates on the drug release behaviour;
- the stability under various storage conditions over a period of three months with respect to drug release, potency, moisture content, tablet hardness and surface morphology;

- the influence of formulation excipients on drug release;
- the influence of tablet hardness on drug release characteristics;
- scanning electron microscopic and energy dispersive x-ray microprobe analyses; and
- x-ray diffraction studies.

Although all modified release drug delivery systems aim to achieve the same objective, the method employed to achieve this endpoint can vary considerably. The formulation of oral modified release matrix preparations of diclofenac sodium will allow the investigation and development of appropriate technologies employed in the formulation of novel dosage forms. Matrix systems are economical as well as suitable for process development and scale-up points of view. The use of Eudragit® polymers would expand the use of the tabletting technique in the formulation of modified release drug delivery systems. If the technology is developed in South Africa, then there is the facilitation of phasic adoption of technological advancement. This will provide a gradual stimulus of local industry, and will be a point of initiating the process to encourage technological diversification in the South African pharmaceutical industry.

Chapter Two

Oral Modified Release Drug Delivery: Concept, Approaches and Techniques

2.1 ORAL MODIFIED DRUG DELIVERY

2.1.1 *INTRODUCTION*

In the past, one of the major aims of pharmaceutical research was the synthesis or discovery of new drug entities with desirable therapeutic properties void of undesirable adverse effects (Banerjee and Robinson, 1991). However, over the past two decades, pharmacokinetic and pharmacological studies have demonstrated that the rate and extent of drug absorption, rather than the dose, eventually determine therapeutic properties in systemic treatment (Urquhart *et al.*, 1984). Thus the focus of research and development in the pharmaceutical sciences, particularly in technology, shifted from the dose to the rate determining components of the dosage form. Consequently an array of drug delivery systems has been developed reflecting the numerous and diverse attempts to tailor the release rate of the drug from the delivery system to effectively control the rate of systemic uptake (Banakar, 1994a).

Peroral administration of drugs prepared in modified release delivery systems has gained extreme popularity, possibly due to the simultaneous convergence of various factors involved in the development of these delivery systems. These factors include the discovery of novel polymers and devices; a better understanding of formulation and physiological constraints and expiration of existing patents; and the prohibitive cost of developing new drug entities. However, the problems associated with the route include unpredictable bioavailability and variability in the length of time that a drug delivery system spends in the gastrointestinal tract. The oral route therefore presents challenges to the pharmaceutical scientist engaged

in the assessment and development of modified release drug products. Some major considerations that have been identified include: drug delivery systems and the associated inherent problems, gastrointestinal transit time and presystemic elimination (Banakar, 1987).

Research in modified release delivery systems aims at designing an optimal system with a zero-order input for specific biopharmaceutical requirements of an active agent, producing steady-state plasma drug levels. The basic modified release formulation consists of a drug and a carrier that may be a single polymer or a combination of different polymers and excipients so as to allow the active agent to be released over a period of time at a controlled rate (Fassihi and Ritschel, 1993).

The ultimate goals in designing modified release drug delivery systems are to reduce the frequency of dosing; or to increase the effectiveness of the drug by localizing it at the site of action, thereby reducing the dose required; or to provide uniform drug delivery (Grass and Robinson, 1990).

2.1.2 *TERMINOLOGY AND CONCEPT OF MODIFIED RELEASE*

Since the inception of the concept of modified drug delivery, numerous terms have been used to describe drug delivery systems from which a prolonged therapeutic response is achieved by a galenical approach (De Haan and Lerk, 1984). The USP XXIII Supplement 4 (1996) describes a modified release dosage form as one in which the 'drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms'. Other nomenclature that are commonly associated with these types of dosage forms are listed in Table 2.1, together with their definitions.

Table 2.1: Nomenclature associated with modified release drug delivery systems

TERMINOLOGY	DEFINITION
sustained release	▫ drug is initially made available to the body in an amount that is sufficient to cause a desired therapeutic response ▫ thereafter the drug is released at a constant rate to maintain therapeutic activity over a period of time (Shargel and Yu, 1985)
prolonged release	▫ no initial dose is included ▫ drug is released at a rate that will cause a therapeutic response over a period of time (De Haan and Lerk, 1984)
repeat action products	▫ dose is released immediately upon administration, and a second dose is released some time after administration (De Haan and Lerk, 1984)
controlled release	▫ drug release occurs at a predetermined rate which is based on a desired therapeutic concentration and the drug's pharmacokinetic characteristics (Ritschel, 1989)
extended release	▫ allows at least a two-fold reduction in the dosing frequency compared with the conventional dosage form (USP XXIII Supplement 4, 1996)
delayed release	▫ drug release occurs at a time other than promptly after administration (USP XXIII Supplement 4, 1996)
slow release	▫ releases an active substance more slowly than its conventional form, but not to such a degree that there is an appreciable reduction in dosing frequency (Rauws, 1991)

Throughout the ensuing discussion, modified release will be used as a collective term to describe any preparation from which the onset of action or the rate of drug release is altered, relative to a conventional release preparation. Idealised release profiles of some of the above-mentioned formulations, as well as that of an immediate release product, are depicted in Figure 2.1 to illustrate the relationship between drug concentration and time.

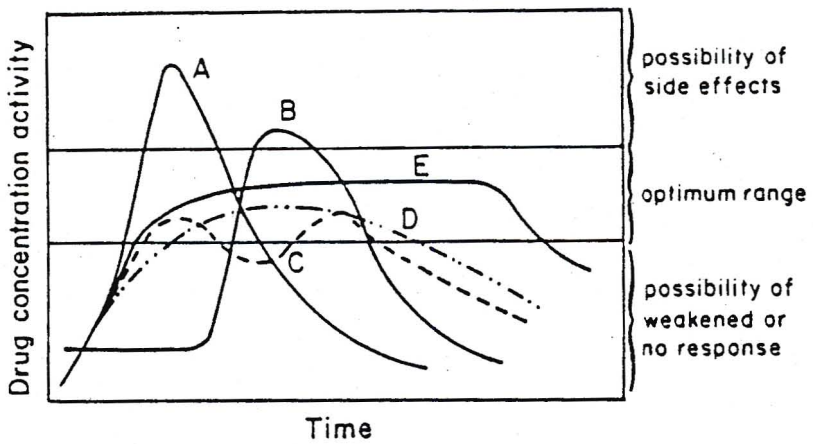


Figure 2.1: Relationship between drug concentration and time for products possessing various release profiles
Key: A - immediate release, B - delayed release, C - repeat action, D - prolonged release, E - controlled/sustained release
(Abdou, 1989 - page 215)

Drugs are often repeatedly administered to maintain a therapeutic level of active compound in the blood or tissues, particularly where continuous therapeutic activity is desired, in order to obtain a uniform response over an extended period of time. This can be achieved by different combinations of dose and dosage interval. From the point of view of patient compliance however, the dosage regimen of an orally administered drug may be considered to be optimal when the therapeutic effect is maintained for the desired duration of the treatment at the lowest frequency of administration (De Haan and Lerk, 1984).

With conventional release dosage forms, the blood level may rise above the therapeutic range causing an unwanted reaction, fall within the therapeutic range for perhaps an hour or two, then finally, the concentration may drop below this range, rendering the drug inactive pharmacologically. When the next dose is taken, the drug concentration in the blood goes through the same cycle. The net result is that the drug produces its desired effect perhaps 40-60% of the time (Sanders, 1985). Thus, it has long been the goal of researchers to find an ideal drug delivery system capable of minimising the 'saw-tooth' fluctuations of drug levels that accompany periodic dosing. In the clinical situation, the simplest approach to 'steady-state' blood levels is by intravenous infusion. However, the disadvantages of

intravenous infusion are that it is invasive and requires direct medical intervention. The oral route is therefore preferable and a constant therapeutic level is best attained by modified release technology, achieved by adjusting the dose and release rate of the drug from the device (Wilson and Washington, 1985).

Modified release delivery would be suitable for drugs with a rapid clearance from plasma or drugs that cause adverse effects locally or systemically (Källstrand and Ekman, 1983). Present peroral modified release drug delivery systems are clinically effective for a maximum of 24 hours. Such systems are primarily for drugs of short elimination half-life. However, drugs with long half-life qualify if a reduction in steady-state fluctuation is desired (Ritschel, 1989). The ideal modified release formulation is one which releases its contents at an appropriate, constant rate and becomes exhausted at precisely the dosage interval. With strict compliance the patient will, after four or five elimination half-lives, establish a constant and therapeutically effective blood level (Ganderton, 1985).

2.1.3 *RATIONALE FOR THE FORMULATION OF ORAL MODIFIED RELEASE DOSAGE FORMS*

Modified release dosage forms are as important for their scientific creativity as for their therapeutic success. They offer several advantages over conventional release products and can be categorised either as having convenience benefits or therapeutic benefits (Colaizzi and Pitlick, 1982).

Controlled therapeutic blood levels of the drug instead of the 'see-saw' fluctuations in blood levels that are characteristic of conventional release dosage forms can be achieved with modified release forms (Chien, 1982; Bruck, 1983). Therefore, both unnecessarily high and toxic peak concentrations with consequent adverse reactions, and sub-therapeutic levels with a possible consequence of symptom breakthrough, can be prevented (Szylkarski *et al.*, 1991). With lower peak concentrations, less drug is wasted by levels that exceed the minimum effective concentration. Controlled release rates may also provide smoother absorption, and frequently, less gastrointestinal irritation (Colaizzi and Pitlick, 1982).

Since less frequent dosing is required, patient compliance is likely to be improved (Krówczyński, 1987; Newton, 1992). Patients are less likely to forget taking doses with an increased convenience of drug administration.

Studies have shown that daily treatment with modified release products can be a less expensive approach to equivalent therapy (using conventional release products) due to better drug utilisation. Also, fewer doses can result in decreased nursing costs and would avoid interruption of sleep for night time dosing (De Haan and Lerk, 1984).

Modified release dosage forms offer little benefit for drugs which have a half-life in excess of 12 hours, since the conventional dosage form requires infrequent administration and results in similar drug plasma profiles. However, modified release dosage forms may still be advantageous if the therapeutic index of the drug is exceptionally low (Livingstone and Livingstone, 1988).

Finally, an improved dosage form of an existing drug may enhance its properties so markedly that the development of a new drug entity for the same purpose may become unnecessary (Sanders, 1985).

2.1.4 *LIMITATIONS OF ORAL MODIFIED RELEASE DOSAGE FORMS*

In order to develop oral modified release drug delivery systems, the formulation scientist is often faced with the difficulty of restraining and localising the system at targeted areas of the gastrointestinal tract. Water soluble drugs are considered difficult to deliver in the form of modified release preparations, due to their susceptibility to the 'dose dumping' phenomenon (Morella and Fisher, 1990). Consequently, toxic blood levels can occur as a result of premature release in clinical situations due to the incorporation of two or more doses into the dosage form (Livingstone and Livingstone, 1988; Banerjee and Robinson, 1991). Therefore, should an adverse effect develop, it is highly likely to be prolonged, because prompt termination of the dosage regimen to avoid adverse effects would not be possible. Accumulation of drug can also occur when the rate of drug elimination is low (Krówczyński,

1987).

Drugs which undergo substantial 'first-pass' metabolism may be entirely metabolised prior to reaching the systemic circulation (Livingstone and Livingstone, 1988). Another drawback of modified release dosage forms is the loss of flexibility in use (De Haan and Lerk, 1984).

Generally, with modified release drug delivery systems, it takes a longer time to achieve therapeutic blood concentrations and there is a possible increased variation in bioavailability following oral administration (Ranade, 1991a). Also, single unit dosage forms which contain large doses may not be amenable to being manufactured as modified release products, as the dosage form may become too bulky to be easily swallowed, thus making it less acceptable to the general population (Colaizzi and Pitlick, 1982).

2.1.5 *DRUG SUITABILITY AND MODIFIED RELEASE DOSAGE FORMS*

Although modified release drug delivery systems would be highly desirable for all drugs, a drug must possess certain attributes so that its incorporation into these types of delivery systems is possible. These attributes are summarized in Tables 2.2 and 2.3.

Table 2.2: Physicochemical factors influencing oral modified release dosage form design

PROPERTY	EXPLANATION
Dose size	◘ there is an upper limit to the bulk size of the dose to be administered ◘ a single dose of 0.5-1 g is considered maximal
Ionisation	◘ since the uncharged form of a chemical entity preferentially permeates across lipid membranes, presenting the drug in an uncharged form is an advantage
Aqueous solubility	◘ compounds with very low solubility (<0.01 mg/ml) are inherently sustained since their release over the time course of a dosage form in the gastrointestinal tract will be limited by dissolution of the drug ◘ the lower limit for the solubility of a drug to be formulated into a modified release system is 0.1 mg/ml
Partition coefficient	◘ compounds with a relatively high partition coefficient are predominantly lipid soluble ◘ they can localise in the lipid membrane of cells and persist in the body for long periods
Stability	◘ drugs that are unstable in the stomach show increased bioavailability in the modified release form ◘ drugs that are unstable in the small intestine may demonstrate decreased bioavailability due to the fact that more drug is delivered to the small intestine and is subject to degradation

(Grass and Robinson, 1990)

Table 2.3: Biological factors influencing oral modified release dosage form design

PROPERTY	EXPLANATION
Absorption	◘ drugs that are slowly absorbed or absorbed at a variable absorption rate are poor candidates for modified release systems
Distribution	◘ drugs with high apparent volumes of distribution, which in turn influences the rate of elimination of the drug, are poor candidates
Metabolism	◘ modified release systems for drugs which are extensively metabolised are possible as long as the rate of metabolism is not too great
Duration of action	◘ drugs with short half-lives and high dose impose a constraint because of the dose size needed while those with long half-lives are inherently sustained
Therapeutic range	◘ drugs with a narrow therapeutic range require precise control of the blood levels of drug, placing a constraint on modified release dosage forms

(Chang and Robinson, 1990)

2.1.6 *CLASSIFICATION OF ORAL MODIFIED RELEASE DRUG DELIVERY SYSTEMS*

The plethora of preparations that release drug at a constant rate is the most visible sign of the revolution of drug delivery systems. Many drugs can be released at a controlled rate with these formulations (Check, 1984). A perusal of the literature has indicated that different formulation scientists adopted different approaches to classifying oral modified release drug delivery devices. Rachev *et al.* (1989) based their classification on physical, chemical or bioengineering systems, while Flynn (1982) described chemical, physical, mechanical, biological control and feedback systems. Chien (1990) proposed that modified release can be achieved by either a diffusion controlled or a modulation controlled process. The scientific concepts behind the development of these drug delivery systems are outlined in Table 2.4.

Table 2.4: Summary of oral modified release drug delivery systems

TYPE OF SYSTEM	CHARACTERISTICS
1. DIFFUSION CONTROLLED	
1.1 Matrices of insoluble polymers	Skeleton-type preparations can be prepared by granulating the active ingredient with an inert plastic material (Ranade, 1991b)
1.2 Matrices of fats and waxes	Drugs can be dissolved or suspended in a mixture of digestible and non-digestible fatty substances. Drug release from these fat/wax matrices occurs by leaching of the drug by water penetrating the matrix and gradual surface erosion of the tablet (Szylkarski *et al.*, 1991)
1.3 Hydrophilic matrices	This type of matrix is prepared by mixing the active ingredients with nondigestible hydrophilic gums. Hydration and gelation of the gum at the tablet/liquid interface result in the formation of a viscous gel barrier through which the drug diffuses (Ranade, 1991b)
1.4 Microporous membrane coated tablets	A tablet is coated with a water-insoluble polymer containing a dispersed water-soluble pore-creating substance. The membrane is insoluble in the gastrointestinal tract and the aqueous soluble component yields porosity to the dosage form when it comes into contact with gastrointestinal fluid (Källstrand and Ekman, 1983)
1.5 Solubility membrane controlled drug delivery system	A core tablet containing an aqueous soluble drug is coated with a layer of thermoplastic polymer to create a solubility membrane in the gastrointestinal tract (Banakar, 1994a)
2. MODULATION CONTROLLED	
2.1 Osmotic system	The system consists of an osmotically active core, including the drug, surrounded by a rate controlling semi-permeable membrane with an orifice of controlled size. Rate-controlled drug delivery is dependent on the water permeability of the semi-permeable membrane and the osmotic pressure of the core formulation (Lippold, 1991)

2.2 Ion exchange resins	Resins are water insoluble materials containing salt forming groups in repeating positions on the resin chain. Drug molecules attached to the resin are exchanged by appropriately charged ions in contact with the ion exchange groups, and the released drug molecule diffuses out of the resin (Ranade, 1991b)
2.3 Intragastric floating drug delivery device	This device consists of an immediate release layer and a sustained release layer. Once the immediate release layer is exhausted, the sustained release layer forms an impermeable colloidal gel layer on its surface, reducing the bulk density to less than one, thus maintaining its buoyancy in the stomach until the entire loading dose is released (Banakar, 1994a)
2.4 Gastroinflatable drug delivery devices	An inflatable chamber containing liquid that gasifies at room temperature is incorporated into a drug delivery device. The gas liquifies at room temperature, prolonging the residence time of the device in the stomach, and after a predetermined interval, the inflatable chamber collapses, thereby permitting spontaneous ejection of the device from the stomach (Banakar, 1987)
2.5 pH independent formulations	Buffers are added to the drug to achieve pH independent drug release. When the gastroinflatable fluid penetrates the device, the buffering agents adjust the pH to a constant value at which the drug can dissolve and permeate outwards at a constant rate (Park *et al.*, 1984)
2.6 Pulsatile delivery systems	This system usually consists of two parts: an active ingredient and disintegrating agent, and a poorly water permeable outer shell. The outer shell can delay the water penetration to provide a long lag time. Once the outer fluid reaches the inside, the core tablet swells until the outer shell finally breaks, resulting in rapid release of drug (Ishino *et al.*, 1992)
2.7 Altered density: drug coated micropellets	Empty globular shells with an apparent density of less than that of the gastric juice are undercoated with a polymeric material, which is further coated by a drug-polymer layer mixture. The device floats on the gastric juice for an extended period of time while slowly releasing the drug (Park *et al.*, 1984)

2.8 Bioadhesive systems	Prolonging the duration of drug presence in the gastrointestinal tract can be achieved by localising it within a specific region by binding the product to the epithelial/mucin surface of the gastrointestinal tract (Ranade, 1991b)
2.9 Thixotrophic bilayer tablet	The tablet consists of two layers each of which is prepared by dissolving or dispersing the medicament in a gel prepared from thixin and a volatile solvent. A drug dispersing matrix is formed upon solvent evaporation. Thixin absorbs water to form a hydrophobic gel through which drug diffuses (Banakar, 1987)
2.10 Multilaminated sustained release tablets	The system comprises more than one laminate with the ability to release the contents from each laminate at various rates. A loading dose of drugs is dispersed in a water soluble polymer which is sandwiched between water swellable polymers. Drug release is controlled by the barrier formed by the swelling of the crosslinked polymers (Banakar, 1994a)
2.11 Enteric coated controlled release dosage form	Preparations from this type of coating are designed to resist or reduce dissolution of the active compound in the stomach in order to prevent destruction and inactivation of the drug by the gastric contents, or to protect the stomach from the drug (De Haan and Lerk, 1984)

2.1.7 *MATRIX TABLETS*

One of the least complicated approaches to the manufacturing of modified release dosage forms involves the direct compression of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternatively, retardant-drug blends may be granulated prior to compression (Lordi, 1986).

2.1.7.1 Plastic Matrix Tablets

Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be prepared by one of the following methods (Ranade, 1991b):

- the drug powder can be mixed with plastic granules for direct compression;
- the drug powder and plastic powder can be mixed and kneaded with a solution of the same plastic material in an organic solvent and then granulated; or
- a solid-solid solution of the drug in plastic particles may be produced by dissolving the drug in the plastic-containing organic solvent and granulating it. Upon evaporation of the solvent, a solid-solid solution of the drug in the plastic particles is produced.

Commonly used plastic matrix materials are polyvinylchloride, polyethylene, vinyl acetate/ vinyl chloride copolymer, vinylidene chloride/acrylonitrile copolymer, acrylate/methyl methacrylate copolymer, ethyl cellulose, cellulose acetate and polystyrene (Chang and Robinson, 1990).

These matrices may be homogeneous or granular with drug release predominantly controlled by diffusion. In a homogeneous matrix, the suspended drug dissolves and diffuses through the polymer, while a granular matrix allows penetration of surrounding fluid through pores and spaces created by channelling excipients or previously leached drug. The drug diffuses out through the fluid filled pores within the matrix (Szylkarski *et al.*, 1991).

Drug release from inert plastic matrices can be affected by varying formulation factors such as the matrix material, the amount of drug incorporated in the matrix, solubility of the drug in the dissolution media and matrix, matrix additives and the release media. Since the mechanism of controlling drug release in the plastic matrix is the pore structure of the matrix, any formulation factor affecting the release of a drug from the matrix may be a consequence of their primary effect on apparent porosities and tortuosities of the matrices. These release factors have been summarised by Chang and Robinson (1990) as follows:

- the release rate increases as the solubility of the drug increases;
- the release rate increases as the drug concentration increases, due to changes in the matrix tortuosity and decreased diffusional resistance by shortening the length of the capillary joining any two drug particles;
- the release rate can be modified by the inclusion of hydrophilic or hydrophobic additives to the matrix. Release rates of sparingly used substances can be increased by the addition of a physiologically inert but readily soluble material;
- the release rate from plastic matrix tablets could be decreased without changing the release mechanism by exposure to acetone vapour, the extent of reduction being dependent on the amount of acetone absorbed. Heating the polymer matrix above the glass-transition temperature results in an increase in the tensile strength of the tablets; and
- an increase in the compaction pressure up to the final consolidation point decreases the number of pores formed among the polymer particles, leading to a slower drug release rate.

2.1.8 *MECHANISM OF DRUG RELEASE*

The purpose of modified release systems is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to that eliminated by the body. Historically, pharmaceutical researchers have experimented with numerous types of mechanisms to prolong the release of drugs in the body. Currently, technology utilises one of three basic mechanisms. The first is dependent on a diffusion or solution diffusion-controlled process,

where a reservoir or a matrix medium is used as the depot. The second is based on chemical reactions, where the drug is chemically bound to the backbone of a polymer, and is released upon hydrolytic or enzymatic cleavage. The third mechanism is based on solvent-activated processes, such as osmosis (Abdou, 1989).

In the embedded matrix model (Figure 2.2), drug is dispersed in a matrix of the retardant material, which may be encapsulated in particulate form or compressed into tablets. Release is controlled by a combination of several physical processes, which include permeation of the matrix by water; leaching (extraction or diffusion) of drug from the matrix; and erosion of matrix material. Alternately, drug may dissolve in the matrix material and be released by diffusion through the matrix material or partitioned between the matrix and extracting fluid (Lordi, 1986).

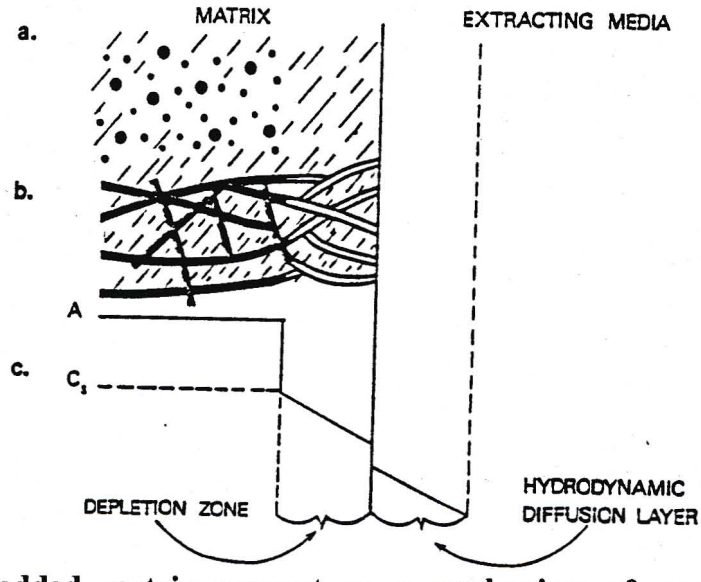


Figure 2.2: Embedded matrix concept as a mechanism of controlled release in modified release dosage form design
Network model (a): drug is insoluble in the retardant material;
Dispersion model (b): drug is soluble in the retardant material; and
Diffusion profile (c): characterises drug release from a matrix system (Lordi, 1986 - page 443)

Figure 2.3 represents drug release profiles from different dosage form planar models, including zero-order (A), first-order (B), square root of time (C) and matrix controlled release with diffusion (D). In the planar case, erosion should be zero-order, a function of the product of the drug concentration in the matrix and the effective dissolution rate of the retardant. Release due to erosion is generally more rapid than matrix-controlled release (Lordi, 1986).

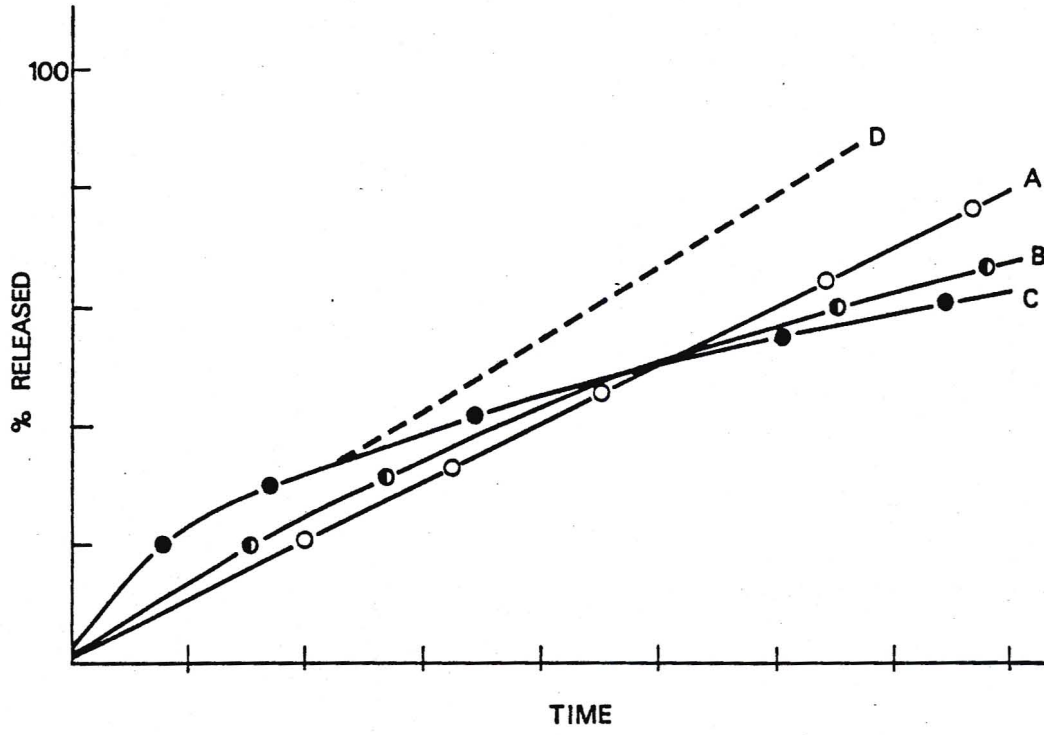


Figure 2.3: Drug release profiles characteristic of different dosage form models representing embedded matrix systems. A - zero-order model; B - first-order model; C - diffusion model; D - diffusion model with erosion (Lordi, 1986 - page 445)

2.2 TABLETS AND TABLETTING

2.2.1 *HISTORICAL PERSPECTIVE AND INTRODUCTION*

The origin of compressed tablets dates back to 1843, when William Brocken was granted a patent on a machine for manufacturing compacts from particulate matter (Rubinstein, 1992). The development of drugs, excipients and tabletting machines during the past decade has made tablet manufacture a science, and tablets the most commonly used dosage form (Reimerdes, 1993).

Compressed tablets are defined as solid-unit dosage forms made by compaction of a formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the dosage product (Bandelin, 1989).

Throughout their history, compressed tablets have been designed primarily for swallowing. More recently, specialised tablets have been developed for chewing, dissolving in the mouth (lozenges, sublingual forms), dissolving in water (effervescent forms) and implantation. In the early 1930s tablets were designed specifically to modify the release of drug via a variety of new technologies. This resulted in a significant improvement and expansion in the field of modified drug delivery. During the early phase of modified release, the technology was confined to encapsulated beads, but with the advent of the less expensive and less problematic compressed tablet, modified release technology has become somewhat simpler (Mendes, 1991).

2.2.2 *ADVANTAGES OF TABLETS*

The advantages of tablets over other dosage forms have been summarised by Banker and Anderson (1986) as follows:

- they are a unit dosage form, and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability;
- their cost is the lowest of all dosage forms;

- they are the lightest and most compact of all dosage forms;
- they are in general the easiest and cheapest to pack and transport of all dosage forms;
- product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face;
- they may provide the greatest ease of swallowing with the least tendency for 'hang-up' above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid;
- they lend themselves to certain special release profile products, such as enteric or delayed release products;
- they are better suited to large-scale production than other unit oral forms; and
- they have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

2.2.3 *COMPRESSED TABLETS*

2.2.3.1 Characteristics And Quality

There are numerous properties of tablets that are used as standards of quality control and that may influence the efficacy of tablet dosage forms. These characteristics include tablet weight, tablet thickness, mechanical strength, content uniformity, disintegration time and dissolution.

2.2.3.1.1 Tablet weight

Weight variation in tablets indicates a corresponding variability in the total drug content for the active ingredient of the tablet (Ansel and Popovich, 1990).

2.2.3.1.2 Tablet thickness

Variations in tablet thickness indicate formulation or processing problems. At a constant compressive load, variations in tablet thickness are indicative of changes in die fill and, consequently, tablet weight, whereas with a constant fill, thickness variations reflect changes in compressive force (Rosanske *et al.*, 1990).

2.2.3.1.3 Mechanical strength

Mechanical strength may be defined as the capacity of a tablet to resist the external forces it encounters. The following tests are used to measure the overall strengths of a tablet:

- tablet hardness test: measures resistance to diametral compression;
- friability test: measures resistance to abrasion; and
- flexure breaking test: measures resistance to bending (Gold *et al.*, 1983).

2.2.3.1.4 Content uniformity

The content uniformity tests are designed to evaluate the homogeneity of the batch (Marshall and Rudnic, 1990).

2.2.3.1.5 Disintegration time

Disintegration testing is used purely as a guide in the formulation and preparation of an optimum tablet formula and as an in-process control test to ensure lot to lot uniformity (Banker and Anderson, 1986). The usual tests of disintegration time reflected in pharmacopoeias do not apply to oral modified release dosage forms, since the release rate per unit time has been reported to be the critical factor (Banakar, 1992).

2.2.3.1.6 Dissolution

Dissolution is defined as the rate at which a solid substance dissolves (Abdou, 1989). When conducted appropriately, dissolution analysis of pharmaceutical dosage forms has emerged as the single most important test that will ensure the quality of a product (Prasad *et al.*, 1983a).

Scientific evidence has shown that a properly designed dissolution test serves one or more of the following functions:

- to determine the stability of drug products during accelerated short-term stability testing, in terms of deviations from the original drug release profile (Chetty, 1990);
- to elucidate the mechanism of drug release from a dosage form (Govender, 1992);
- to guide formulation/process development and optimisation;
- to monitor the performance of the manufacturing process both during development and upon product approval;
- to minimise the risk of bioinequivalence from batch to batch; and
- to gain regulatory approval of solid oral dosage forms (Skoug *et al.*, 1996).

2.2.3.1.6.1 *Dissolution Rate*

Dissolution rate may be defined as the amount of active ingredient in a solid-dosage form dissolved per unit time under standardised conditions of liquid/solid interface, temperature and solvent composition (Abdou, 1989). The traditional mathematical expression for this definition is the Noyes-Whitney equation, as modified by Underwood and Cadwallader (Hanson, 1982):

$$dW/dt = kS (C_{sat} - C_{sol}) \qquad \textit{Equation 2.1}$$

where, dW/ dt is the dissolution rate;

k is the dissolution constant;

S is the surface area of the solid;

C_{sat} is the concentration of a saturated solution; and

C_{sol} is the concentration at any time.

By keeping the volume of solvent large with respect to saturation point, sink conditions are approximated. Sink conditions thus become one of the main experimental parameters to be controlled during dissolution testing, that is, $C_{sat} >> C_{sol}$ (Hanson, 1982). Sink conditions are considered to be maintained when the concentration of the solute remains below 10-20% of its maximum solubility in the dissolution medium (Mehta, 1994).

2.2.3.1.6.2 *Dissolution Of Tablets*

To date, compressed tablets maintain the status of being the most widely used dosage form. Factors that influence the physicochemical properties of the dosage form also influence the dissolution performance of the drug from the tablet (Banakar, 1992). Wagner proposed a scheme for the processes involved in the dissolution of drug from solid dosage forms (Figure 2.4) (Abdou, 1989).

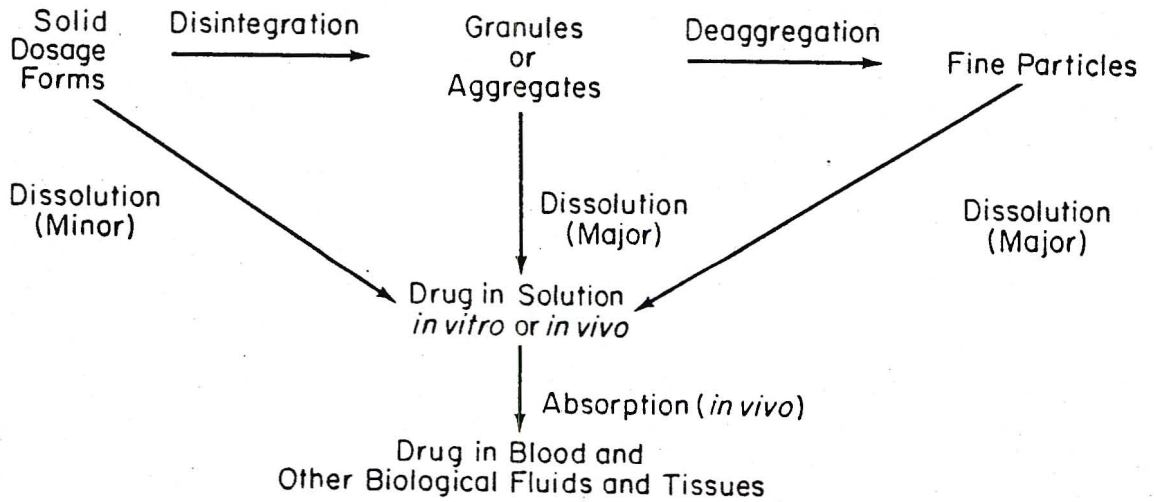


Figure 2.4: Schematic representation of the dissolution of drug from a tablet dosage form (Abdou, 1989 - page 37)

This scheme was however later modified to include other factors that preceed the dissolution process of solid dosage forms. The following scheme was then proposed by Carstensen (Abdou, 1989):

- an initial lag mechanism;
- wetting of the dosage form;
- penetration of the dosage form by the dissolution medium;
- disintegration;
- disaggregation of the dosage form and dislodgement of the granules;
- dissolution; and
- occlusion of some particles of the drug.

Figure 2.5 shows the different stages of the dissolution process that usually exhibits an S-shaped curve.

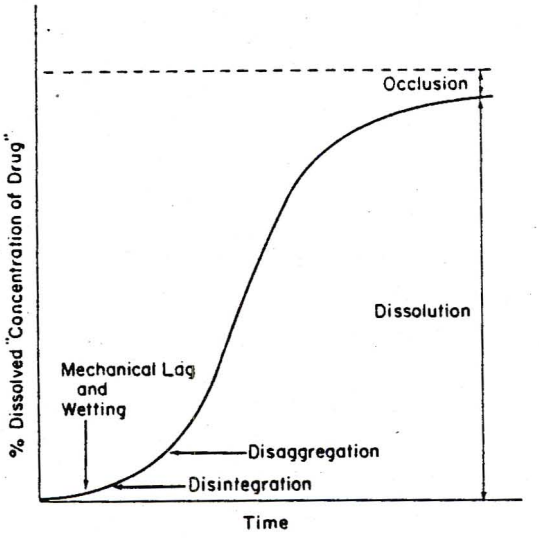


Figure 2.5: The S-shaped dissolution curve of solid dosage forms (Abdou, 1989 - page 38)

According to Hanson (1982), the surface area of a solid dosage from will change during dissolution. This effect is more pronounced in disintegrating dosage forms than in the non-disintegrating types. The surface area of non-disintegrating forms is gradually decreased during the dissolution process, while disintegrating forms are subject to complicated disintegration and deaggregation as they release particles of different sizes and specific

gravities into the dissolution medium. A non-disintegrating solid exhibits a reduction in surface area, while with a disintegrating aggregate, the surface area increases significantly. The dissolution curve of a disintegrating solid does not change as abruptly as indicated in Figure 2.6, but as the process of disintegration into granules and disaggregation into fine particles takes place, significant changes in the slope of the dissolution curve do occur. The various, typical dissolution curve profiles are shown in Figure 2.7.

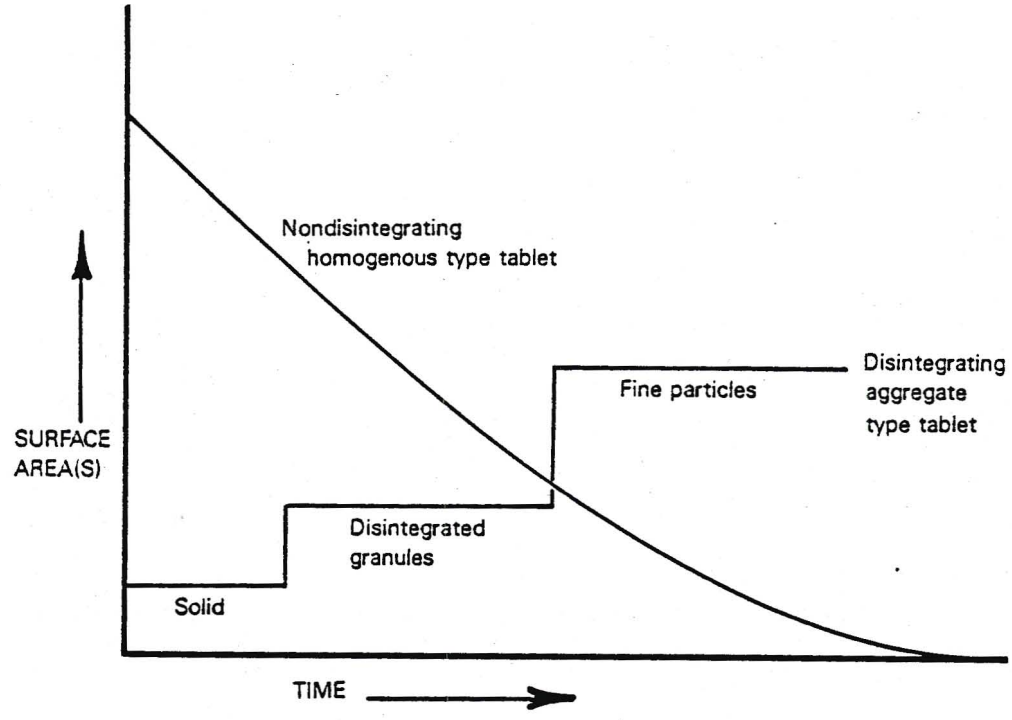


Figure 2.6: Change in surface area with time for solids of non-disintegrating and disintegrating types (Hanson, 1982 - page 19)

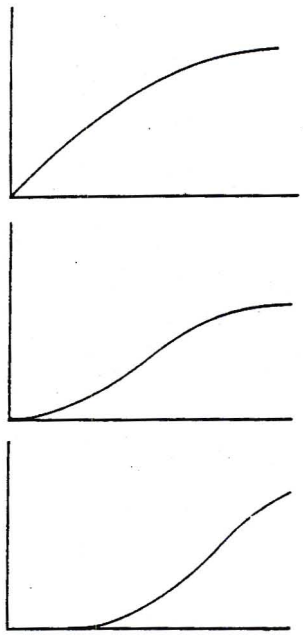


Figure 2.7: Dissolution curve profiles of non-disintegrating and disintegrating solid dosage forms. Ordinates, concentration of ingredient dissolved; abcissas, time a) non-disintegrating tablet; b) rapidly disintegrating tablet and c) slowly disintegrating tablet (Hanson, 1982 - page 20)

2.2.3.1.6.3 *Mean Dissolution Time And Mean Residence Time*

The arithmetic mean value of any dissolution profile is called the 'mean dissolution time'. If the content of drug substance, which is still in the dosage form, is plotted as a function of time, the arithmetic mean of the so-called residence profile is the 'mean residence time' of the drug substance molecules in the dosage form (Podczeck, 1993). The parameters, mean dissolution time and mean residence time, have been used not only to describe dissolution or residence profiles with the aim to reduce the data, but also to test the equivalence of dissolution profiles (Brockmeier *et al.*, 1983), to calculate the *in vitro/in vivo* correlation of dissolution profiles (Brockmeier, 1986), and to model the input function of the drug absorption (Voegele *et al.*, 1988), or to compare different profiles statistically. A comparison of the different methods that have been proposed to calculate values of mean dissolution time and mean residence time is outlined by Podczeck (1993).

2.2.3.1.6.4 *Dissolution Methodology*

There has been an abundance of literature regarding dissolution apparatus over the last two decades. A survey of methods was presented by Pernarowski who noted over 150 different apparatus designs (Carstensen *et al.*, 1978), while recent studies of the different dissolution methods have been reported by Dakkuri and Shah (1982), Abdou (1989) and Govender (1992). On the other hand, Hanson (1982) and Cohen *et al.* (1990) have outlined the development of dissolution testing.

Although the USP XXIII (1995) currently recognises seven Official methods, the rotating basket system suggested by Pernarowski in 1968 and the rotating paddle system suggested by Poole in 1969, after many modifications, have become the most commonly used methods for the dissolution of oral dosage forms (Hanson, 1982).

2.2.3.1.6.5 *Rotating Paddle Method Versus The Rotating Basket Method*

Besides accommodating the need for meeting the legal requirements for Compendial drugs, dissolution testing is increasingly used for oral dosage forms not yet listed in the Compendia. The selection of either method will ultimately depend on the nature of the dosage form, as well as the needs for total automation of the procedure. A detailed comparison of the rotating paddle and rotating basket apparatus is described by Pillay (1996).

2.2.3.1.6.6 *Factors Influencing Dissolution Testing*

The various factors affecting the dissolution rate of a drug from a dosage form can be classified into six categories. These factors have been extensively reviewed by Banakar (1992) and are listed in Table 2.5.

Table 2.5: Factors influencing dissolution testing

◘ Factors related to the physicochemical properties of the drug
• solid phase characteristics • polymorphism • precipitation and/or complexation
◘ Factors related to drug product formulation
• excipients and additives • particle size • granulating agents and binders • disintegrating agents • lubricants • interfacial tension between the drug and the dissolution medium • surfactants
◘ Factors related to the dosage from
• manufacturing procedures • granule size • drug-excipient interactions • compression force • deaggregation • storage of dosage form
◘ Factors related to the dissolution testing device
• eccentricity of agitation (stirring) element • vibration • agitation intensity • stirring element alignment • flow pattern disturbances • sampling probes, positions and filters • dosage form position • type of device
◘ Factors related to the dissolution test parameters
• temperature • dissolution medium • dissolved gases-air • dissolution media composition and pH • viscosity • surface tension • ions or surfactants
◘ Miscellaneous factors
• adsorption • sorption • humidity • detection errors

2.2.3.1.6.7 *Dissolution Of Modified Release Dosage Forms*

The rate of drug release from modified release solid dosage forms depends on the rate of dissolution. The mechanism of release of drugs from various modified release dosage forms may be different for each form. It has been reported that these dosage forms are not only drug products, but also devices, and therefore no single *in vitro* test will completely reflect the availability of the drug (Banakar, 1992).

2.2.3.1.6.8 *Dissolution From Matrices*

Theoretically expected rates of release of solid drugs incorporated into solid matrices have been derived for several model systems. Mathematical relations have been obtained for two types of systems:

- where the drug particles are dispersed in a homogeneous matrix which acts as the diffusional medium; and
- where the drug particles are incorporated in an essentially granular matrix and released by the leaching action of the penetrating solvent (Higuchi, 1963).

2.2.3.1.6.8.1 *Release from a planar system having a homogeneous matrix*

In this system, the drug is assumed to go successively from the crystal surfaces into the uniform matrix and out into the bathing solvent which acts as a perfect sink. The amount of drug released is determined by the following relationship:

$$Q = [Dt\,(2A - C_s)\,C_s]^{1/2} \qquad \textit{Equation 2.2}$$

where, Q is the amount of drug released after time t per unit exposed area;

D is the diffusivity of the drug in the homogeneous matrix media;

A is the total amount of drug present in the matrix per unit volume; and

C_s is the solubility of the drug in the matrix substance (Higuchi, 1963).

2.2.3.1.6.8.2 *Release from a planar system having a granular matrix*

Drug release occurs by leaching of the medicament by the bathing fluid which is able to enter the drug-matrix phase through pores, cracks and intergranular spaces. The drug is assumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent. The amount of drug released is represented as follows:

$$Q = [D\epsilon/\tau\ (2A - \epsilon C_s)\ C_s t]^{1/2} \qquad \textit{Equation 2.3}$$

where, Q is the amount of drug released after time t per unit exposed area;

D is the diffusivity of the drug in the permeating fluid;

τ is the tortuosity factor of the capillary system;

A is the total amount of drug present in the matrix per unit volume area;

C_s is the solubility of the drug in the permeating fluid; and

ϵ is the porosity of the matrix.

The porosity refers to the leached portion, and differs from the initial porosity of the initially formed matrix. The difference corresponds to the volume of free space, previously occupied by the extracted component. Hence, for systems where the drug is the only extractable component,

$$\epsilon = \epsilon_0 + KA \qquad \textit{Equation 2.4}$$

where, ϵ_0 is the initial porosity; and

K is the specific volume of the drug.

If the initial porosity ϵ_0, is very small or the fraction of the matrix volume occupied by the drug is relatively large, ϵ approximates KA, and the equation 2.2 is modified to:

$$Q = A[DK/\tau\ (2 - KC_s)\ C_s t]^{1/2} \qquad \textit{Equation 2.5}$$

The derivations of equations 2.2 and 2.3 are based on the existence of a pseudo steady-state condition during the release process and on the assumption that the drug particles are small relative to the average distance of diffusion and are uniformly distributed in the matrix (Higuchi, 1963).

Figure 2.8 illustrates the mechanism of drug release from homogeneous and granular matrices.

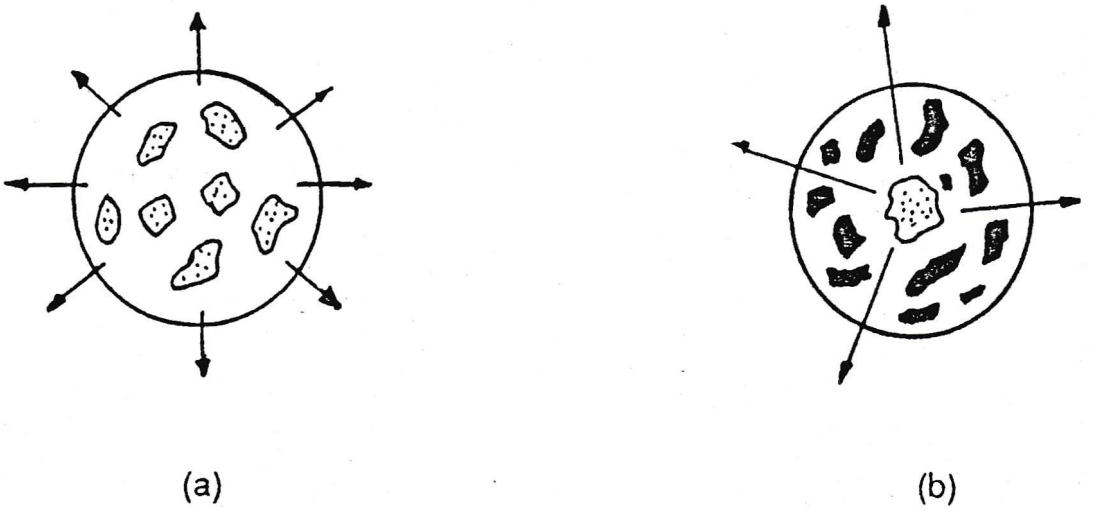


Figure 2.8: Drug release from a) a homogeneous matrix; and b) a granular matrix (Higuchi, 1963 - page 1146)

2.2.3.2 In-process Quality Control: Processing Problems

The processing problems that may arise during tabletting are summarised in Table 2.6.

Table 2.6: Processing problems during tabletting

◘ Capping and lamination
Capping is the term used to describe the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet, while lamination is the process of separation of a tablet into two or more distinct layers. Capping and lamination can be due to the deformational properties of the formulation during and immediately following compression, lack of cohesion of a granulation, materials with poor compression properties, tablet tooling and incorrect setting of the press.
◘ Picking and sticking
Picking is the term used to describe the surface material from a tablet that is sticking to and being removed from the tablet's surface by a punch. Punches with engraving or embossing are apt to cause picking. Sticking refers to tablet material adhering to the die wall. This is more prone to occur if excessive moisture is present, or if a low-melting-point substance is present.
◘ Mottling
Mottling is an unequal distribution of colour on a tablet, with light or dark areas standing out in an otherwise uniform surface. Mottling may be caused by: a drug whose colour differs from the tablet excipients or a drug whose degradation products are coloured; a dye can cause degradation by migrating to the surface of a granulation during drying. In direct compression, mottling can be caused by the uneven distribution of the dye or a large particle size.
◘ Weight variation
• Granule size and size distribution before compression Variations in the ratio of small to large granules and the magnitude of difference between granule size influence the fill of the void spaces between particles. Therefore, although the apparent volume of the die is the same, the difference in the proportions of small and large particles leads to variations in the weight of the tablet. • Poor flow The die fill process is based on a continuous and uniform flow of the granulation from the hopper to the die. Incomplete filling of the die occurs when the granulation does not flow well or if the machine speed is in excess of the granulations' flow capabilities. • Poor mixing When lubricants and glidants are not distributed evenly, the flow of particles is impaired and the granules do not efficiently fill the dies.
◘ Hardness variation
The causes of variations in weight are applicable to variations in hardness, since hardness is dependent on the weight of the material and the space between the punches at compression. Thus, if the volume of material or the distance between the punches varies, hardness will be inconsistent.

(Banker and Anderson, 1986)

2.2.4 *GRANULATION*

Many pharmaceutical powders cannot be compressed directly into tablets since they lack the proper characteristic of binding or bonding together to form a compact entity, or they do not possess the lubricating and disintegrating properties that are necessary for tabletting. Therefore, drugs are pretreated, alone or in combination with excipients to form granules that are gathered together into larger, permanent aggregates to render them into a free-flowing state (Bandelin, 1989).

The potential benefits associated with granulations have been summarised by Gordon and Fonner (1990):

- an improvement in powder flow;
- an increase in bulk density;
- a more uniform particle size;
- a reduction in punch face adherence;
- a reduction in capping tendencies; and
- an improvement in operator safety.

2.2.4.1 Wet Granulation

Wet granulation is the process by which a liquid is added to a powder in a vessel equipped with any type of agitation mechanism that will produce agglomeration or granules (Bandelin, 1989).

Wet granulation essentially consists of sticking the particles together using an adhesive material, thereby increasing the particle size and improving flow properties.

The powdered ingredients are sieved and mixed, and then the granulating liquid (solution, suspension or slurry) with or without a binder is incorporated to provide a slightly moist doughy mass (Colaizzi and Pitlick, 1982). The granulating liquid is a key component in the process. Liquid bridges are formed between the particles, and the tensile strength of the

bonds increases as the amount of added liquid is increased. The surface tension forces and capillary pressure are primarily important for initial granule formation and strength. After the granulating liquid has been added, mixing continues until a uniform dispersion is attained. The length of time of the granulating process is dependent upon the wetting properties of the powder mixture and the granulating liquid, and the efficiency of the mixer (Banker and Anderson, 1986). The degree of moisture of the wet granulation must be carefully controlled during the granulating process. If the moistened mass is too wet, granule formation will not occur properly and the dried granules will become too hard and result in compression problems and mottling of the tablets, while an insufficiently moistened mass will form granules that are too soft and fragile (Colaizzi and Pitlick, 1982; Ansel and Popovich, 1990). The wet screening process involves the conversion of the moist mass into granules by passage through a granulator. This is done to further consolidate granules, increase particle contact points, and increase surface area to facilitate drying. A drying procedure is required to remove the solvent that was used in the granulating process, and to reduce the moisture content to the optimum level of concentration within the granules (Banker and Anderson, 1986). Excessive residual moisture can affect drug stability, tablet appearance and the ability of the dried granules to undergo proper compression. Once drying is complete, the dried granules are screened to a more uniform particle size (Colaizzi and Pitlick, 1982). Sizing of the granules is necessary so that the small die cavity, for the production of small tablets, may be completely filled by the flowing granulation. The voids or air spaces left by large granules in a small die cavity would likely result in the production of tablets of varying evenness. Prior to compression, a dry lubricant is generally added to the granules (Ansel and Popovich, 1990).

2.2.4.1.1 Advantages of wet granulation

Wet granulation is a versatile process, and its application in tablet formulation is unlimited. The advantages of this process have been summarised by Shangraw (1989):

- permits mechanical handling of powders without loss of mix quality;
- increases and improves the uniformity of powder density;
- improves cohesion during and after compaction;

- reduces air entrapment;
- reduces the level of dust and cross-contamination;
- allows for the addition of a liquid phase to powders; and
- makes hydrophobic surfaces hydrophilic.

2.2.4.1.2 Particle bonding mechanisms

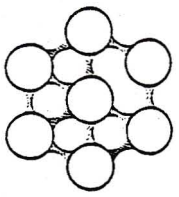
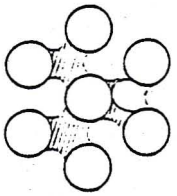
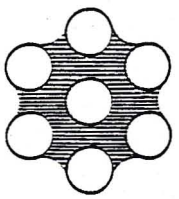
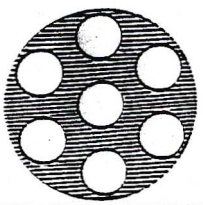
In the formation of granules, bonds must be formed between powder particles so that they adhere. The bonds must be strong enough to prevent breakdown of the granule to powder during subsequent handling. In 1962, Rumpf distinguished five primary bonding mechanisms between particles (Summers, 1988):

- adhesion and cohesion forces in immobile liquid films;
- interfacial forces in mobile liquid films;
- solid bridges;
- attractive forces between solid particles; and
- interlocking bonds.

2.2.4.1.3 Stages in the wet granulation process

The stages in the wet granulation process are summarized in Table 2.7.

Table 2.7: Summary of the stages in the wet granulation process

STAGE	DESCRIPTION
Pendular 	Liquid films will be formed on the surface of the powder particles if they are wetted during the initial stage, which may combine to produce discrete liquid bridges at points of contact. The surface tension and negative capillary pressure in such bridges provide the cohesive forces in this stage. The mechanical strength is comparatively low.
Funicular 	As the liquid content increases, several bridges coalesce to form this state, with a modest increase in granule strength.
Capillary 	As more liquid is added, and as the mass is kneaded, particles are brought in closer proximity, and the void spaces are entirely eliminated. Bonding is due to the interfacial forces at the granulate surface and a negative capillary pressure throughout the interior liquid-filled space.
Droplet 	Further addition of liquid results in this stage. The particles are still held together by surface tension, but without the intragranular forces. These structures are weaker.

(Marshall, 1986 - page 76)

The capillary state coincides with the maximum strength of the wet granules, and optimisation of the many granulation processes involved ensures that this state is achieved (Marshall, 1986).

2.2.4.1.4 Mechanism of granule formation

In the wet granulation method, the liquid that is added to the dry powders has to be distributed through the powder by the mechanical agitation produced in the granulator. The particles adhere to each other because of liquid films and further agitation and/or liquid addition causes more particles to adhere to one another. The mechanism of granulation can be divided into three stages (Summers, 1988). These stages are described in Table 2.8.

Table 2.8: Mechanism of granule formation

MECHANISM OF GRANULE FORMATION
Nucleation ▫ granulation starts with particle-particle contact and adhesion due to liquid bridges ▫ numerous particles join to form the pendular state ▫ further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth
Transition ▫ nuclei can grow by two possible mechanisms: • single particles can be added to the nuclei by pendular bridges • two or more nuclei may combine ▫ this stage is characterised by the presence of a large number of small granules with a fairly wide size distribution ▫ this point represents a suitable end-point for granules used in tablet manufacture
Ball growth ▫ further granule growth produces large, spherical granules, and the mean particle size increases with time ▫ if agitation is continued, granule coalescence will continue and produce an unstable, overmassed system

The mechanisms of ball growth and have been summarised by Summers (1988):

- coalescence
  - two or more granules join to form a larger granule
- breakage
  - granules break into fragments which adhere to other granules forming a layer of material over the surviving granule
- abrasion transfer
  - agitation of the granule bed leads to attrition of material from granules
  - this abraded material adheres to other granules, increasing their size
- layering
  - when a second batch of powder mix is added to a bed of granules, the powder will adhere to the granules forming a layer over the surface increasing the granule size.

Figure 2.9 illustrates the mechanisms of ball growth during granulation.

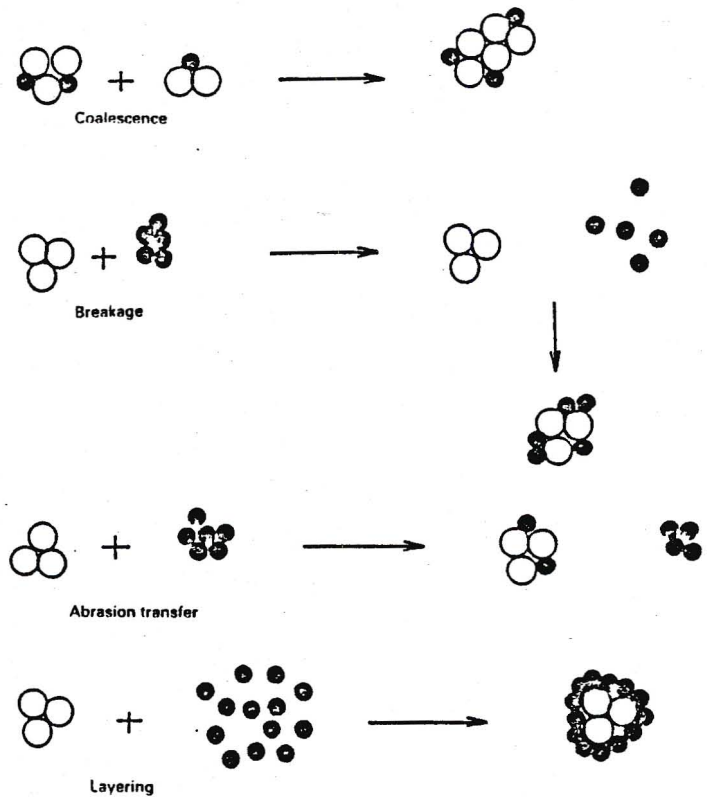


Figure 2.9: Mechanisms of ball growth during granulation (Summers, 1988 - page 622)

2.2.4.2 Dry Granulation

The dry granulation technique offers an alternative to direct compression with many of the same advantages (Connolly *et al.*, 1990). This technique is used when the effective dose of a drug is too high for direct compression, and the drug is sensitive to heat or moisture, or both, which precludes wet granulation (Banker and Anderson, 1986). After weighing and mixing the ingredients in the same manner as in the wet granulation method, the powder is 'slugged' or compressed into large flat tablets or pellets (Ansel and Popovich, 1990). The compacted masses are called slugs, and the process is referred to as 'slugging'. The slugs are broken up by gentle milling and the portion in a reasonable size range separated. The coarse fraction is remilled and the fine portion recompressed and remilled. By this process, the powder is converted into agglomerates of a size which allows flow and hence good weight control of the final tablet. The features not accomplished which are imparted by wet granulation are hydrophilization and uniformity (Carstensen, 1980). Finally, the slugs are screened, lubricated and compressed. Instead of the slugging method, compaction mills may be used to increase the density of a powder by pressing it between high-pressure rollers. The densified material is then broken up, sized, and lubricated, and tablets are prepared by compaction in the usual manner (Ansel and Popovich, 1990).

2.2.5 *DIRECT COMPRESSION*

Direct compression is used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients, which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary (Shangraw, 1989). In addition to the use of special excipients, forced or induced feeders which have been developed permit the preparation of certain additional tablets by direct compression because the deaerating action of the feeder on light, bulky powders makes them more dense and permits them to flow evenly and completely into the die cavities under moderate pressure (Ansel and Popovich, 1990).

2.2.6 *EXCIPIENTS*

An excipient is defined as a substance mixed with a medicine to give it consistence or which is used as a vehicle for its administration. Although drugs are responsible for therapeutic activity, it is a medicine and not the drug that the patient receives in the treatment of a disease. The difference separating a medicine from a drug is the presence in medicines of pharmacologically inert ingredients or excipients which modify a whole variety of physical, physicochemical and physicomechanical properties of the drug, which may lead to changes in the biopharmaceutical performance of the system (Staniforth, 1993).

Excipients must meet certain criteria so that their incorporation into dosage forms becomes possible. These criteria have been summarised by Banker and Anderson (1986) and Bandelin (1989).

Numerous types of excipients have been extensively reviewed in the literature by Shangraw (1989), Chowan (1993) and Banakar (1994b). The functions of excipients generally employed in tablet formulations are summarized below.

2.2.6.1 Diluents

Tablet fillers or diluents comprise a heterogeneous group of substances (Bandelin, 1989). Although diluents are considered to be inert ingredients, they can significantly affect the biopharmaceutic, chemical, and physical properties of the tablet (Peck *et al.*, 1989). Diluents are designed to make up the desired bulk of the tablet when the drug dosage is inadequate to produce this bulk (Banker and Anderson, 1986).

2.2.6.2 Binders

Binders add cohesiveness to powders to provide the necessary bonding to form granules. The primary criterion to consider when choosing a binder is its compatibility with other

tablet components. Also, it must impart sufficient cohesion to the powders to allow for normal processing, yet allow the tablet to disintegrate and the drug to dissolve upon digestion, releasing the active ingredients for absorption (Peck *et al.*, 1989).

2.2.6.3 Disintegrants

Disintegrants constitute a group of materials that, on contact with water, may either swell, hydrate, change in volume or form, or react chemically to produce a disruptive change in the tablet. They can be incorporated into the tablets either by an external addition or internal addition process (Bandelin, 1989).

2.2.6.4 Lubricants

The primary attributes of lubricants are that they: reduce the friction between the die wall and the powder as the tablet is formed and ejected; and prevent powder from sticking to the tooling (Chowhan, 1993).

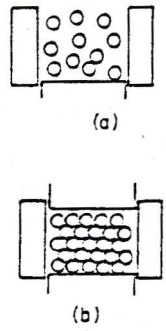
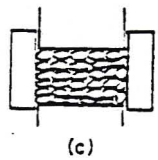
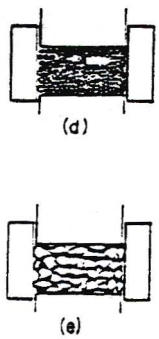
2.2.6.5 Glidants

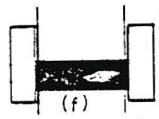
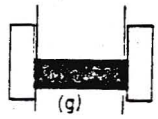
The main function of a glidant is to improve the fluidity of powder blends during mixing, transfer operations, and, finally, in the hopper feed-frame and die cavities of the tablet presses. The exceptionally small and generally spherical shape of glidant particles allows them to separate surfaces of like materials and act as moisture scavengers; both these functions lead to a decrease in interparticulate friction (Shangraw *et al.*, 1981).

2.2.7 *PHYSICS OF TABLET COMPRESSION*

The steps that occur during the formation of a tablet are summarised in Table 2.9.

Table 2.9: Processes occurring during the formulation of a tablet

DIAGRAM	EXPLANATION
a, b 	◘ Rearrangement • As the powder flows into the tablet die it will be of a structure corresponding to the cascaded (untrapped) apparent density. The powder rearranges to become a closely packed ensemble, referred to as 'rearrangement' or 'packing'.
c 	◘ Elastic particle deformation • As the punch comes down on the most closely-packed arrangement of particles, the particles begin to deform to reduce the void space. This can be viewed as an elastic particle deformation, i.e. if the punch pressure were released at this particular point, the particles would rebound back into the most closely-packed arrangement.
d, e 	◘ Plastic deformation/brittle fracture • Elastic limits will be reached for the particles and they will either undergo plastic deformation or they will fracture.

f, g   	◘ Fusion • The plasticity of the deformed particles allows for the arrangement of molecules from one particle with relation to another and for the proper alignment and distance of molecules of the various particles so as to form a chemical bond. In the case of brittle fracture new surfaces are formed, which are free of absorbed gas and allow alignment, permitting a pseudo-ideal match of the positions and distances of the molecules in another particle, therefore giving rise to a chemical bond. In both instances, the particle contact areas are increased, and this, together with the mobility that the fluid or fractured system possesses, promotes bond formation.

(Carstensen, 1980 - page 187)

2.2.7.1 Properties Of Tablets Influenced By Compression

These properties have been extensively reviewed by Parrott (1990), and include:

- density and porosity;
- hardness and tensile strength;
- specific surface area;
- disintegration; and
- dissolution.

2.3 EUDRAGIT® ACRYLIC RESINS

Research over the past decade has led to increasingly sophisticated approaches to sustain drug delivery. Currently the majority of these systems is based on synthetic polymers used as excipients. These differ in their degree of erodability, swellability and sensivity to their intended biological environment. These polymeric excipients substantially influence, if not control, the release mechanism of the active ingredient (Banakar, 1994b).

Eudragit® polymers are acrylic resins that are marketed by Röhm Pharma GmbH, Westerstadt, Germany. The different methacrylate copolymers offer a range of physiological properties that are used in a variety of modified release applications (Davies *et al.*, 1989). The IUPAC names of some of the Eudragit® polymers are presented in Table 2.10.

Table 2.10: IUPAC names of some methacrylate copolymers

TRADE NAME	IUPAC NAME
Eudragit® S	Poly(methacrylic acid, methyl methacrylate)
Eudragit® L	Poly(methacrylic acid, methyl methacrylate)
Eudragit® E	Poly(butyl methacrylate, 2-dimethyl aminoethyl)
*Eudragit® RL/RS	Poly(ethyl acrylate, methyl methacrylate)

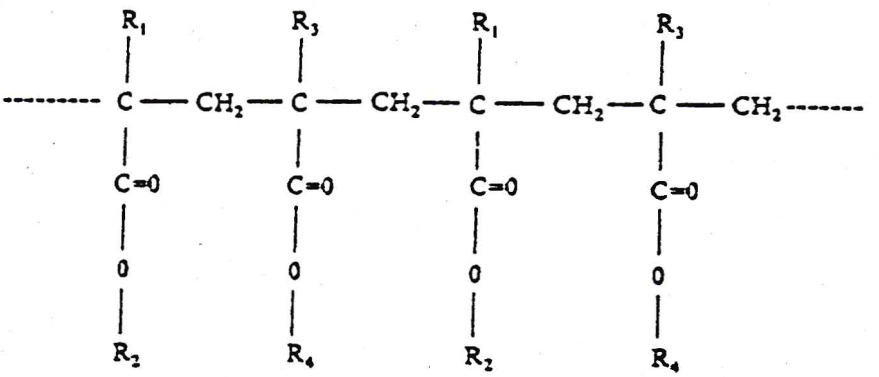
* Eudragit® RL/RS refers to the Eudragit® RL and Eudragit® RS polymers respectively.

(Davies *et al.*, 1989)

Eudragit® polymers have recently received increased attention for preparing modified release dosage forms because of their inertness, solubility in relatively non-toxic solvents and availability of resins with different properties. Different types of polymers display different retardation effects on drug release. Eudragit® RL and Eudragit® RS polymers are biocompatible, non-degradable acrylic resins, being copolymers of acrylic and methacrylic esters. They are insoluble over the entire pH range of the digestive tract, but they swell in an aqueous medium and exhibit a distinct pH independent permeability for water and water-

soluble substances (Efentakis *et al.*, 1990; Alvarez *et al.*, 1991).

The structures of the different types of Eudragit® polymers available, are illustrated in Figure 2.10, while their analytical information is presented in Table 2.11.



For *Eudragit E*:
$R_1, R_3 = CH_3$
$R_2 = CH_2CH_2N(CH_3)_2$
$R_4 = CH_3, C_4H_9$
For *Eudragit L* and *S*:
$R_1, R_3 = CH_3$
$R_2 = H$
$R_4 = CH_3$
For *Eudragit RL* and *RS*:
$R_1 = H, CH_3$
$R_2 = CH_3, C_2H_5$
$R_3 = CH_3$
$R_4 = CH_2CH_2N(CH_3)_3^+Cl^-$
For *Eudragit NE 30 D*:
$R_1, R_3 = H, CH_3$
$R_2, R_4 = CH_3, C_2H_5$
For *Eudragit L 30 D-55* and *L 100-55*:
$R_1, R_3 = H, CH_3$
$R_2 = H$
$R_4 = CH_3, C_2H_5$

Figure 2.10: Structure of the different Eudragit® polymers (Shukla, 1994 - page 362)

Table 2.11: Eudragit® products and analytical information

TYPE	MAJOR APPLICATIONS	CHARACTER	SOLUBILITY/ PERMEABILITY	RECOMMENDED SOLVENT OR DILUENT	TRADE NAME
Eudragit® E	readily disintegrating coatings	cationic	soluble in gastric juice to pH 5; expandable and permeable above pH 5	alcohols, acetone, methyl chloride	Eudragit® E12.5 Eudragit® E100
Eudragit® L	coatings resistant to gastric juice; coatings resistant to topical conditions, lozenges, insulating layers	anionic	soluble in intestinal juice from pH 6	alcohols, acetone, methylene chloride	Eudragit® L12.5P Eudragit® L12.5 Eudragit® L100
			soluble in intestinal juice from pH 5.5		Eudragit® L100-55
			soluble in intestinal juice from pH 5.5	water	Eudragit® L30D
Eudragit® S	coatings resistant to gastric juice; pH dependent retarding	anionic	soluble in intestinal juice from pH 7	alcohols, acetone, methylene chloride	Eudragit® S12.5P Eudragit® S12.5 Eudragit® S100
Eudragit® RL	delayed action preparations; pH independent	neutral	readily permeable	alcohols, acetone, methylene chloride	Eudragit® RL12.5 Eudragit® RL100 Eudragit® RLPO
	delayed action preparations; pH independent, readily disintegrating coatings			water	Eudragit® RL30D
Eudragit® RS	delayed action preparations; pH independent	neutral	poorly permeable	alcohols, acetone, methylene chloride	Eudragit® RS12.5 Eudragit® RS100 Eudragit® RSPO
				water	Eudragit® RS30D
Eudragit® NE	delayed action preparations; pH independent	neutral	expandable, permeable	water	Eudragit® NE30D

(Eudragit® Data Sheets, 1989)

2.3.1 *EUDRAGIT® RL30D AND EUDRAGIT® RS30D*

Eudragit® RL30D and Eudragit® RS30D are acrylic resin lacquers used in the form of aqueous dispersions. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)acrylic esters is 1:20 in the case of Eudragit® RL30D and 1:40 in the case of Eudragit® RS30D. The mean molecular weight is about 150 000 (Eudragit® Data Sheets, 1989).

Modified release dosage forms are designed to provide drugs to the body with greater efficacy, creativity and versatility (Newton, 1992). The literature review presented serves to highlight the potential for using the matrix device together with the granulation technology as a means of modifying drug delivery. In view of this, the tabletting technique was investigated in an attempt to formulate an optimum modification for the release of diclofenac sodium.

Chapter Three

Diclofenac Sodium

3.1 INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of compounds that share certain common therapeutic activities and adverse effects. They are often chemically unrelated (most are, however, organic acids), but their pharmacological action depends primarily on the inhibition of prostaglandin formation (Woodhouse and Wynne, 1987). The NSAIDs are used widely for their analgesic and anti-inflammatory effects. Amongst their large number of other pharmacological effects, they also possess antipyretic activity (Graham, 1987).

The purpose in developing diclofenac sodium was to synthesize a NSAID with high activity and outstanding tolerability. The factors considered were the drug transport through biological membranes, the atomic and spatial structure of the molecule and the electronic structure. Based on the analysis of other NSAIDs, it was postulated that an effective antirheumatic agent should have the following characteristics: an acidity constant between 4 and 5; a partition coefficient of approximately 10 and two aromatic rings twisted in relation to one another. The result was diclofenac sodium, which has an acidity constant of 4 and a partition coefficient of 13.4. The structural elements (Figure 3.1) include a phenylacetic acid group, a secondary amine group, and a phenyl ring containing chlorine atoms, which causes maximum twisting of the ring. Experimental and clinical findings obtained to date have indicated that diclofenac sodium was synthesised on well founded principles (Sallmann, 1986).

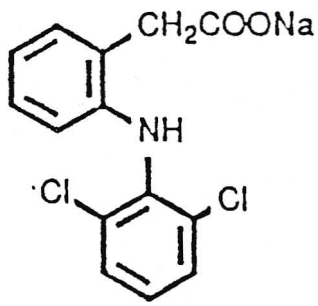


Figure 3.1: Structure of diclofenac sodium (Adeyeye and Li, 1990 - page 124)

3.2 PHYSICOCHEMICAL PROPERTIES

Chemical names:

- 2-[(2,6-dichlorophenyl)amino]benzene acetic acid monosodium salt
- [0-(2,6-dichloroanilino)phenyl]acetic acid sodium salt
- sodium[0-[(2,6-dichlorophenyl)amino]phenyl]acetate

Description:

An odourless, white to off-white crystalline, slightly hygroscopic powder

Empirical formula:

$C_{14}H_{10}Cl_2NO_2Na$

Molecular weight:

318.13

Melting point range:

283-285°C

Dissociation constant:

4 (water)

Partition coefficient:

13.4 (n-octanol/aqueous buffer)

(Adeyeye and Li, 1990)

Solubility:

The aqueous solubility of diclofenac sodium is strongly pH dependent (Figure 3.2). The insolubility at low pH reflects the low water solubility of the drug when its carboxyl group is undissociated. When pH values are above the pKa, the water solubility increases rapidly and reflects the abundant water solubility of the ionised compound (Maitani *et al.*, 1991).

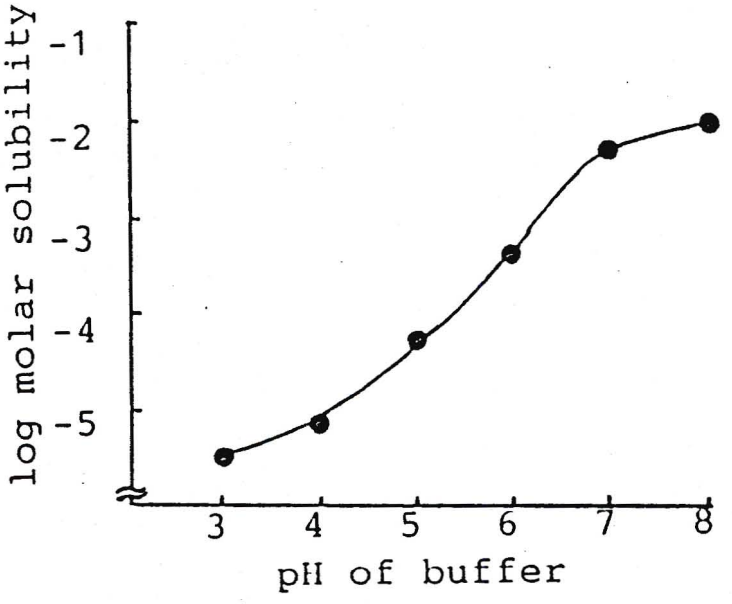


Figure 3.2: Aqueous solubility of diclofenac sodium with respect to buffer pH (Maitani *et al.*, 1991 - page 108)

The solubility of diclofenac sodium in various solvents is presented in Table 3.1.

Table 3.1: Solubilities of diclofenac sodium in different solvents

SOLVENT	SOLUBILITY (mg/ml)
Methanol	>24
Acetone	6
Acetonitrile	<1
Cyclohexane	<1
pH 1.1 (HCl)	<1
pH 7.2 (PO_4 buffer)	6

(Adeyeye and Li, 1990)

3.2.1 *STABILITY*

Kubala *et al.* (1993) studied the stability of diclofenac sodium in pharmaceutical dosage forms. Formulations stressed under accelerated storage conditions (90°C with 55% humidity), resulted in the formation of 1-[2,6-dichlorophenyl]-2-indolin-2-one as a degradation product. However, analysis of samples stored at 40°C with 50% humidity did not show the presence of any degradation products. The identification of the degradation product therefore proved that the cyclisation of diclofenac to an indolinone derivative is a valid degradation pathway for this drug in solid dosage forms when stressed under humidity and heat. The results also suggest that excipients and drug content in formulations may decrease the diclofenac stability.

3.3 PHARMACODYNAMIC PROPERTIES

Many of the pharmacological effects of diclofenac, as with other NSAIDs, are believed to be mediated by the inhibition of prostaglandin synthesis (Todd and Sorkin, 1988).

3.3.1 *BIOCHEMICAL MODE OF ACTION*

The analgesic and anti-inflammatory activities of the NSAIDs are thought to result primarily from the inhibition of arachidonic acid metabolism. In response to inflammatory stimuli, arachidonic acid is released from membrane phospholipids and then metabolised by either of two pathways, the prostaglandin pathway or the leukotriene pathway. Both routes result in the production of mediators of inflammation and both are blocked by NSAIDs. Arachidonic acid, when metabolised by the prostaglandin pathway, is converted by cyclo-oxygenase into the cyclic endoperoxides, prostaglandin G_2 and prostaglandin H_2, with the concomitant production of toxic free radicals thought to be responsible for tissue destruction. The endoperoxides are further metabolised along alternate pathways to form either prostaglandins (PGE_2 and PGF_2), prostacyclin (PGI_2), or thromboxane (TXA_2). Alternatively, arachidonic acid may be metabolised by lipoxygenases in the leukotriene pathway. With variable effectiveness, all of the NSAIDs also block this pathway (Boynton *et al.*, 1988).

The biochemical sites of action of diclofenac sodium on the arachidonic acid cascade are illustrated in Figure 3.3.

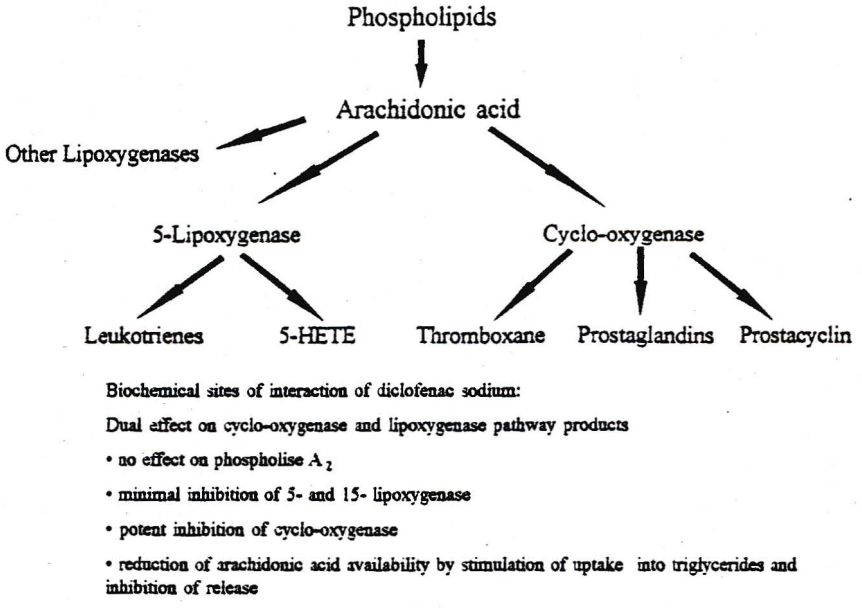


Figure 3.3: Biochemical sites of action of diclofenac sodium (Scholer *et al.*, 1986 - page 37)

3.4 PHARMACOKINETIC PROPERTIES

3.4.1 *ABSORPTION*

Diclofenac is completely absorbed after oral, rectal (Riess *et al.*, 1978) and intramuscular injection (Derendorf *et al.*, 1986). Absorption is rapid after administration of the drug as an oral solution, rectally or intramuscularly, with peak plasma concentrations occurring in 10-30 minutes, while with enteric-coated tablets, peak concentrations are delayed until about 1.5-2.5 hours (Todd and Sorkin, 1988). *In vitro* tests showed that complete dissolution of a 100 mg slow release tablet of diclofenac sodium took as long as 17 hours. Thus, after administration, no clear peak plasma concentrations were observed (Dittrich and Brunner, 1981). The absorption kinetics of diclofenac sodium do not vary with age (Todd and Sorkin, 1988).

Paroni *et al.* (1991) compared the bioavailability of diclofenac sodium administered orally, vaginally and rectally in healthy females. The vaginal route produced a significantly greater area under the curve than the oral route, and vaginal diclofenac total absorption was comparable to absorption via the rectal route.

Terhaag *et al.* (1991) studied the influence of food on the absorption of diclofenac (as a pure substance). Food significantly delayed the time to reach peak levels and diminished the maximum plasma levels, but did not affect the area under the curve.

3.4.2 *DISTRIBUTION*

Similar to most other NSAIDs, diclofenac is highly protein bound ($\geq$99.5%) to human serum proteins, mostly to albumin. Diclofenac binds to two specific sites on human serum albumin, a high affinity site likely to be the benzodiazepine site, and a low affinity site which is common with the warfarin site (Chamourd *et al.*, 1985). In healthy subjects the mean total volume of distribution of diclofenac is about 0.12-0.17 l/kg, and that of the central compartment about 0.04 l/kg (Todd and Sorkin, 1988).

The pharmacokinetic model used by Willis *et al.* (1979) to describe diclofenac plasma levels following intravenous doses suggests extensive uptake of drug by extravascular tissues. This study also demonstrated rapid distribution of drug between the central and shallow peripheral compartments, slow drug interchange between the central and deep peripheral compartment, and slow release of drug from deep-seated tissues back into the central compartment.

Diclofenac penetrates synovial fluid and is eliminated less rapidly from this site than from plasma (Fowler *et al.*, 1983). Benson *et al.* (1985) reported peak plasma concentrations in 2 hours compared to 4 hours in synovial fluid. However, subsequent to 4 hours after administration, synovial fluid concentrations were maintained considerably higher than in plasma. Fowler *et al.* (1986) found that a 100 mg polymer matrix modified release formulation of diclofenac sodium (Voltarol Retard®) had rapidly falling plasma concentrations, but high concentrations in synovial fluid were maintained for up to 25 hours.

Diclofenac and its metabolites cross the placenta in animals, and small amounts may be found in the breast milk of women (Todd and Sorkin, 1988).

3.4.3 *METABOLISM AND ELIMINATION*

Diclofenac is metabolised in the liver by conjugation to a range of phenolic compounds (Dollery, 1991). The principal metabolite in humans, 4′-hydroxydiclofenac, has about 1/40 th the activity of the parent compound against adjuvant-induced arthritis (Menassè *et al.*, 1978). The other metabolites, 3′-hydroxydiclofenac, 5′-hydroxydiclofenac and 4′,5′-dihydroxydiclofenac do not have any pharmacological activity (Riess *et al.*, 1978). Drug disposition in patients with hepatic impairment is comparable to that in normal subjects (Todd and Sorkin, 1988) and there is no evidence of enterohepatic circulation in man (Dollery, 1991).

Figure 3.4 reflects the pathways for the biotransformation of diclofenac sodium.

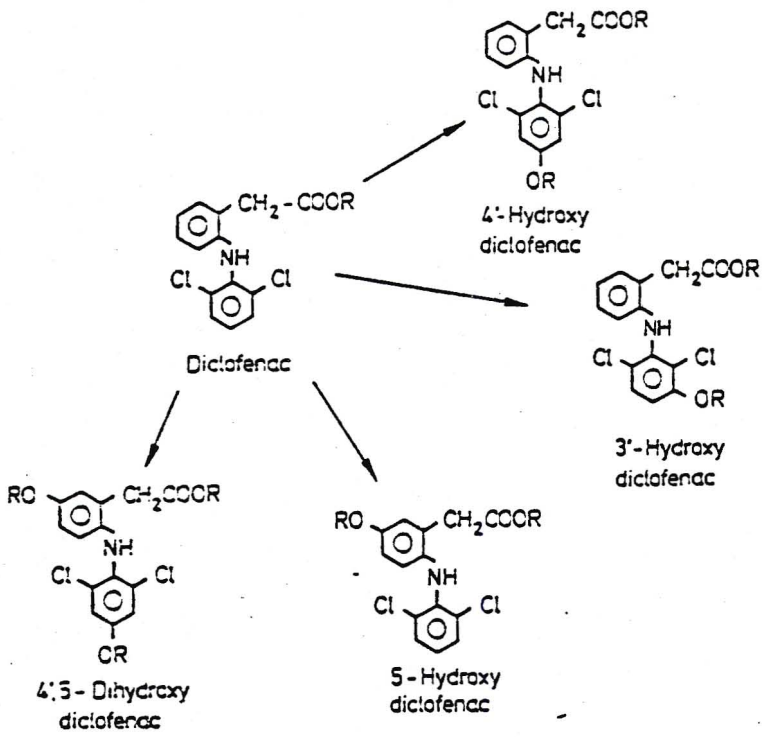


Figure 3.4: Pathways of biotransformation of diclofenac sodium in man (Fowler *et al.*, 1983 - page 389)

Diclofenac is eliminated by urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites (Stierlin and Faigle, 1979). Urinary excretion of 4'-hydroxydiclofenac accounts for 20-30% of the dose; while biliary excretion of this metabolite accounts for 10-20%. The other metabolites excreted in urine each accounts for 10-20% of the dose. Smaller amounts are excreted in the bile. Conjugates of unchanged diclofenac recovered in urine and bile account for 5-10% and <5% of the dose respectively. Unchanged diclofenac excreted in urine accounts for only 0.7% of the dose (Todd and Sorkin, 1988).

About 90% of an oral dose of diclofenac is excreted within 96 hours. The mean elimination half-life of unchanged drug is 1.2-1.8 hours (Todd and Sorkin, 1988). The elimination half-life was found to be similar between adults and children (Korpela and Olkkola, 1990). Elimination rates in renally impaired patients are comparable to those in other patients. The steady-state concentrations of total metabolites in patients with severe renal impairment are

four times higher than in those subjects with normal renal function, but they exert no pharmacological effects (Stierlin *et al.*, 1978).

3.4.4 *HALF-LIFE*

The serum half-life of diclofenac is 2 hours (Fowler *et al.*, 1983), while the synovial fluid half-life is 3 times longer than the plasma half-life, which supports once daily or twice daily dosing for diclofenac (Calabro and Ehrlich, 1986). The half-life of the metabolites is 25.8-33 hours (Brogden *et al.*, 1980).

3.5 THERAPEUTIC USES

Numerous studies have demonstrated the efficacy of diclofenac sodium preparations in a wide array of clinical conditions. Amongst others, diclofenac sodium can be used in the treatment of:

- gout (Holman and Celinska, 1981);
- dysmenorrhoea (Rihiluoma *et al.*, 1981);
- biliary colic (Broggini *et al.*, 1984);
- dental or oral pain following tooth extraction, restorative dentistry or oral surgery (Matthews *et al.*, 1984);
- renal colic (Hethering and Philp, 1986);
- acute migraine attacks (Del Bene *et al.*, 1987);
- postpartum pain, acute soft tissue injuries, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis (Todd and Sorkin, 1988); and
- occular inflammation following eye surgery (Kraff *et al.*, 1990).

3.6 DRUG INTERACTIONS

In a study by Riess *et al.* (1978), salicylic acid was shown to significantly decrease serum protein binding of diclofenac from 99.7% to 98.7%. The displacement of diclofenac from its binding sites by salicylic acid led to more rapid elimination, resulting in lower plasma diclofenac concentrations, peak plasma concentrations and area under the curve values.

The antihypertensive efficacy of hydrochlorothiazide may be attenuated by diclofenac in patients with essential hypertension (Koopmans *et al.*, 1987). Acute renal failure can occur in patients receiving diclofenac and triamterine (Härkönen and Ekblom-Kullberg, 1986).

Diclofenac together with lithium leads to decreased lithium clearance and consequently increased lithium plasma concentrations (Riemann and Frölich, 1981). Severe, sometimes fatal, toxicity has occurred after the administration of methotrexate concomitantly with NSAIDs, including diclofenac, in patients with rheumatoid arthritis or malignant neoplasms (Ellison and Servi, 1985; Daly *et al.*, 1986). The exact mechanism of this interaction has not been established, but may involve NSAID inhibition of methotrexate renal elimination, leading to toxic concentrations of methotrexate in circulation.

3.7 ADVERSE EFFECTS

The adverse effects of diclofenac sodium have been described in numerous reviews. They are usually mild and transient, and occur during the first six months of treatment (Ciccolunghi *et al.*, 1979). In addition, the frequency of adverse effects is reported to be unrelated to age or the dosage of diclofenac administered (Wilkens, 1985).

The common gastrointestinal adverse effects reported with diclofenac include nausea, vomiting, gastric discomfort, poor appetite and ulcers (Wilkens, 1985). Central nervous system symptoms include headache, dizziness, insomnia, irritability and abnormal co-ordination. Fluid retention and oedema have been observed in some patients (Todd and Sorkin, 1988).

Other adverse effects rarely reported include hepatitis (Dunk *et al.*, 1982), anaphylactic reactions, skin reactions, loss of hair, photosensitivity and disturbance of sensation, behaviour and learning (Dollery, 1991).

3.8 DOSAGE AND ADMINISTRATION

The initial daily dosage of diclofenac is 150 mg, administered as 2 or 3 divided doses with meals, for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout attacks, acute painful shoulder, and acute sprains and strains. In most patients, therapeutic control can be maintained on 100 mg daily as divided doses. In children the usual daily dosage is 2-3 mg/kg. A modified release formulation of diclofenac (100 mg) can be administered with the convenience of a once daily regimen, avoiding the peak plasma concentrations which may be associated with some adverse effects. Diclofenac 100-150 mg daily can also be administered as suppositories, in single or divided doses. Intramuscular diclofenac, 75 mg, can be administered for the prompt relief of pain (Todd and Sorkin, 1988).

As diclofenac crosses the placenta and may pass into breast milk, the decision to treat pregnant or lactating women should take into account the relative risks and benefits of the drug to the mother (Todd and Sorkin, 1988). However, Needs and Brooks (1985) have suggested that diclofenac is suitable for use in lactating mothers since the drug is minimally transferred to breast milk and glucuronide formation is low.

Diclofenac is contra-indicated in patients with known hypersensitivity to the product and in patients who have shown sensitivity to aspirin or other NSAIDs (Szczeklik *et al.*, 1977).

Dosage reductions are not necessary in the elderly or in patients with renal or hepatic impairment (Todd and Sorkin, 1988).

3.9 THE PLACE OF DICLOFENAC SODIUM IN THERAPY

The relative place of diclofenac sodium in therapy has become better defined due to experience gained with the drug from numerous clinical trials. The drug is available in numerous administration forms that can be administered orally, rectally, intramuscularly or ophthalmically.

Diclofenac represents a well-evaluated therapeutic alternative for the treatment of rheumatic diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, and in medical conditions where mild to moderate analgesia is desired. Worldwide experience, clinical trials and postmarketing surveillance highlight diclofenac as a drug that has a superior side-effect profile and better tolerability when compared with some other NSAIDs (Skoutakis *et al.*, 1988).

Clinically, diclofenac is effective. Therefore, this places it as another choice in the wide array of NSAIDs (Small, 1989).

Chapter Four

Materials and Methodology

4.1 INTRODUCTION

This chapter serves to outline the quality control procedures, as well as the different materials and methods used to characterise the tabletting technique as an approach to modifying the oral release of diclofenac sodium from Eudragit® matrices. The materials utilised in this study, together with the suppliers thereof, are summarised in Appendix 1. A simplified schematic diagram depicting the chronological approach to this study is presented in Figure 4.1.

4.2 QUALITY CONTROL

For most drugs, drug identification monographs are available in the various pharmacopoeias. However, there is no monograph in the Official pharmacopoeias for diclofenac sodium. Thus, the analytical quality control procedures selected for the identification of diclofenac sodium as raw materials and when present in pharmaceutical dosage forms were based on infrared and ultraviolet analyses, while drug assays were achieved by ultraviolet spectroscopy and high performance liquid chromatography.

4.2.1 *DICLOFENAC SODIUM POWDER*

4.2.1.1 Identification

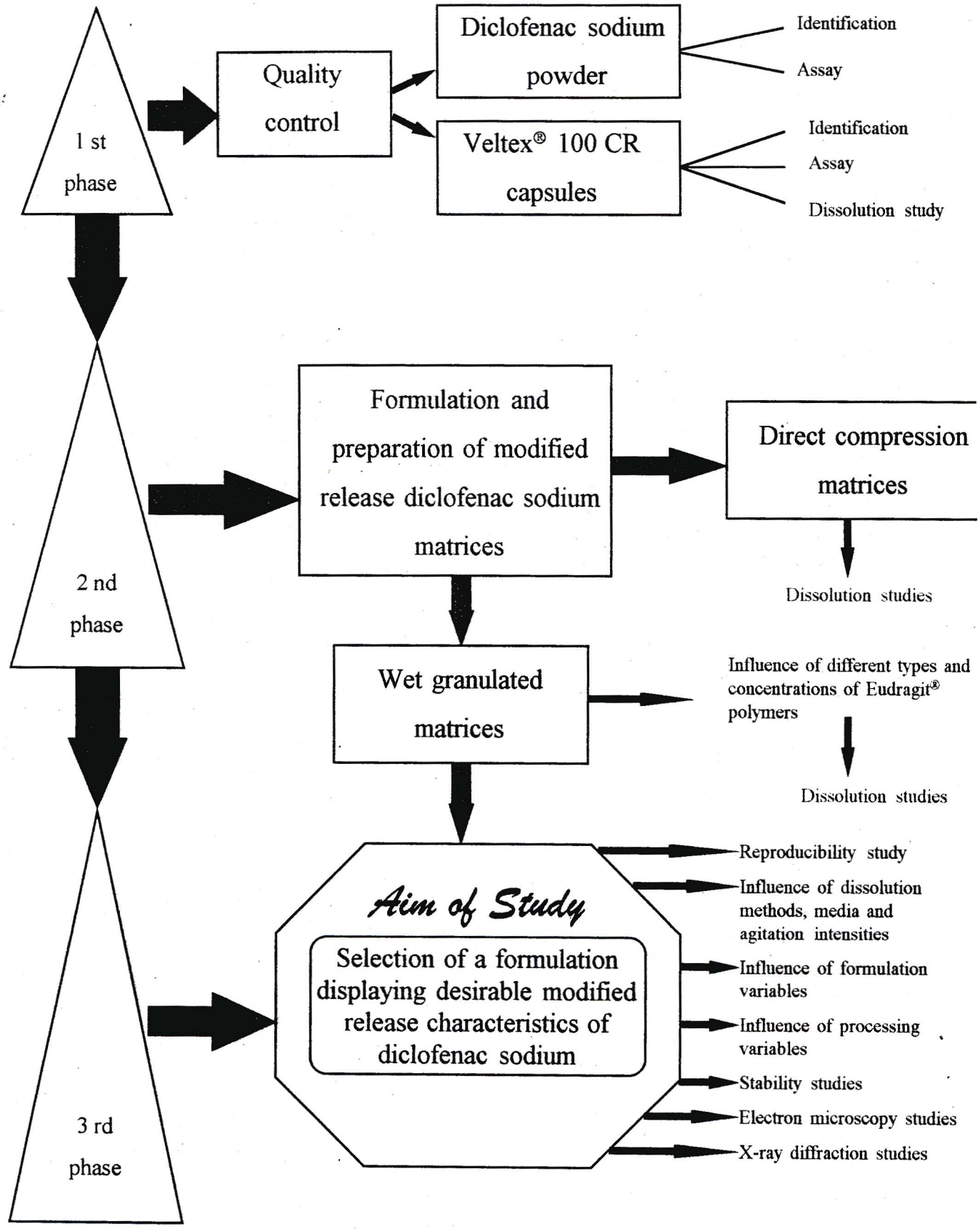


Figure 4.1: Scheme depicting the chronological approach to the study

4.2.1.1.1 Infrared spectroscopy

The infrared absorption spectrum of diclofenac sodium powder was obtained employing a Fourier Transform Infrared Shimadzu model 8108 spectrophotometer that was used in conjunction with the DR 8001 Shimadzu computer software system. The spectrum was obtained using a potassium bromide disc of the drug. The disc was formulated by combining 10 mg diclofenac sodium with 50 mg potassium bromide and triturating the mixture into a fine powder. The powder was subsequently dried under a Gallenkamp infrared lamp for 30 minutes. Thereafter, the powder was placed in a die cavity and compressed with the aid of a RIIC vacuum pump. The disc formed was then placed in a cell and analysed over an absorbance range of 400-2000 nm.

4.2.1.1.2 Ultraviolet spectroscopy

The ultraviolet absorption spectrum of a 10 mg/100 ml solution of diclofenac sodium in methanol was obtained employing the Shimadzu UV-VIS 160A spectrophotometer and 1 mm quartz cells. The solution was filtered through a 0.45 μm Millex®-HV filter and analysed spectrophotometrically, in the wavelength range of 200-400 nm. A solution containing the USP reference standard of diclofenac sodium was prepared and analysed in a similar manner for comparison purposes.

All subsequent ultraviolet analyses were performed using the same spectrophotometer and quartz cells.

4.2.1.2 Assay

An accurately weighed amount of 10 mg of diclofenac sodium powder was dissolved in 100 ml of 0.2 M phosphate buffer pH 6.8 (Appendix 2). The solution was filtered through a 0.45 μm Millex®-HA filter, the absorbance was determined in triplicate at the wavelength of maximum absorbance, as determined in section 4.8.2.1.1, and the concentration

determined against the calibration curve that was constructed using the diclofenac sodium USP reference standard, as described in section 4.8.2.1.2.

4.2.2 *VELTEX® 100 CR CAPSULES*

4.2.2.1 Identification

4.2.2.1.1 Infrared spectroscopy

The contents of five Veltex® 100 CR capsules were crushed using a pestle and mortar and dissolved in 50 ml methanol in a 100 ml beaker. The solution was filtered through a 0.45 μm Millex®-HV filter, and the filtrate was evaporated to dryness. The tablet residue, together with potassium bromide, was compressed into a disc, and subjected to infrared spectroscopy. The potassium bromide disc was prepared as discussed in section 4.2.1.1.1.

4.2.2.1.2 Ultraviolet spectroscopy

Five Veltex® 100 CR capsules were emptied, and the pellets were massed. The pellets were then crushed, and an amount equivalent to the mass of 10 mg diclofenac sodium was transferred to a 100 ml volumetric flask and dissolved in approximately 50 ml of methanol. When the powder went into complete solution, the remainder of the methanol was added to make up the required volume. The solution was then filtered through a 0.45 μm Millex®-HV filter and assayed spectrophotometrically as described in section 4.2.1.1.2.

4.2.2.2 Assay

The drug content was assayed by means of high performance liquid chromatography.

4.2.2.2.1 High performance liquid chromatography (HPLC)

As an Official HPLC method for the analysis of diclofenac sodium was not available at the time of the study, the method proposed by Sane *et al.* (1987), due to its simplicity and accuracy, was considered suitable, after minor modifications.

The HPLC system consisted of a Waters 590 programmable HPLC pump linked to a Lambda-Max LC detector, Model 481. The HPLC apparatus was used in conjunction with the Apex Chromatographic Software Programme®. Separation was effected using a reversed-phase Microbondapak® C_{18} chromatographic column, that was housed in a Z-module radial compression system. Methanol-acetate buffer solution was used as the mobile phase and was filtered and deaerated prior to use, using a Millipore® vacuum filtration unit fitted with a 0.45 μm Millipore®-HV filter.

4.2.2.2.1.1 *Preparation Of Diclofenac Sodium Standard Solution*

An accurately weighed amount of 20 mg diclofenac sodium (USP reference standard) was transferred to a 100 ml volumetric flask and dissolved and made up to volume in methanol.

4.2.2.2.1.2 *Preparation Of Internal Standard Solution*

Para-nitrobenzoic acid was used as the internal standard. An amount of 20 mg of the internal standard was weighed and transferred to a 100 ml volumetric flask. Methanol was added to volume and the solution was mixed.

4.2.2.2.1.3 *Preparation Of Working Standard Solutions*

A series of five 10 ml volumetric flasks were filled with 1, 2, 3, 4 and 5 ml diclofenac sodium standard drug solution respectively. Thereafter, 1 ml of the internal standard solution

was added to the drug solution in each flask. The solutions were then diluted with methanol, to produce solutions with concentrations of 0.02, 0.04, 0.06, 0.08 and 0.10 mg/ml of diclofenac sodium in methanol respectively.

4.2.2.2.1.4 *Preparation Of The Sample Solutions*

The contents of five capsules were emptied and weighed, and the average weight per capsule was calculated. The pellets were powdered using a pestle and mortar. Powder equivalent to the weight of 10 mg diclofenac sodium was accurately weighed and transferred to a 100 ml volumetric flask. The powder was dissolved and then made up to volume in methanol.

4.2.2.2.1.5 *Assay Procedure*

The HPLC operating parameters as outlined in Table 4.1. were used. A 1 ml aliquot of each of the working standard solutions was filtered through a 0.45 μm Millex®-HV filter into a series of 1 ml glass vials. From this, a 10 μl aliquot was withdrawn and injected manually into the injection port of the HPLC system. All injections were performed in duplicate. The peak height ratios of the standard to the internal standard were determined. The mean ratio for each concentration was plotted against the concentration of the sample, to construct a calibration curve (Figure 4.2). The mean ratios, together with the corresponding concentrations, are presented in Table 4.2. A Simstat Version® 3.4 statistical programme was used to obtain a linear regression correlation coefficient of 0.998. All subsequent linear regression analyses were performed using the same statistical programme.

A 5 ml aliquot of the sample preparation was transferred to a 10 ml volumetric flask. Thereafter, 1 ml of the internal standard solution was added to the flask, and made up to volume with methanol. The sample was filtered through a 0.45 μm Millex®-HV filter into a 1 ml glass vial. Thereafter, a 10 μl aliquot was withdrawn and injected in duplicate into the HPLC system, and the peak height ratios were determined. The ratios were then read

against the calibration curve to determine the corresponding concentrations.

Under the described chromatographic conditions, diclofenac sodium and para-nitrobenzoic acid produced clearly defined chromatographic peaks with retention times of 1.925 and 2.532 minutes respectively (Figure 4.3).

Table 4.1: Operating parameters for HPLC studies

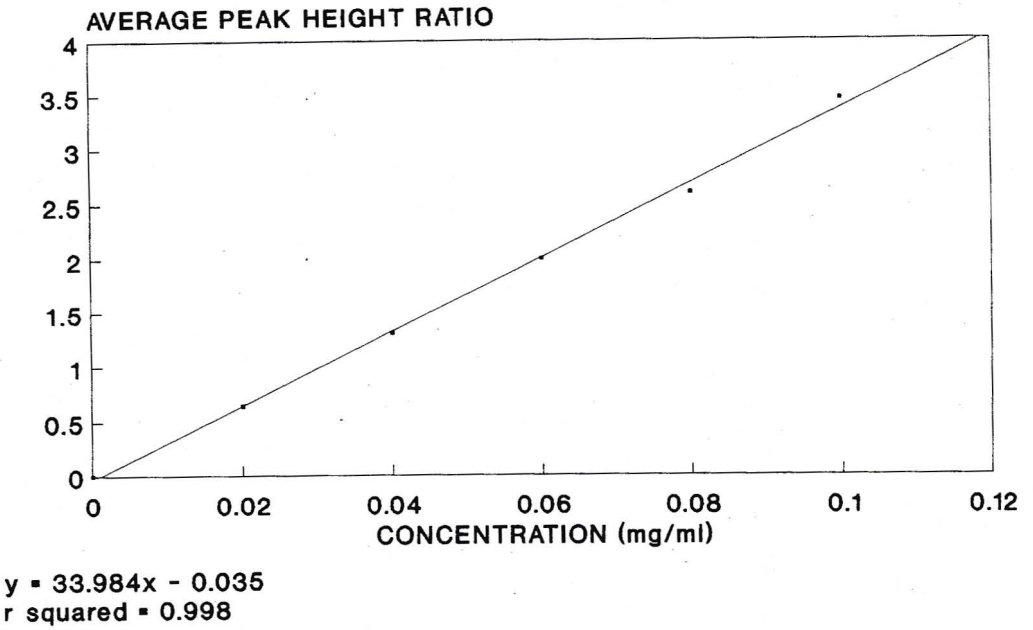
OPERATING PARAMETER	SETTING
Mobile phase	methanol : acetate buffer (pH 3.7) 90 : 10
Flow rate of mobile phase	2 ml/minute
Pressure	450-550 psi
Wavelength	280 nm
Sample volume injected	10 μl
Filters	0.45 μm Millex®-HV

Table 4.2: Average peak height ratios of diclofenac sodium and para-nitrobenzoic acid

DICLOFENAC SODIUM CONCENTRATION (mg/ml)	* AVERAGE PEAK HEIGHT RATIOS DICLOFENAC SODIUM : PARA-NITROBENZOIC ACID
0.02	0.643
0.04	1.306
0.06	1.992
0.08	2.594
0.10	3.450

* Individual values for 2 replicate determinations are shown in Appendix 6.1.

Figure 4.2: HPLC calibration curve for determining the content of diclofenac sodium in Veltex 100 CR capsules



y = 33.984x - 0.035
r squared = 0.998

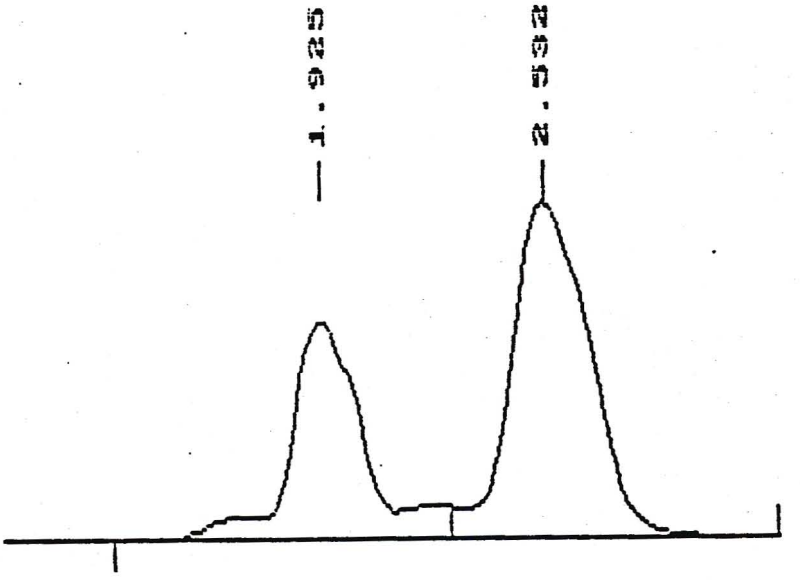


Figure 4.3: HPLC chromatogram of diclofenac sodium (retention time of 1.925 minutes) and para-nitrobenzoic acid (retention time of 2.532 minutes)

4.2.2.3 Dissolution Profile

Since there were no Compendial specifications available on which to model the drug release patterns of diclofenac sodium from modified release preparations, and after an extensive literature search, *in vitro* drug release was determined using the method described by Chetty *et al.* (1994).

Veltex® 100 CR is a commercially available multiple-units preparation of diclofenac sodium. The contents of three capsules were emptied into each of three vessels. The dissolution medium used was 0.2 M phosphate buffer pH 6.8. The Caleva model 7ST dissolution test apparatus was used for all dissolution studies. Table 4.3 outlines the protocol followed for the dissolution study.

Table 4.3: Dissolution protocol for Veltex® 100 CR capsules

OPERATING PARAMETER	SETTING
Apparatus	Rotating paddle
Agitation rate	100 rpm
Medium	0.2 M phosphate buffer pH 6.8
Volume of medium	1000 ml
Temperature of medium	37±0.5 °C
Sampling time (hours)	0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Sample volume withdrawn	5 ml

The analysis of drug content in the dissolution samples was performed at the wavelength of maximum absorbance, 275 nm, using ultraviolet spectroscopy.

A calibration curve of the diclofenac sodium USP reference standard in 0.2 M phosphate buffer pH 6.8 was constructed as described in section 4.8.2.1.2.

4.3 FORMULATION AND PREPARATION OF EUDRAGIT® MATRICES CONTAINING DICLOFENAC SODIUM

Tabletting was selected as the method for the preparation of the diclofenac sodium Eudragit® matrices. Therefore, the direct compression and the wet granulation techniques were investigated.

4.3.1 *DIRECT COMPRESSION MATRICES*

Appropriate amounts of diclofenac sodium powder, lactose (Super-tab®), Eudragit® RLPO, Eudragit® RSPO, Aerosil® 200 and magnesium stearate were weighed and screened through a 850 μm mesh screen to break up any agglomerates that might have been present. The ingredients were then blended for 15 minutes in a Gryphon tumble blender. The tablets were compressed on a single punch tabletting machine (Erweka EKO) using 10 mm flat-faced punches, to a hardness between 4-5 Kp. Tablet hardness was measured using a Pharma Test PTB 311 tablet hardness tester. All subsequent tablet compressions and hardness evaluations were conducted using the same tabletting machine and hardness tester respectively. Each tablet was formulated to contain 100 mg diclofenac sodium.

The in-process quality control tests, as described in section 4.4, were conducted on all the direct compression batches.

The designation PO, refers to the powdered form of the Eudragit® RL and Eudragit® RS polymers. The anhydrous grade of lactose, Super-tab®, was used as the diluent in the direct compression tablet batches. Hereafter, it will be referred to as lactose anhydrous.

Powder flow was evaluated by means of calculating the angle of repose. Repose angle determinations were conducted on all powder blends. This was done by placing the powder in a funnel and allowing it to fall onto a piece of paper. The height of the funnel was adjusted in such a manner that the apex just touched the tip of the funnel. Thereafter, the powder was filled into the funnel and allowed to fall onto the paper. A circle was drawn

around the heap of the powder, and the height of the cone of the powder was measured. The height of the cone and the diameter of the circle were used in the calculation of the angle of repose as indicated in Equation 4.1 (Banker and Anderson, 1986).

$$\tan \Theta = H/R \qquad \textit{Equation 4.1}$$

where, Θ is the angle of repose;

H is the height of the cone; and

R is the radius of the base of the conical pile.

All repose angle determinations were performed in triplicate on all the powder blends.

4.3.1.1 Optimisation Of A Working Formula

4.3.1.1.1 Preliminary studies

Numerous batches containing different concentrations of the Eudragit® RL and RS polymers, were formulated using the direct compression technique. The various constituents of the batches, together with the quantities used thereof, are reflected in Table 4.4. All batches were prepared for an average of 1000 tablets. The tablets of Batches DC1, DC2, DC3 and DC4 were subjected to dissolution testing in 1000 ml of 0.2 M phosphate buffer pH 6.8, using the USP rotating paddle apparatus at 100 rpm. At appropriate time intervals, samples were removed and analysed for drug content at the wavelength of maximum absorbance using ultraviolet spectroscopy.

Table 4.4: Composition of direct compression tablet batches containing various concentrations of Eudragit® RLPO and Eudragit® RSPO

CONSTITUENT	BATCH			
	DC1	DC2	DC3	DC4
Diclofenac sodium	100 g	100 g	100 g	100 g
Lactose anhydrous	60 g	60 g	60 g	60 g
Eudragit® RLPO	20 g	30 g	40 g	50 g
Eudragit® RSPO	20 g	30 g	40 g	50 g
Aerosil® 200	2 g	2 g	2 g	2 g
Magnesium stearate	2 g	2 g	2 g	2 g

- Tablets of Batches DC1, DC2, DC3 and DC4 were compressed to weights of 204, 224, 244 and 264 mg respectively.

4.3.1.1.2 Final formulation

From the preliminary studies, Batch DC2 emerged as a formulation that provided a suitable drug release profile. The criteria used for the selection of this batch were as outlined in section 5.5.

4.3.1.1.2.1 *Optimisation Of Flow Rate*

Although Batch DC2 emerged as a formulation that displayed suitable drug release characteristics, one of the limitations of this particular batch was the lack of suitable flow properties of the powder blend. In an attempt to improve powder flow, two approaches were investigated. One approach was to increase the glidant (Aerosil® 200) concentration, and the other was to use other tablet diluents that may possess better flow properties. Powder flow was evaluated by means of calculating the angle of repose as described in section 4.3.1.

4.3.1.1.2.1.1 *Glidant concentrations*

The composition of the batches containing increasing concentrations of the glidant, Aerosil® 200, is summarised in Table 4.5.

Table 4.5: Composition of direct compression tablet batches containing various concentrations of Aerosil® 200

CONSTITUENT	BATCH			
	DC5	DC6	DC7	DC8
Diclofenac sodium	100 g	100 g	100 g	100 g
Lactose anhydrous	60 g	60 g	60 g	60 g
Eudragit® RLPO	30 g	30 g	30 g	30 g
Eudragit® RSPO	30 g	30 g	30 g	30 g
Aerosil® 200	4 g	6 g	8 g	10 g
Magnesium stearate	2 g	2 g	2 g	2 g

4.3.1.1.2.1.2 *Diluents*

In an attempt to further improve powder flow, microcrystalline cellulose (Avicel® pH 101) and dicalcium phosphate were also used as diluents. The batches prepared were labelled DC9 and DC10 respectively. The differences between these two batches and Batch DC2, was that lactose anhydrous in Batch DC2 was replaced by microcrystalline cellulose in Batch DC9 and by dicalcium phosphate in Batch DC10.

The tablets of Batches DC9 and DC10 were subjected to dissolution testing in 1000 ml of 0.2 M phosphate buffer pH 6.8, using the USP rotating paddle apparatus at 100 rpm. At appropriate time intervals, samples were removed and analysed for drug content at the wavelength of maximum absorbance using ultraviolet spectroscopy.

4.3.2 *WET GRANULATED MATRICES*

Appropriate quantities of the drug and diluent (lactose powder BP, or where applicable, other suitable diluents) were dry screened through an 850 μm mesh screen, to break up any agglomerates. The ingredients were then blended for 15 minutes in a Gryphon tumble blender. Thereafter the ingredients were transferred to a mortar. The granulating agent (containing a mixture of the Eudragit® polymers, starch and water) was added to the powders, and the mixture was subsequently kneaded with the aid of a pestle to form a wet mass, which was then granulated through a 710 μm mesh screen. The granules were dried in a hot air oven (Gallenkamp, model OV 160) at 55°C for 20 minutes. Thereafter, the granules were screened through a 710 μm mesh screen to break up clumps that could have formed during drying.

The granules were sized into the following size ranges:

0-250 μm; and

251-710 μm.

The fraction of granules in the 251-710 μm particle size range was selected for incorporation into the tablet. The granules were lubricated with magnesium stearate (1%) and compressed to a hardness in the range 4-5 Kp on an Erweka EKO tabletting press using 10 mm flat-faced punches. Tablet hardness was evaluated by means of a Pharma Test PTB 311 tablet hardness tester. Each tablet was formulated to contain 100 mg diclofenac sodium.

The in-process quality control tests, as decsribed in section 4.4, were conducted on all the wet granulated batches.

Lactose powder BP and starch amylum BP were used in the wet granulated batches. Hereafter, lactose powder BP will be referred to as lactose, and starch amylum BP will be referred to as starch.

The Eudragit® polymers were incorporated into the granulating fluid in the form of aqueous dispersions, containing a 30% $^{m}/_{m}$ concentration of the Eudragit®, hence the designation 30D.

The formula used for the preparation of granules of Batch NH is presented in Table 4.6.

Table 4.6: Formula of Batch NH

CONSTITUENT	BATCH NH
Diclofenac sodium	20 g
Lactose	40 g
Eudragit® RL30D	5 ml
Eudragit® RS30D	5 ml
Starch	3 g
Water	8 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets were compressed to a weight of 350 mg.

Figure 4.4 reflects a flow diagram of the wet granulation process as used in the present study.

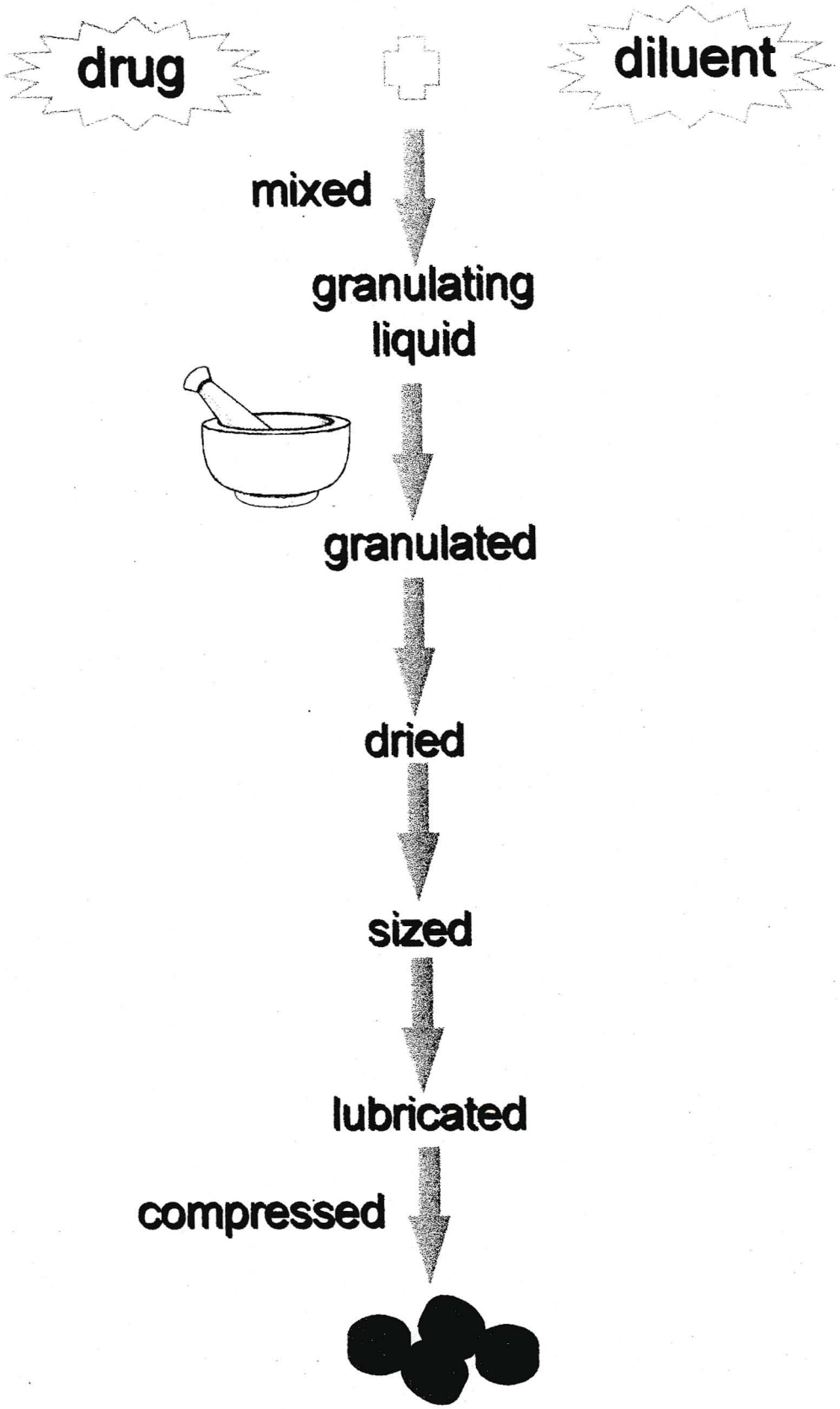


Figure 4.4: Flow diagram of the processes involved in the wet granulation technique

4.3.2.1 Optimisation Of Processing Conditions For Granulation

An optimised validated set of processing conditions was obtained by investigating the following:

- optimal drying temperature and time;
- optimal granule size range; and
- optimal tablet hardness.

4.3.2.1.1 Determination of an optimal drying temperature and time

Differential scanning calorimetric studies were conducted on the Eudragit® RLPO and Eudragit® RSPO polymers to determine the temperature at which the polymers would undergo a thermal change. A Mettler Differential Scanning Calorimeter (Mettler Instrumente AG 1988) was used to perform the analyses. Table 4.7 outlines the measurement conditions.

Table 4.7: Measurement conditions for DSC

OPERATING PARAMETER	SETTING
Starting temperature	50°C
Heating rate	10°C/min
End temperature	350°C
Reference	air atmosphere
Eudragit® RLPO (mass)	9.271 mg
Eudragit® RSPO (mass)	9.400 mg

The samples were placed in aluminium pans and positioned on the sensor plate within the calorimetric chamber. The operating parameters were set and the samples were scanned. The respective peaks were captured using the Mettler TC 11 TA Processor and the Graphware® computer software.

Various lots of Batch NH were prepared, and subjected to different drying temperatures. In addition, samples were removed at different time intervals over a period of 1 hour from each drying condition, and assessed for moisture content, using the AF8 Advanced Volumetric Karl Fischer Titrator. The operating parameters used were as described in section 4.13.2.2. The drying temperatures, together with the times the samples were analysed, are outlined in Table 4.8.

Table 4.8: Investigation into drying temperatures and times for granules

TEMPERATURE (°C)	TIME (MINUTES)
30	20, 40, 60
40	20, 40, 60
55	20, 40, 60

The drying temperature and drying time were optimised to ensure a suitable moisture content of the granules.

4.3.2.1.2 Determination of an optimal granule size range

Batch NH was prepared as previously described. A wide variation in the mass of the tablets led to the investigation of an optimal size range of the granules for tabletting. The following ranges were identified:

0-250 μm; and

251-710 μm.

The ranges selected were sufficiently large to produce granules over a range that was suitable for tabletting. Granules from both ranges were lubricated with 1% magnesium stearate and compressed to a hardness in the range 4-5 Kp.

The drug release profiles of Batches NHH (granule size range 0-250 μm) and NH (granule size range 251-710 μm) were obtained using the USP rotating paddle dissolution apparatus

at 100 rpm in 1000 ml of 0.2 M phosphate buffer at pH 6.8. Hence, an optimal granule size range was selected, on the basis of the drug release patterns.

4.3.2.1.3 Determination of an optimal tablet hardness

Four lots of Batch NH were prepared as previously described. The granules from each batch were compressed to different hardnesses, and the tablets formed were then tested for friability. Ten tablets from each batch were placed in a 12 paddle Erweka friabilator and rotated at 25 rpm for 4 minutes (total of 100 revolutions). The tablets were then removed from the friabilator, and dusted. The friability was then determined using Equation 4.2.

$$\% \text{ friability} = (I - F)/I \times 100 \qquad \textit{Equation 4.2}$$

where, I is the initial mass of tablets; and

F is the final mass of tablets.

A friability of 1.5% was set as the upper limit of acceptability.

The tablet hardnesses of the different lots of Batch NH are depicted in Table 4.9.

Table 4.9: Tablet hardness ranges for different lots of Batch NH

LOT PREPARATION OF BATCH NH	TABLET HARDNESS RANGE (Kp)
NH (a)	3-4
NH (b)	4-5
NH (c)	6-7
NH (d)	9-10

Based on the friability values obtained from the above formulations, an optimal range of tablet hardness was selected, i.e. between 4-5 Kp.

4.4 IN-PROCESS QUALITY CONTROL TESTS

4.4.1 *DRUG CONTENT UNIFORMITY*

All tablets were theoretically prepared to contain 100 mg of diclofenac sodium per tablet. Drug content uniformity was determined using ultraviolet spectroscopy.

A total number of 5 tablets from each batch was crushed. An amount of powder equivalent to 10 mg diclofenac sodium was dissolved in 0.2 M phosphate buffer pH 6.8 and made up to volume. The solutions were filtered through a 0.45 μm Millex®-HA filter and analysed. The absorbance was determined in triplicate, and the concentration determined against the calibration curve, which was constructed using the diclofenac sodium USP reference standard as described in section 4.8.2.1.2.

4.4.2 *UNIFORMITY OF MASS*

Ten tablets from each batch were weighed using a Mettler Toledo balance to determine the variation in tablet mass.

4.4.3 *FRIABILITY*

Ten tablets from each batch were subjected to friability testing, as described in section 4.3.2.1.3.

4.4.4 *UNIFORMITY OF TABLET THICKNESS, DIAMETER AND HARDNESS*

Ten tablets from each batch were tested to determine the uniformity in tablet thickness, diameter and hardness, using the Pharma Test PTB tablet hardness tester.

4.5 INFLUENCE OF EUDRAGIT® POLYMER ON DRUG RELEASE

4.5.1 *INFLUENCE OF DIFFERENT TYPES OF EUDRAGIT® POLYMERS*

The ensuing batches of the diclofenac sodium Eudragit® matrices were prepared as described in section 4.3.2.

Five different types of Eudragit® polymers were used to formulate diclofenac sodium matrices. All Eudragit® polymers were incorporated into the tablets as a dispersion containing the Eudragit® in a concentration of 30% $^{m}/_{m}$. Since Eudragit® L and Eudragit® S polymers were only available as powders, a 30% $^{m}/_{m}$ solution was prepared by dissolving an appropriate amount of Eudragit® in water. Table 4.10 depicts the different Eudragit® polymers as well as the quantities thereof investigated in the study. All dissolution testing was conducted in 1000 ml of 0.2 M phosphate buffer pH 6.8, using the USP rotating paddle apparatus at 100 rpm.

Table 4.10: Formulation of diclofenac sodium matrices using different types of Eudragit® polymers

CONSTITUENT	BATCH				
	NRL	NRS	NN	NL	NS
Diclofenac sodium	20 g	20 g	20 g	20 g	20 g
Lactose	40 g	40 g	40 g	40 g	40 g
Eudragit® RL30D	10 ml				
Eudragit® RS30D		10 ml			
Eudragit® NE30D			10 ml		
Eudragit® L				10 ml	
Eudragit® S					10 ml
Starch	3 g	3 g	3 g	3 g	3 g
Water	8 ml	8 ml	8 ml	8 ml	8 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets of Batches NRL, NRS, NN, NL and NS were compressed to a mass of 350 mg.

4.5.2 *INFLUENCE OF EUDRAGIT® RL AND EUDRAGIT® RS CONCENTRATIONS*

Tablet batches were prepared, with each batch containing different concentrations of Eudragit® RL and Eudragit® RS. The Eudragit® polymers, as indicated in section 4.3.2 were added to the tablet formulations as aqueous dispersions, by being incorporated into the granulating liquid. The quantities of the various ingredients used for the preparation of the different batches are summarised in Table 4.11.

Table 4.11: Formulation of batches containing different concentrations of Eudragit® RL and Eudragit® RS polymers

CONSTITUENT	BATCH				
	RLRS21	NH	RLRS12	NRL	NRS
Diclofenac sodium	20 g	20 g	20 g	20 g	20 g
Lactose	40 g	40 g	40 g	40 g	40 g
Eudragit® RL30D	10 ml	5 ml	5 ml	10 ml	0 ml
Eudragit® RS30D	5 ml	5 ml	10 ml	0 ml	10 ml
Starch	3 g	3 g	3 g	3 g	3 g
Water	3 ml	8 ml	3 ml	8 ml	8 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets of Batches RLRS21, NH, RLRS12, NRL and NRS were compressed to a weight of 350 mg.

The tablets from each batch were subjected to *in vitro* dissolution studies in 1000 ml of 0.2 M phosphate buffer pH 6.8, using the USP rotating paddle apparatus at 100 rpm.

4.6 SELECTION OF A WORKING FORMULA FOR THE MATRICES

The selection process was based on the drug release data obtained from batches described in Tables 4.10 and 4.11. Dissolution studies, as described in section 4.2.2.3, were conducted on a commercially available modified release formulation containing diclofenac sodium, Veltex® 100 CR, to use as a reference in the selection of an appropriate formulation.

Although the release pattern obtained for Batch NH did not resemble that of the commercially available formulation, it was selected for further manipulation. The criteria used for the selection of the above-mentioned batch are discussed in detail in section 5.5.

4.6.1 *PREPARATION OF BATCH NH FOR ANALYSIS*

The process variables used in the preparation of Batch NH were as described in section 4.3.2. The specific quantities used to formulate the batch were as outlined in Table 4.6.

4.7 REPRODUCIBILITY STUDY

Two lots of Batch NH were prepared as previously described. Each lot was subjected to dissolution studies in 1000 ml of 0.2 M phosphate buffer pH 6.8, at 100 rpm using the method outlined in Table 4.3.

4.7.1 *VALIDATION OF THE REPRODUCIBILITY STUDY*

The data generated from the reproducibility study were compared and evaluated graphically as well as statistically.

4.7.1.1 Statistical Analysis

An analysis of variance (ANOVA) test was performed using the Simstat Version® 3.4 statistical programme. A 95% confidence interval for the difference between the means was calculated.

4.8 *IN VITRO* DISSOLUTION STUDIES ON DICLOFENAC SODIUM EUDRAGIT® MATRICES

In vitro dissolution studies employing the rotating paddle apparatus, were used to characterise the drug release behaviour from the diclofenac sodium Eudragit® matrices. The dissolution media were prepared as outlined in Appendix 2. For all dissolution tests, a minimum of three replicate determinations were performed.

4.8.1 *DISSOLUTION METHODOLOGY*

4.8.1.1 Rotating Paddle Apparatus

The USP XXIII (1995) specifications for the rotating paddle apparatus (Apparatus 2) are presented in Appendix 3. The operating parameters used in the study are summarised in Table 4.12.

Table 4.12: Operating parameters for the rotating paddle apparatus

OPERATING PARAMETER	SETTING
Agitation rates	50, 100, 150 rpm
Media	◘ buffers at pH 1.5, 4.5, 6.2, 6.8, 7.5 and 8 ◘ 0.1 M phosphate buffer pH 6.8 ◘ distilled water pH 6.2 ◘ phosphate buffer pH 6.8 (USP)
Volume of media	1000 ml
Temperature of media	37±0.5°C
Sampling times (hours)	0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume withdrawn	5 ml

The dissolution apparatus consisted of six 1 litre round-bottomed dissolution vessels immersed in a water bath, thermostatically controlled at 37±0.5°C. The stainless steel rods

were screwed into an electrically controlled device. Into each of three dissolution vessels, 1000 ml of deaerated dissolution medium was introduced.

A tablet was placed in each dissolution flask, and the paddles were switched on. At the end of the appropriate time intervals, the dissolution apparatus was switched off and a 5 ml aliquot was removed from each vessel using a 10 ml syringe. The samples were filtered, while being withdrawn, through a 0.45 μm Millex®-HA filter, that was attached to the end of the sampling rod that was immersed in the dissolution medium.

To remove any medium that was lodged in the tube and rod from the previous sample, the sampling tube for each station was flushed back twice by withdrawing and reinjecting the medium, prior to removal of the subsequent sample. The apparatus was switched off during sampling and switched on immediately after sampling. The samples were immediately analysed using ultraviolet spectroscopy, at the wavelength of maximum absorbance to determine drug content.

An equal volume to that of the aliquot removed i.e. 5 ml, of fresh drug-free medium was replaced into each dissolution vessel, to maintain a constant volume of medium during the dissolution test. The whole process of sample withdrawal and replacement was completed in approximately one minute.

4.8.1.1.1 Agitation rates

The influence of agitation rates on the drug release characteristics of the tablets of Batch NH were also investigated using a 0.2 M phosphate buffer pH 6.8 as the dissolution medium. A tablet was placed into each dissolution flask, and agitation rates of 50, 100 and 150 rpm respectively over a period of 8 hours were investigated in three different dissolution studies. At appropriate time intervals, the samples were withdrawn and analysed for drug content at the wavelength of maximum absorbance using ultraviolet spectroscopy.

4.8.1.1.2 pH of dissolution media

Tablets of Batch NH were subjected to dissolution studies in media with pH levels of 1.5, 4.5, 6.2, 6.8, 7.5 and 8 respectively. All buffers were prepared as described in Appendix 2. Spectroscopic scans were performed to determine the wavelength of maximum absorbance (section 4.8.2.1.1) in each medium. Thereafter, calibration curves were obtained for each of the different pH levels (section 4.8.2.1.2). Samples were withdrawn at appropriate time intervals and analysed for drug content by ultraviolet spectroscopy at the wavelength of maximum absorbance.

Thereafter, *in vitro* dissolution testing was conducted on Batch NH to simulate drug release behaviour in the gastrointestinal tract using buffers of different pH levels for various times. The method used to simulate the conditions of the gastrointestinal tract was adapted and modified from a study conducted by Pillay (1996). Table 4.13 indicates the sequence in which the buffers were used, and the duration of time that the tablets were subjected to the different buffers.

Table 4.13: Protocol for simulation of gastrointestinal milieu with buffer solutions

BUFFER pH	DURATION
Hydrochloric acid buffer pH 1.5	one hour (1st hour)
0.2 M Phosphate buffer pH 4.5	one hour (2nd hour)
0.2 M Phosphate buffer pH 6.8	three hours (3rd, 4th and 5th hour)
0.2 M Phosphate buffer pH 7.5	three hours (6th, 7th and 8th hour)

A 5 ml aliquot was withdrawn from each dissolution vessel and analysed for drug content by ultraviolet spectroscopy at appropriate time intervals. When a change in buffer was required, the previous buffer was decanted from the dissolution medium and the next buffer, prewarmed to $37 \pm 0.5°C$ and deaerated, was added to the dissolution flask. The dissolution process was then allowed to continue. The study was conducted over a period of 8 hours.

4.8.1.1.3 Media ionic concentration

The ionic concentration of the media was changed to determine its effect on drug release patterns from the matrices. Phosphate buffers, pH 6.8, of ionic concentrations 0.1 and 0.2 M were employed. The buffers were prepared as described in Appendix 2. Wavelength scans (section 4.8.2.1.1) and calibration curves (section 4.8.2.1.2) were obtained for the buffers at each of the different ionic concentrations.

4.8.1.1.4 Types of dissolution media

Dissolution studies were conducted on tablets of Batch NH in distilled water, phosphate buffer pH 6.8 (USP) and a 0.2 M phosphate buffer pH 6.8, to determine the effects of different types of media on drug release behaviour. Wavelength scans (section 4.8.2.1.1) and calibration curves (section 4.8.2.1.2) were obtained for each of the different media.

4.8.1.2 Rotating Basket Apparatus

The USP XXIII (1995) specifications for the rotating basket apparatus (Apparatus 1) are presented in Appendix 4. The method used to conduct dissolution testing was similar to that of the rotating paddle, with 2 distinct features:

- the paddle was replaced with a shaft into which the basket was screwed; and
- the tablet was introduced into the basket, which was then screwed onto the shaft.

Table 4.14 outlines the working conditions for the rotating basket apparatus

Table 4.14: Operating parameters for the rotating basket apparatus

OPERATING PARAMETER	SETTING
Agitation rates	50, 100, 150 rpm
Medium	0.2 M phosphate buffer pH 6.8
Volume of medium	1000 ml
Temperature of medium	37±0.5°C
Sampling times (hours)	0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume withdrawn	5 ml

At the appropriate time intervals, the samples were removed and assayed for drug content using ultraviolet spectroscopy, at the wavelength of maximum absorbance.

4.8.1.3 Rotating Bottle Apparatus

In addition to the Official dissolution methods, studies were also conducted on the rotating bottle apparatus. Although this is an Unofficial method, it still remains popular, and was used in the present study to investigate the influence of the different dissolution methods on the drug release behaviour of tablets of Batch NH.

Dissolution studies were conducted using the Hanson Research dissolution apparatus, dissolution drive control, model 3725 and temperature control, model 6041.

The apparatus consisted of a water bath, thermostatically controlled at 37±0.5°C by circulating water. Attached to the inner wall of the waterbath was a horizontal rectangular bar that could accommodate twenty round 100 ml bottles. The dissolution drive control can maintain rotational speeds in the range 35-50 rpm.

The operating conditions for the rotating bottle apparatus are presented in Table 4.15.

Table 4.15: Operating parameters for the rotating bottle apparatus

OPERATING PARAMETER	SETTING
Agitation rate	50 rpm
Medium	0.2 M phosphate buffer pH 6.8
Volume of medium	100 ml
Temperature of medium	37±0.5°C
Sampling time (hours)	0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume withdrawn	5 ml

A tablet of Batch NH was introduced into each of three 100 ml round amber bottles, which contained 100 ml of prewarmed and deaerated 0.2 M phosphate buffer pH 6.8. The bottles were tightly capped and attached to the bar and rotated at 50 rpm. At appropriate time intervals, the apparatus was switched off, the bottles were removed from the bar, and a 5 ml aliquot was removed and filtered through a 0.45 μm Millex®-HA filter attached to a 10 ml syringe. Thereafter, a 5 ml replacement buffer was added to each bottle, and the bottles were capped and reattached to the bar. The process of withdrawal and replacement of the samples was accomplished in approximately 2 minutes. The samples were analysed for drug content at the wavelength of maximum absorbance using ultraviolet spectroscopy.

A suitable calibration curve for a 100 mg/100 ml solution of diclofenac sodium in 0.2 M phosphate buffer pH 6.8 was obtained, as described in section 4.8.2.1.2.

4.8.2 *ANALYSIS OF DISSOLUTION SAMPLES*

4.8.2.1 Quantitation Of Drug In Dissolution Media

Samples were analysed for drug content using ultraviolet spectroscopy. A standardised process was used to obtain the wavelength of maximum absorbance and a calibration curve for diclofenac sodium in each of the different dissolution media.

4.8.2.1.1 Determination of the wavelength of maximum absorbance

Stock solutions were prepared for each of the different buffers. An amount of 10 mg diclofenac sodium USP reference standard was dissolved in 50 ml of each medium by sonicating for ten minutes. On complete solution of the drug, the remaining volume of buffer was added to each 100 ml volumetric flask to produce solutions with a concentration of 10 mg/100 ml.

With buffers of pH 1.5 and 4.5, 1 mg diclofenac sodium USP reference standard was dissolved in 2 ml methanol and then made up to volume with the appropriate buffer in a 100 ml volumetric flask.

All solutions were filtered through a 0.45 μm Millex®-HA filter and then spectroscopically scanned to determine the wavelength of maximum absorbance for each medium in the wavelength range 200-400 nm. The wavelength of maximum absorbance in each medium is reflected in Table 4.16.

Table 4.16: Wavelength of maximum absorbance

MEDIUM	WAVELENGTH OF MAXIMUM ABSORBANCE (nm)
hydrochloric acid buffer pH 1.5	206
0.2 M phosphate buffer pH 4.5	207
0.2 M phosphate buffer pH 6.2	273
0.2 M phosphate buffer pH 6.8	275
0.2 M phosphate buffer pH 7.5	275
0.2 M phosphate buffer pH 8.0	273
distilled water pH 6.2	276
phosphate buffer pH 6.8 (USP)	276
0.1 M phosphate buffer pH 6.8	275

4.8.2.1.2 Preparation of calibration curves for drug content determination

Stock solutions were prepared as described in section 4.8.2.1.1. The solutions were diluted to produce a series of standard solutions to contain diclofenac sodium in concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively in 10 ml volumes. However, with the solutions of pH 1.5 and 4.5, stock solutions containing 2, 4, 6, 8 and 10 mg/1000 ml in 10 ml volumes were produced. The stock solution for the 100 mg/100 ml sample was prepared by dissolving 100 mg diclofenac sodium USP reference standard in 3 ml methanol, and then adding the 0.2 M phosphate buffer and to bring the solution up to volume in a 100 ml volumetric flask. This solution was then diluted to prepare a series of standard solutions with concentrations of 20, 40, 60, 80 and 100 mg/100 ml diclofenac sodium in 10 ml volumes. The absorbance values for the different concentrations of the various media are outlined in Table 4.17.

Using each medium as the reference (blank), the ultraviolet absorbance of each standard solution was determined at the wavelength of maximum absorbance, as determined in section 4.8.2.1.1. The measured absorbance for each standard solution was plotted against the concentration of the solution, to produce calibration curves (Figures 4.5-4.14). Linear regression correlation coefficients were obtained for all curves using the Simstat Version®3.4 statistical programme.

Table 4.17: Data on calibration curves used for studies in different dissolution media

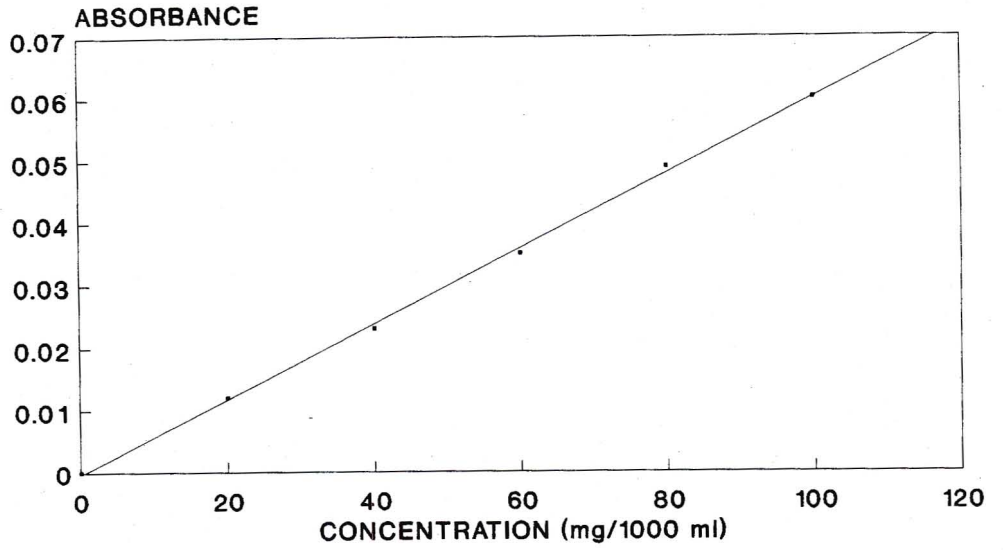
ABSORBANCE VALUES IN DIFFERENT MEDIA									
pH 1.5 ■	pH 4.5 ●	pH 6.2 □	pH 6.8 ○	pH 7.5 ⧗	pH 8 ⊠	pH 6.2 ⌂	pH 6.8 ◆	pH 6.8 ☼	pH 6.8 ▲
0.012	0.034	0.065	0.064	0.071	0.056	0.062	0.063	0.070	0.389
0.023	0.068	0.131	0.127	0.143	0.110	0.125	0.126	0.140	0.774
0.035	0.102	0.195	0.195	0.214	0.170	0.190	0.187	0.207	1.165
0.049	0.133	0.258	0.255	0.283	0.223	0.253	0.251	0.279	1.550
0.060	0.168	0.323	0.320	0.356	0.282	0.315	0.312	0.348	1.940

Key:

The concentrations of the samples used to determine the absorbances recorded in Table 4.17 are presented below.

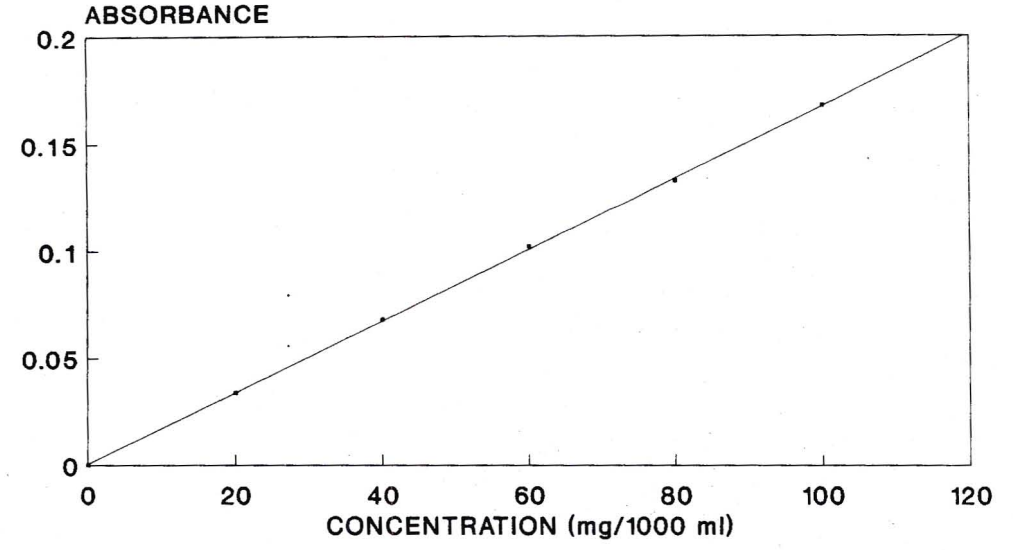
■ hydrochloric acid buffer pH 1.5 (diclofenac sodium concentrations of 2, 4, 6, 8 and 10 mg/1000 ml respectively)
● 0.2 M phosphate buffer pH 4.5 (diclofenac sodium concentrations of 2, 4, 6, 8 and 10 mg/1000 ml respectively)
□ 0.2 M phosphate buffer pH 6.2 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
○ 0.2 M phosphate buffer pH 6.8 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
⧗ 0.2 M phosphate buffer pH 7.5 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
⊠ 0.2 M phosphate buffer pH 8 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
⌂ distilled water pH 6.2 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
◆ USP phosphate buffer pH 6.8 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
☼ 0.1 M phosphate buffer pH 6.8 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/1000 ml respectively)
▲ 0.2 M phosphate buffer pH 6.8 (diclofenac sodium concentrations of 20, 40, 60, 80 and 100 mg/100 ml respectively)

Figure 4.5: Calibration curve for diclofenac sodium in pH 1.5 hydrochloric acid buffer



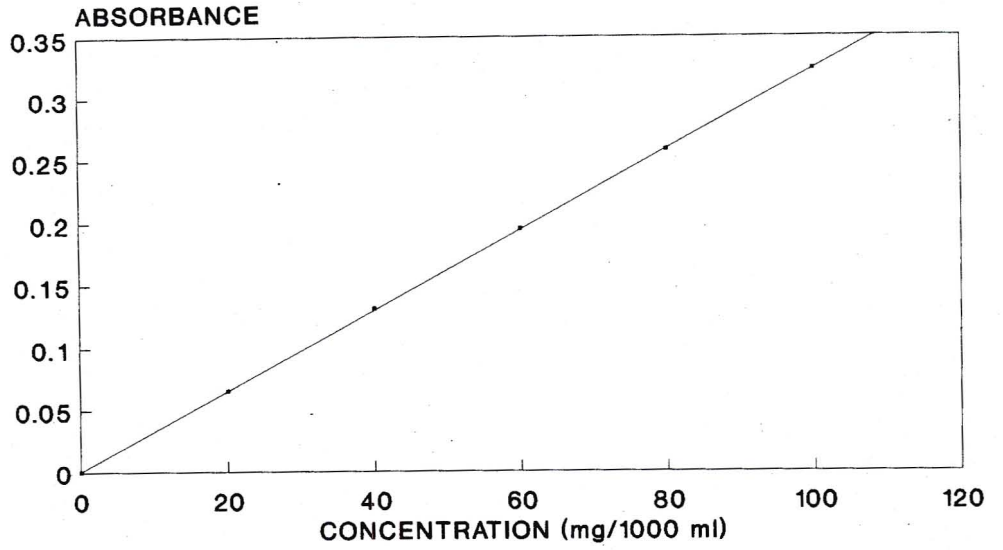
y = 0.006x - 0.0004
r squared = 0.999

Figure 4.6: Calibration curve for diclofenac sodium in pH 4.5 phosphate buffer (0.2 M)



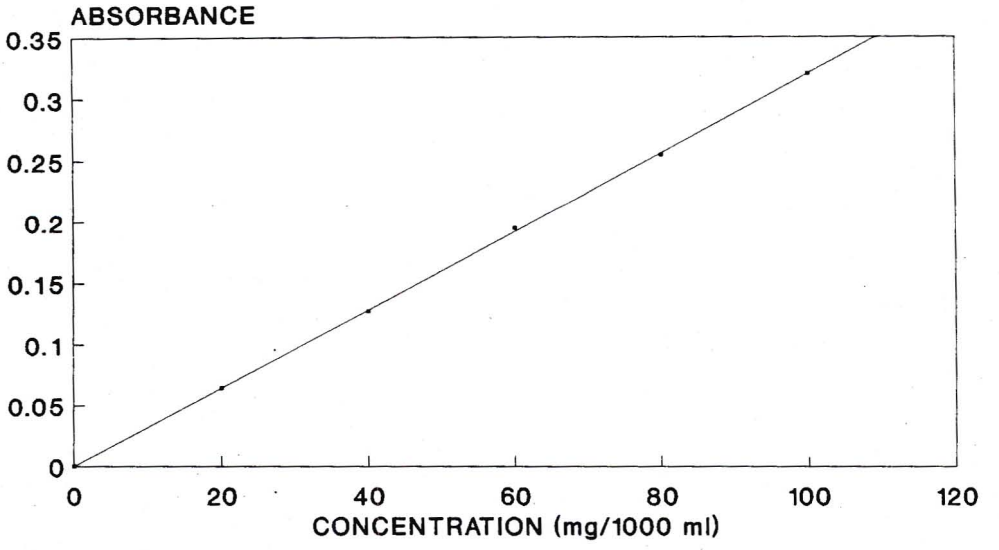
y = 0.0167x + 0.0005
r squared = 0.999

Figure 4.7: Calibration curve for diclofenac sodium in pH 6.2 phosphate buffer (0.2 M)



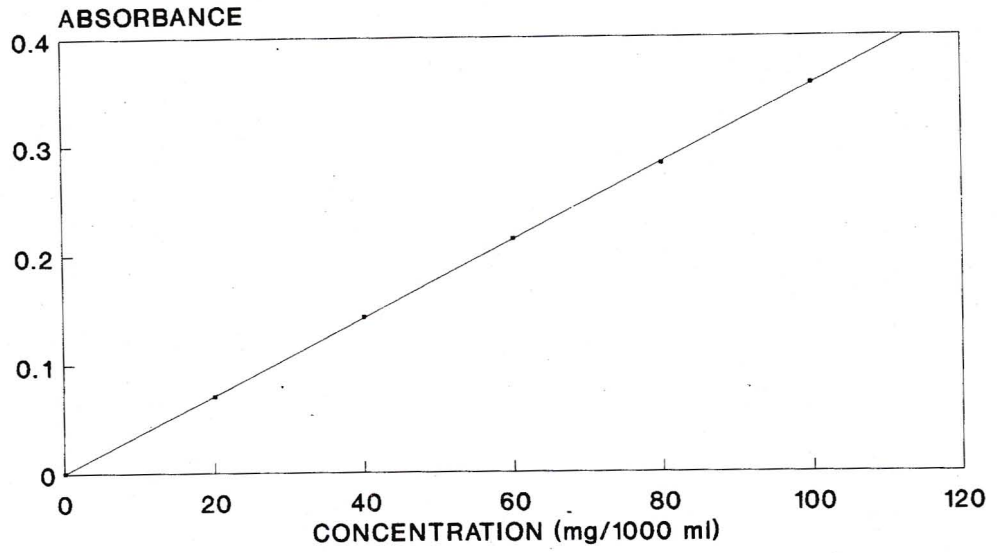
y = 0.0032x + 0.0007
r squared = 1

Figure 4.8: Calibration curve for diclofenac sodium in pH 6.8 phosphate buffer (0.2 M)



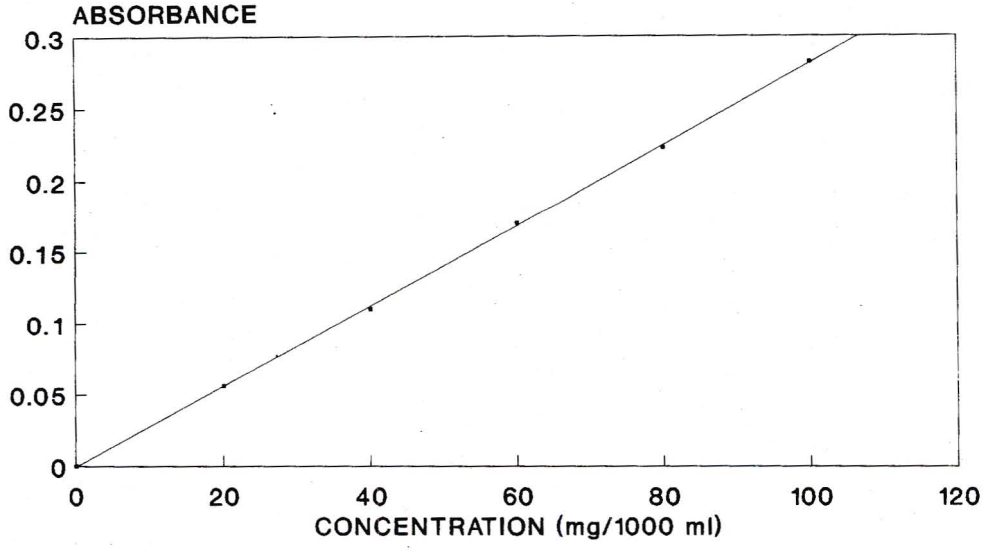
y = 0.0032x + 0.0001
r squared = 0.999

Figure 4.9: Calibration curve for diclofenac sodium in pH 7.5 phosphate buffer (0.2 M)



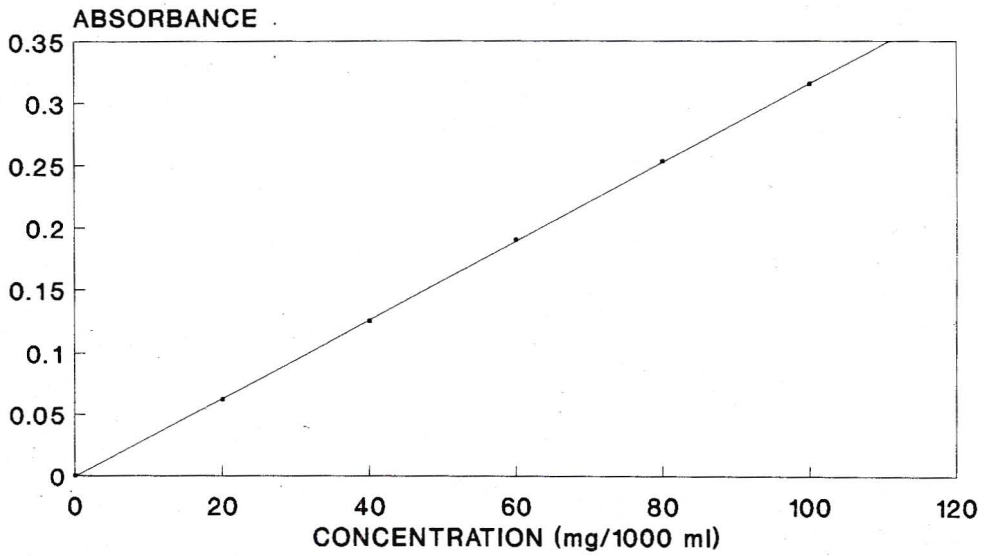
y = 0.0036x + 0.0002
r squared = 1

Figure 4.10: Calibration curve for diclofenac sodium in pH 8 phosphate buffer (0.2 M)



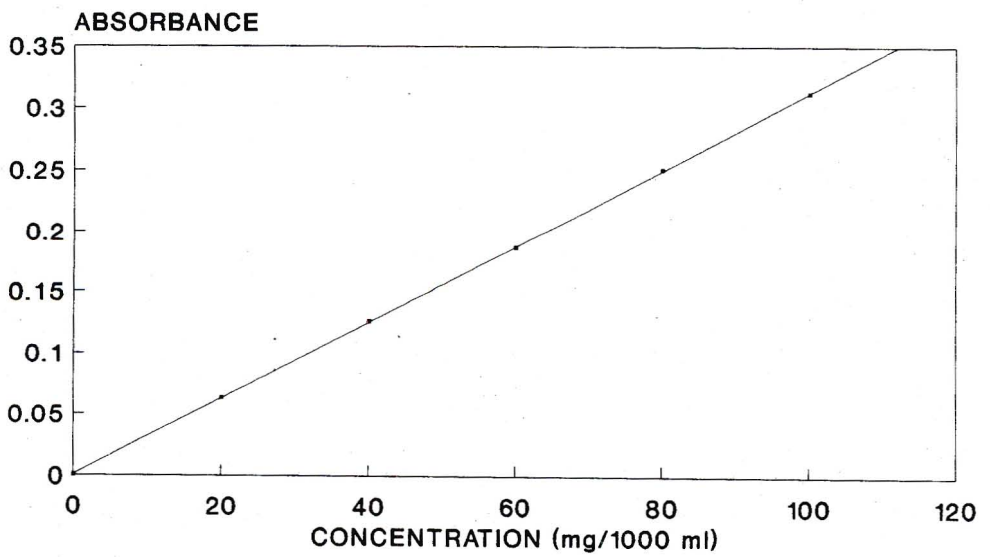
y = 0.0028x - 0.0006
r squared = 0.999

Figure 4.11: Calibration curve for diclofenac sodium in pH 6.2 distilled water



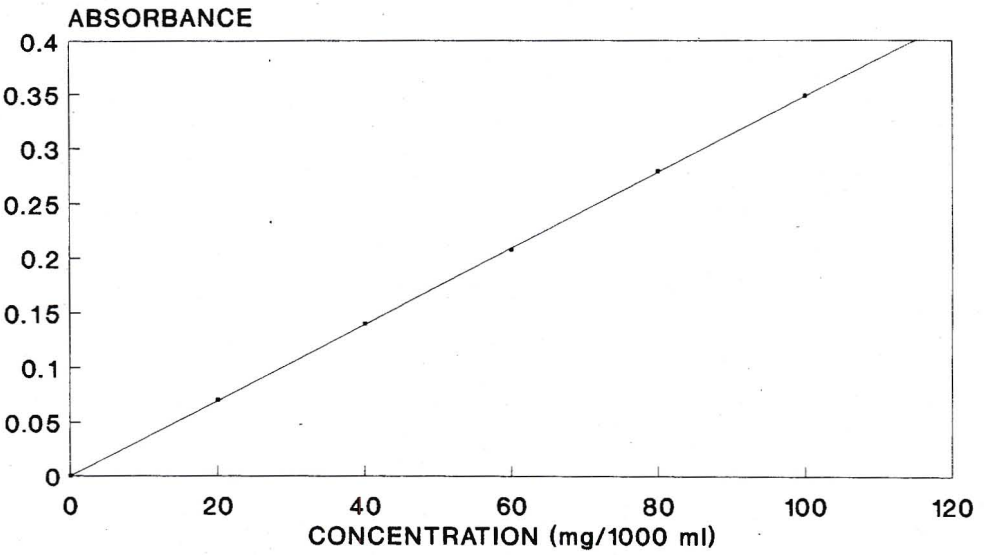
y = 0.0032x - 0.0006
r squared = 1

Figure 4.12: Calibration curve for diclofenac sodium in pH 6.8 phosphate buffer (USP)



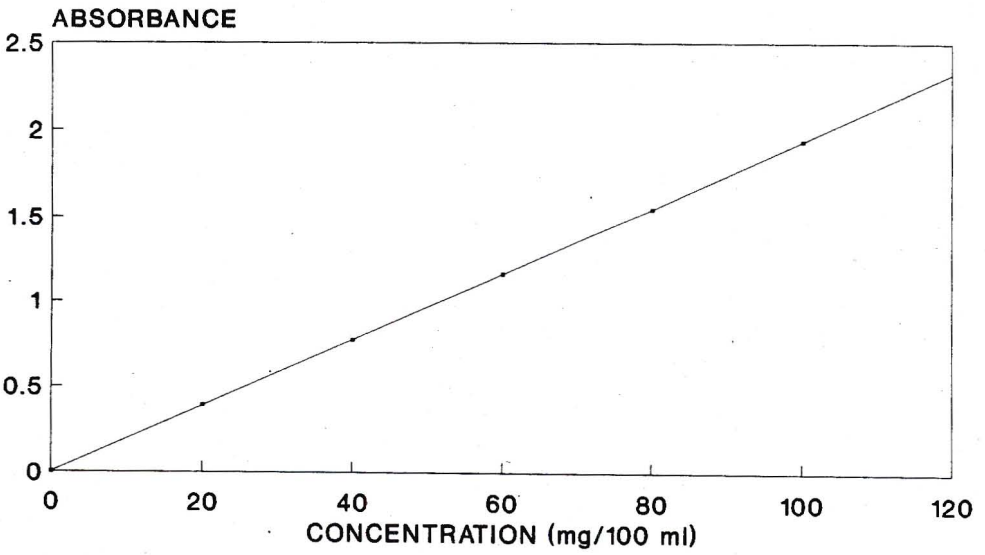
y = 0.0031x + 0.0004
r squared = 1

Figure 4.13: Calibration curve for diclofenac sodium in pH 6.8 phosphate buffer (0.1 M)



y = 0.0035x + 0.0001
r squared = 0.999

Figure 4.14: Calibration curve for diclofenac sodium (mg/100 ml) in pH 6.8 phosphate buffer (0.2 M)



y = 0.0194x + 0.0001
r squared = 1

4.8.2.2 Computation Of Dissolution Data

The data that were fed into the ultraviolet spectrophotometer for the calibration curves were in units of mg per 1000 millilitres (mg/1000 ml), except for the data used of the rotating bottle method, where the units were in mg per 100 millilitres (mg/100 ml). The values generated were thus in the same units. The concentration of drug that was present in the 5 ml aliquot, at specified time intervals, was calculated from the calibration curves. However, the values obtained were representative of the total concentration of the drug in the dissolution medium at the particular time point, and therefore did not account for the drug in the previous samples that were removed for ultraviolet analysis and subsequently discarded. It was therefore necessary to correct for the quantity of drug that was present in the 5 ml aliquot.

The method used to correct for the amount of drug in the samples removed is exemplified below:

- at 0.5 hour, 5 ml of medium containing 10 mg/1000 ml of drug was removed;
- at 1 hour, 5 ml of medium containing 15 mg/1000 ml of drug was removed;
- at 1.5 hours, 5 ml of medium containing 20 mg/1000 ml of drug was removed; and
- at 2 hours, 5 ml of medium containing 25 mg/1000 ml of drug was removed

The correction factor is the value by which the concentration increased to account for the drug 'lost'.

The 0.5 hour sample was the initial sample taken. The correction factor was 0, thus the corrected value would be equal to the concentration.

At 1 hour, the calculation for the correction factor was as follows:

· 10/1000 X 5 = x correction factor = x

The correction factor, added to the concentration at 1 hour, will be the corrected value for the concentration at 1 hour i.e.

$x + 15$

At 1.5 hours, the calculation of the correction factor was as follows:

$15/1000 \times 5 = y$ correction factor $= x + y$

The correction factor obtained was added to the correction factor of the previous sample to account for the cumulative amount of drug 'lost'.

At 2 hours, the calculation of the correction factor was as follows:

$20/1000 \times 5 = z$ correction factor $= x + y + z$

The correction factor obtained was added to the previous correction factors obtained, which was then added to the concentration, to calculate the corrected concentration.

The concentration values in the above example were divided by 1000 to bring the values to units of mg/ml, and multiplied by five, to account for the volume of sample removed. The same principle was used to correct for the amount of drug 'lost' with the rotating bottle method, but instead of dividing the concentration value by 1000, the concentration was divided by 100.

To facilitate data analysis, the Quattro Pro Version® 6 computer software programme was used to construct a spreadsheet to calculate the correction factor, corrected concentration, percentage drug released, the mean percentage drug released and the standard deviations at each time point. A stepwise cell format of the spreadsheet is presented in Appendix 5.

4.9 INFLUENCE OF FORMULATION EXCIPIENTS ON DRUG RELEASE

During the course of the study, numerous excipients were incorporated into the dosage form to determine their effect on modifying drug release characteristics. The formulation of the

batches prepared for investigation are outlined. All batches were prepared as outlined in section 4.3.2. All batches were subjected to *in vitro* dissolution testing in 1000 ml of 0.2 M phosphate buffer pH 6.8, using the USP rotating paddle apparatus at 100 rpm.

4.9.1 *INFLUENCE OF LACTOSE*

The concentration of lactose was varied in an attempt to determine its influence on the drug release characteristics from the Eudragit® matrices. Tablet batches were prepared and investigated as outlined in Table 4.18.

Table 4.18: Formulation of batches containing different concentrations of lactose

CONSTITUENT	BATCH		
	NHL30	NH	NHL50
Diclofenac sodium	20 g	20 g	20 g
Lactose	30 g	40 g	50 g
Eudragit® RL30D	5 ml	5 ml	5 ml
Eudragit® RS30D	5 ml	5 ml	5 ml
Starch	3 g	3 g	3 g
Water	6 ml	8 ml	10 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets of Batches NHL30, NH and NHL50 were compressed to a weight of 345, 350 and 355 mg respectively.

4.9.2 *INFLUENCE OF DIFFERENT TYPES OF DILUENTS*

In addition to lactose, the use of other additives as suitable diluents to be incorporated into the tablets was determined. The diluents selected for use in the present study were dicalcium phosphate and microcrystalline cellulose (Avicel® pH 102). The tablet batches formulated for investigation are outlined in Table 4.19.

Table 4.19: Formulation of batches containing different types of diluents

BATCH	CONSTITUENT	QUANTITY
DCP	Diclofenac sodium	20 g
	Dicalcium phosphate	40 g
	Eudragit® RL30D	5 ml
	Eudragit® RS30D	5 ml
	Starch	3 g
	Water	11 ml
MCC	Diclofenac sodium	20 g
	Avicel® pH 102	40 g
	Eudragit® RL30D	5 ml
	Eudragit® RS30D	5 ml
	Starch	3 g
	Water	20 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets of Batches DCP and MCC were compressed to a weight of 350 and 355 mg respectively.

4.9.3 *INFLUENCE OF STARCH*

The starch concentrations of Batch NH were varied to demonstrate the influence of starch on drug release behaviour. The various concentrations of starch that were investigated are outlined in Table 4.20.

Table 4.20: Formulation of batches containing different concentrations of starch

CONSTITUENT	BATCH		
	NHS2	NH	NH4
Diclofenac sodium	20 g	20 g	20 g
Lactose	40 g	40 g	40 g
Eudragit® RL30D	5 ml	5 ml	5 ml
Eudragit® RS30D	5 ml	5 ml	5 ml
Starch	2 g	3 g	4 g
Water	8 ml	8 ml	8 ml

- Granules were lubricated with 1% magnesium stearate prior to compression.
- Tablets of Batches NHS2, NH and NH4 were compressed to a weight of 346, 350 and 354 mg respectively.

4.9.4 *INFLUENCE OF MAGNESIUM STEARATE*

The effect of incorporating magnesium stearate as an internal lubricant (Batch NHM), as opposed to an external lubricant (Batch NH), on drug release was investigated. The various quantities of the constituents used in this comparative study remained the same. The difference was in the method of incorporation of magnesium stearate. The constituents and quantities thereof used in the preparation of Batch NHM are outlined in Table 4.21, while Batch NH was prepared as previously described in Table 4.6.

Table 4.21: Formulation of Batch NHM, containing magnesium stearate as an internal lubricant

CONSTITUENT	BATCH NHM
Diclofenac sodium	20 g
Lactose	40 g
Eudragit® RL30D	5 ml
Eudragit® RS30D	5 ml
Starch	3 g
Magnesium stearate	0.7 g
Water	8 ml

- Tablets of Batch NHM were compressed to a weight of 350 mg.

4.10 INFLUENCE OF PROCESSING VARIABLES

4.10.1 *INFLUENCE OF TABLET HARDNESS*

The influence of tablet hardness on drug release characteristics of Batch NH was investigated. Dissolution studies were conducted on batches compressed to different hardnesses. The tablet hardness ranges selected for the study are presented in Table 4.22.

Table 4.22: Tablet hardness ranges selected for investigating the effect of compression force on drug release patterns

BATCH	TABLET HARDNESS RANGE (Kp)
HARD 34	3-4
NH	4-5
HARD 67	6-7

4.11 ELECTRON MICROSCOPY

Electron microscope evaluations were conducted on the tablets using scanning electron microscopy and energy dispersive x-ray microprobe analysis.

4.11.1 *SCANNING ELECTRON MICROSCOPY (SEM)*

SEM was used as an aid in an attempt to evaluate the integrity and surface morphology as well as cross-sectional characteristics of the tablets.

Whole, intact tablets as well as horizontal and vertical cross-sections of the tablets were mounted on circular brass stubs (12 mm in diameter) using double-backed adhesive tape. The cross-sections were prepared by slicing the tablet, either horizontally or vertically, with a sharp sterile scalpel blade. The surface morphology of the tablets that had been subjected to stability testing under the different conditions (as described in section 4.13.2.5), and that of the tablets that had been compressed to different hardnesses (as described in section 4.10.1) was also investigated.

The mounted stubs were sputter-coated under an argon atmosphere with gold-palladium for 5 minutes in the Polaron SEM coating unit E5000, which is a direct contact sputter coating device. Thereafter, the samples were removed from the coating device and viewed under the Joel Scanning Electron Microscope, model 6100. Different magnifications were used to detail areas of the samples. Images were captured on an Ilford Pan-F black and white 35 mm film.

4.11.2 *ENERGY DISPERSIVE X-RAY MICROPROBE ANALYSIS (EDX)*

EDX was performed to examine the elemental composition of the tablets from Batch NH. The technique operated in conjunction with SEM. A particular section of the sample was selected, of which the elemental composition was determined. The Voyager® computer

software programme was used to obtain the EDX spectrum.

The tablet that was selected for the EDX study was mounted onto the circular brass stubs as described in section 4.11.1 and carbon coated in a Polaron E 4500 vacuum evaporator.

4.12 POWDER X-RAY DIFFRACTION

The x-ray diffraction patterns of the following samples were obtained:

- diclofenac sodium powder;
- Eudragit® RLPO;
- Eudragit® RSPO;
- granulated Eudragit® RLPO;
- granulated Eudragit® RSPO;
- magnesium stearate powder;
- lactose powder;
- starch;
- physical mixture of diclofenac sodium/Eudragit® RLPO/Eudragit® RSPO/lactose/starch and magnesium stearate;
- granules*; and
- tablets**

* lubricated granules of Batch NH

** tablets of Batch NH

Granulations of Eudragit® RLPO and Eudragit® RSPO were obtained by granulating the respective Eudragit® polymers with water, and then drying the granules at 55°C for 20 minutes.

A Phillips X-ray Diffractometer was used in the study. The measurement conditions are outlined in Table 4.23.

Table 4.23: Measurement conditions for x-ray diffraction

OPERATING PARAMETER	SETTING
Temparature	21 ± 1°C
Target	Co (Kα radiation)
Voltage	40 kV
Current	32 mA
Time constant	1 second
Counting range	6000 cpm
Scanning rate	1° 2Θ/min
Chart speed	10 mm/minute
Scanning range	4-45 degrees 2Θ

A graphite monochromator was used to select Kα radiation, from of a mixture of Kα and Kβ radiation, after diffraction. The sample was placed on an aluminium sample holder with a glass backing and gently packed with the aid of a glass slide. The sample holder was then placed in the diffractometer and scanned using the above measurement conditions.

4.13 STABILITY STUDIES

Stability testing was conducted on Batch NH over a period of 3 months under various temperature and humidity conditions. A total number of 420 tablets was prepared for the stability study.

The stability of the tablets was analysed using the following techniques:

- high performance liquid chromatography;
- Karl Fischer moisture content determination;
- hardness testing;
- *in vitro* dissolution testing; and
- scanning electron microscopy.

High performance liquid chromatography was used to assay diclofenac sodium content and to detect the presence of any degradation products that may have formed. Moisture content of the tablets was determined by the Karl Fischer method. This test was performed to determine the possibility of having developed a hygroscopic drug delivery system or the use of inappropriate storage containers which could have allowed the ingress of moisture. Moisture content determination could also provide information on the suitability of the storage condition. Hardness testing was used to investigate changes in tablet hardness over the duration of the stability testing period under various storage conditions. Dissolution testing was done to detect any deviations in the drug release patterns from the control, Batch NH. Scanning electron microscopy was used to determine the changes in surface morphology that may have occurred in the tablets upon storage.

4.13.1 *INFLUENCE OF STORAGE CONDITIONS ON POTENCY, MOISTURE CONTENT, TABLET HARDNESS, DRUG RELEASE AND SURFACE MORPHOLOGY*

An amount of 100 tablets was placed in each of four 100 ml round, amber glass bottles. Two sachets of the desiccant, activated silica gel (Mass = 2 g), were placed in each bottle. The bottles were closed tightly with plastic screw-top lids. Each bottle was thereafter stored under different storage conditions. The remainder of the tablets were used to assess the potency, moisture content, tablet hardness, drug release characteristics and surface morphology of the tablet matrices of Batch NH prior to storage. The tablets in each of the four bottles were analysed after the following time intervals:

- 4 weeks;
- 8 weeks; and
- 12 weeks.

The storage conditions that the tablets were subjected to were as follows:

- room temperature (21 ± 1°C);
- low temperature (5 ± 1°C).
- 37 °C with 80% relative humidity; and

- 40 °C.

4.13.1.1 Storage At Room Temperature (21±1°C)

A 100 ml amber glass bottle containing 100 tablets and the desiccant was stored away from light in a cupboard (temperature 21±°C).

4.13.1.2 Storage At Low Temperature (5±1°C)

A 100 ml round amber glass bottle, containing 100 tablets and desiccant was placed in a fridge at 5±1°C.

4.13.1.3 Storage At 37°C With 80 % Relative Humidity

A saturated solution of ammonium chloride was prepared in accordance with the Merck Tables for the Chemical Laboratory to achieve a constant humidity of 80%. The solution was poured into a glass desiccator. The base of the lid was smeared with petroleum jelly, and the lid was replaced. Negative pressure was applied for thirty minutes to create a vacuum in the desiccator. The desiccator was allowed to equilibrate with its surroundings at 37°C in an air heated Gallenkamp oven, model OV 160. Thereafter, the desiccator was removed from the oven, and a round amber glass bottle containing 100 tablets was introduced into the desiccator. The bottle was placed on a circular porous porcelain support that maintained the bottle above the saturated solution. The lid was replaced on the desiccator, a vacuum was created once again by means of negative pressure, and the desiccator was replaced into the oven.

4.13.1.4 Storage At 40°C

A 100 ml round amber bottle containing 100 tablets and the desiccant was placed in a Heraeus warmer, type FB 420. The temperature was thermostatically maintained at 40°C.

4.13.2 *TECHNIQUES USED TO STUDY STABILITY AND MOISTURE CONTENT OF THE TABLET MATRICES*

4.13.2.1 High Pressure Liquid Chromatography (HPLC)

The HPLC method used to assay drug content was as described in section 4.2.2.2.1. The standard and sample preparations were prepared and each sample was injected in duplicate into the HPLC system. A calibration curve was obtained for each lot of assay, to compensate for fluctuations in the pressure of the system between assay periods.

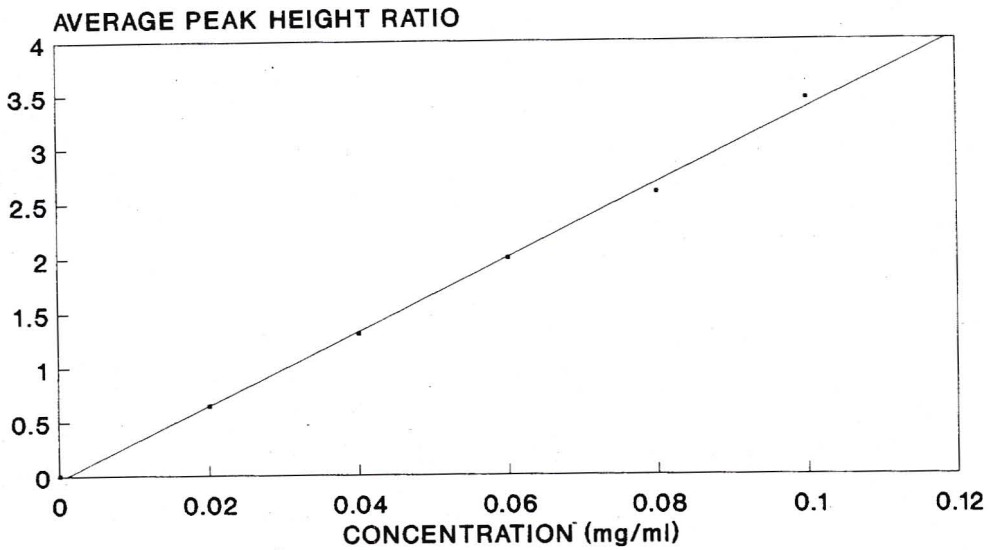
Table 4.24: HPLC calibration curve data for determining the content of diclofenac sodium in the Eudragit® matrices

DICLOFENAC SODIUM CONCENTRATION (mg/ml)	* AVERAGE PEAK HEIGHT RATIOS DICLOFENAC SODIUM : PARA-NITROBENZOIC ACID			
	0 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.02	0.643	0.727	0.686	0.591
0.04	1.306	1.285	1.279	1.171
0.06	1.992	1.918	1.887	1.749
0.08	2.594	2.522	2.569	2.322
0.10	3.450	3.166	3.212	2.931

* Individual values for two replicate determinations are shown in Appendices 6.2, 6.3, 6.4 and 6.5 respectively.

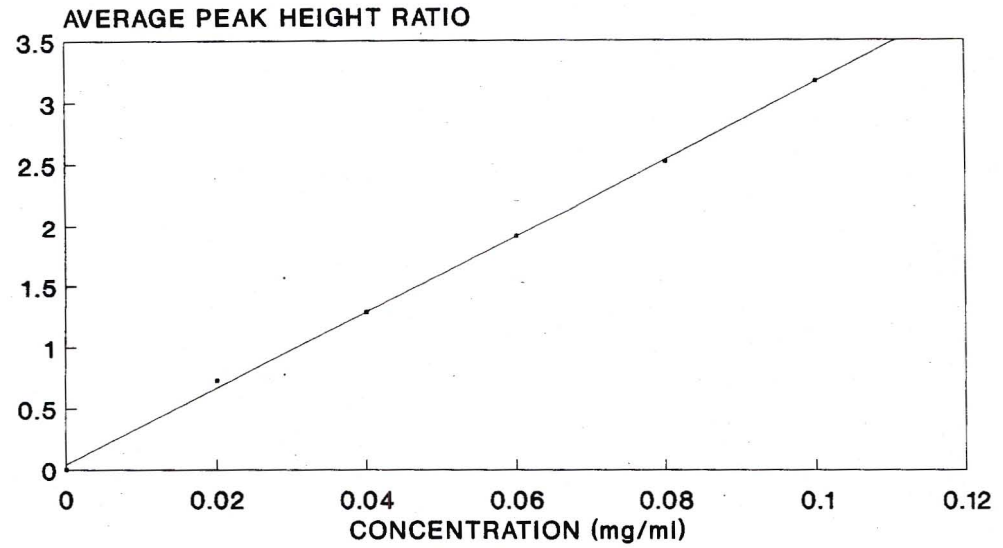
The calibration curves for the various samples are presented in Figures 4.15-4.18.

Figure 4.15: HPLC calibration curve for determining the content of diclofenac sodium in tablets of Batch NH (0 weeks)



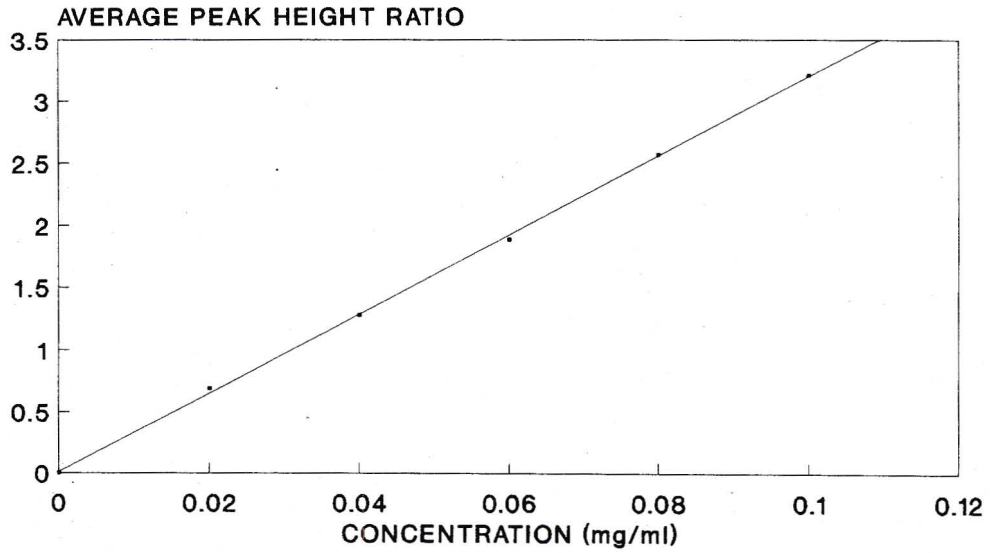
y = 33.984x - 0.035
r squared = 0.998

Figure 4.16: HPLC calibration curve for determining the content of diclofenac sodium in tablets of Batch NH (4 weeks)



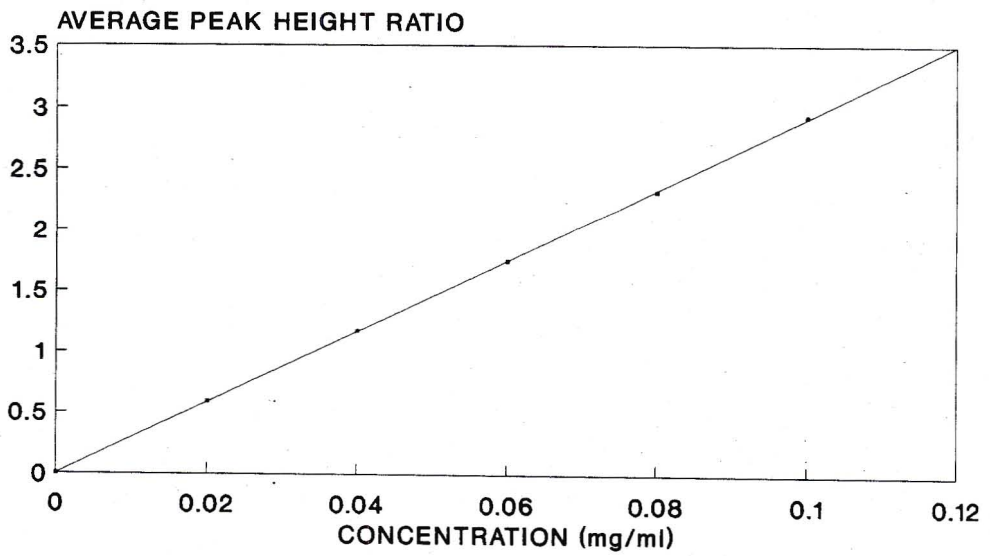
y = 31.211x + 0.0424
r squared = 0.999

Figure 4.17: HPLC calibration curve for determining the content of diclofenac sodium in tablets of Batch NH (8 weeks)



y = 31.881x + 0.0114
r squared = 0.999

Figure 4.18: HPLC calibration curve for determining the content of diclofenac sodium in tablets of Batch NH (12 weeks)



y = 29.18x + 0.0017
r squared = 0.999

4.13.2.2 Karl Fischer Method

Karl Fischer analyses were conducted to determine the moisture content of the tablet matrices of Batch NH. The analyses were performed initially and 4, 8 and 12 weeks after subjecting the tablets to different storage conditions, using the AF8 Advanced Volumetric Karl Fischer Titrator. Each moisture content determination was performed in triplicate. Distilled water was used as the solvent to calibrate the instrument. During each moisture content determination, the tablet to be analysed was weighed and placed in the titration chamber. The Karl Fischer Reagent was introduced into the chamber by an automatic, synchronised titrator. Table 4.25 outlines the calibration settings used in all titrations.

Table 4.25: Calibration data for the Karl Fischer method

OPERATING PARAMETER	SETTING
Stirrer speed	5
Step level	+10
End point level	12
End point time	15 seconds

4.13.2.3 Hardness Testing

The hardness of five tablets of each batch was determined at appropriate time intervals using the Pharma Test PTB tablet hardness tester.

4.13.2.4 *In Vitro* Dissolution Testing

All *in vitro* dissolution tests were performed using the USP rotating paddle apparatus at 100 rpm in 1000 ml of 0.2 M phosphate buffer pH 6.8.

4.13.2.5 Surface Morphology

The surface morphology of the tablets stored at the various storage conditions was evaluated at the beginning and end of the 12 week storage period using SEM, as described in section 4.11.1.

Chapter Five

Results and Discussion

5.1 QUALITY CONTROL

5.1.1 *DICLOFENAC SODIUM POWDER*

5.1.1.1 Identification

The infrared absorption spectrum was concordant with the reference spectrum (Moffat *et al.*, 1986) obtained. The spectrum of the sample, as well as that of the reference spectrum is indicated in Appendix 7.

The ultraviolet absorption spectrum of diclofenac sodium in methanol exhibited a wavelength of maximum absorption at 281 nm. This wavelength corresponded to the wavelength obtained with the USP reference sample of diclofenac sodium (Appendix 8).

5.1.1.2 Assay

The ultraviolet assay of diclofenac sodium in 0.2 M phosphate buffer pH 6.8 gave a mean percentage purity of 100.19±0.12% (100.04%, 100.23%, 100.31%).

5.1.2 *VELTEX® 100 CR CAPSULES*

5.1.2.1 Identification

Infrared and ultraviolet spectroscopy positively identified the presence of diclofenac sodium in the sample of the pellets analysed.

5.1.2.2 Assay

The calibration curve for the high performance liquid chromatographic assay of diclofenac sodium from the commercially available Veltex® 100 CR is presented in Figure 4.2. The average percentage of diclofenac sodium in Veltex® 100 CR was 94.0±0.00% (94.0%, 94.0%) (Appendix 6.1).

5.1.2.3 Dissolution Study

The drug release data of diclofenac sodium from Veltex® 100 CR in 0.2 M phosphate buffer pH 6.8 using the rotating paddle method is presented in Tables 5.1 and 5.2 and Figures 5.1 and 5.2 respectively. The samples were analysed for drug content at the wavelength of maximum absorbance using ultraviolet spectroscopy.

Table 5.1: Mean cumulative drug release data for Veltex® 100 CR capsules

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD
0.25	3.79±063
0.5	7.71±0.49
1	14.47±0.48
1.5	20.20±0.49
2	24.79±0.54
3	33.44±0.48
4	43.85±0.36
5	48.50±0.19
6	54.80±0.17
7	60.09±0.65
8	67.42±0.19
9	70.80±0.34
10	74.30±0.02
11	77.39±0.62
12	81.11±0.02

* Individual values for 3 replicate determinations are shown in Appendix 9.

Table 5.2: Mean release rates of diclofenac sodium from Veltex® 100 CR capsules

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)
1	14.47±0.48
2	10.32±0.79
3	8.66±0.65
4	10.41±0.31
5	4.65±0.18
6	6.29±0.18
7	5.29±0.71
8	7.34±0.61
9	3.38±0.31
10	3.49±0.34
11	3.09±0.61
12	3.71±0.60

* Individual values for 3 replicate determinations are shown in Appendix 66.

Figure 5.1: Drug release profile of diclofenac sodium from Veltex[R]100 CR capsules

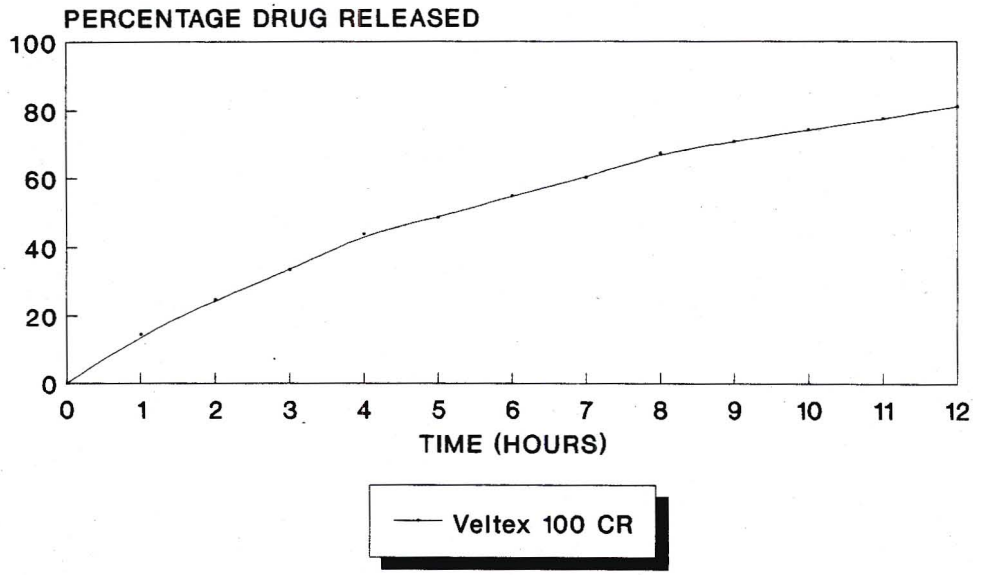
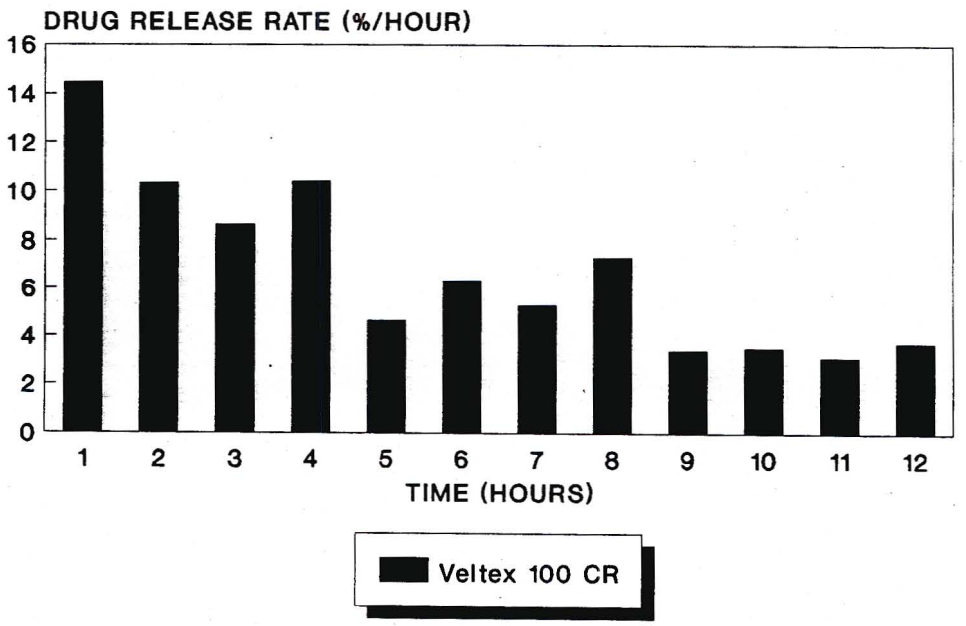


Figure 5.2: Release rates of diclofenac sodium from Veltex[R]100 CR capsules



The dissolution profile of Veltex® 100 CR capsules (Figure 5.1) represented a typical first-order drug release process. The initial four hours demonstrated an almost zero-order drug release pattern (zero-order rate constant = 10.71; r^2 = 0.990). During this phase, an initial fast-release loading dose was released, which was followed by a slower release. It can thus be inferred that the fast-release loading dose would be made available to the body for absorption to initiate a therapeutic effect, while the slower release would provide a sustained effect. During the first four hours, a mean total of 43.85±0.36% of drug was released. However, from the fourth to the eighth hour, drug release was significantly decreased, with an even greater reduction from the eighth hour onwards. The data indicated that the total amount of drug released between the fourth and eighth hour was 23.57±0.47%, while the amount of drug released over the last four hours of the test period was 13.68±0.17%. The mean cumulative amount of drug released over the entire twelve hour study was 81.11±0.02%.

The design of Veltex® 100 CR is based on the pellet-type of drug delivery system. This system is also referred to as the 'bead' type preparation (Shargel and Yu, 1985). The pellets are encapsulated within a hard gelatin capsule and are released in the gastrointestinal tract.

The drug release pattern of Veltex® 100 CR, as depicted in Figure 5.1, was obtained for use as a reference for developing a diclofenac sodium Eudragit® tablet matrix, with a desirable modified release profile. However, due to the markedly retarded drug release characteristics, it was postulated that there would be poor bioavailability of the drug from a dosage form designed to release drug in accordance with the drug release characteristics of Veltex® 100 CR. Hence, the rationale for selecting a formulation displaying suitable drug release characteristics is presented in section 5.5.

5.2 FORMULATION AND PREPARATION OF EUDRAGIT® MATRICES CONTAINING DICLOFENAC SODIUM

5.2.1 *DIRECT COMPRESSION MATRICES*

Diclofenac sodium Eudragit® matrices were formulated using the direct compression technique, as described in section 4.3.1. Various batches comprising different amounts of Eudragit® polymer and other excipients were formulated in an attempt to produce a formulation with optimal drug release characteristics, as outlined in section 5.5.

5.2.1.1 Optimisation Of A Working Formula

5.2.1.1.1 Preliminary studies

Various direct compression tablet batches that contained different concentrations of the Eudragit® RLPO and Eudragit® RSPO polymers were formulated. Tablets from each batch were subjected to *in vitro* dissolution testing in 0.2 M phosphate buffer pH 6.8 to evaluate drug release characteristics. The dissolution data of the direct compression batches are tabulated in Table 5.3 and graphically illustrated in Figure 5.3. The mean repose angles, as determined on the powder blends of Batches DC1, DC2, DC3 and DC4, are presented in Table 5.4.

Table 5.3: Mean cumulative percentages of diclofenac sodium released from direct compression batches containing different concentrations of Eudragit® RLPO and Eudragit® RSPO polymers

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD			
	BATCH DC1	BATCH DC2	BATCH DC3	BATCH DC4
0.5	9.37±1.11	7.37±1.02	8.11±0.91	7.90±0.55
1	14.14±2.02	10.35±1.11	10.99±0.92	9.94±1.28
1.5	18.51±2.98	18.27±1.42	15.77±0.66	12.40±0.32
2	23.93±3.28	25.47±2.90	19.40±0.64	13.41±1.10
3	31.65±2.64	35.78±5.33	27.33±0.55	17.04±1.03
4	44.02±2.04	48.45±5.48	35.67±0.79	19.53±0.96
5	61.90±1.82	59.05±6.12	42.47±1.27	23.70±1.38
6	75.32±4.45	68.42±5.83	52.26±0.98	26.01±0.30
7	83.38±1.01	76.07±4.99	57.44±2.12	29.57±0.95
8	87.42±1.52	81.10±4.39	65.18±2.15	33.25±0.46

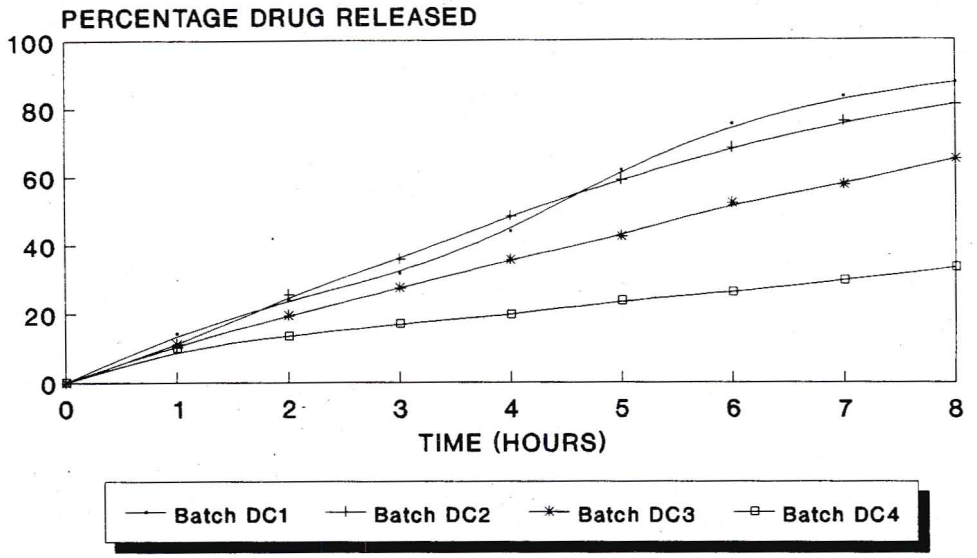
* Individual values for three replicate determinations are shown in Appendices 10, 11, 12 and 13 respectively.

Table 5.4: Mean repose angles of the powder blends of Batches DC1, DC2, DC3 and DC4

BATCH	* MEAN REPOSE ANGLE (°)
DC1	61.21±1.54
DC2	58.08±0.44
DC3	57.62±0.49
DC4	56.14±0.12

* Individual values for 3 replicate determinations are shown in Appendix 92.

Figure 5.3: Drug release profiles of diclofenac sodium from Batches DC1, DC2, DC3 and DC4



The drug release data indicate that as the concentrations of the Eudragit® RLPO and RSPO polymers were increased, there was a decrease in drug release. Hence, the fastest drug release characteristics were observed from Batch DC1, which contained the lowest concentrations of the Eudragit® polymers. A mean total of $87.42 \pm 1.52\%$ drug was released in eight hours. Batch DC2 released $10.35 \pm 1.11\%$ of drug in one hour, and an overall amount of $81.10 \pm 4.39\%$ in eight hours. Drug release from Batch DC3 was more retarded, with $65.18 \pm 2.15\%$ drug being released in 8 hours, while only $33.25 \pm 0.46\%$ drug was released in eight hours from Batch DC4.

The major difficulty experienced in the formulation of the direct compression batches, was the lack of suitable flow properties of the powder blend. The mean angle of repose of the powder blends of Batches DC1, DC2, DC3 and DC4, as indicated in Table 5.4, was above 65°. This further highlighted the poor flow characteristics of the powders. Wells and Aulton (1988) have reported that powders with a repose angle $>40°$ have very poor flow properties.

Therefore, from the preliminary investigations, Batch DC2 was identified as a formulation that released diclofenac sodium in accordance with the specifications outlined in section 5.5. Hence, this formulation was selected to optimise the flow properties of the powder blend.

5.2.1.1.2 Final formulation

5.2.1.1.2.1 *Optimisation Of Flow Rate*

5.2.1.1.2.1.1 *Glidant concentrations*

In an attempt to improve the flow of the powder mix, the glidant (Aerosil® 200) concentrations of Batch DC2 were increased, as reflected in Table 4.5. The mean angle of repose as calculated on the powder blends of the various batches is presented in Table 5.5.

Table 5.5: Mean repose angles of batches containing different concentrations of Aerosil® 200

BATCH	AEROSIL® 200 CONCENTRATION (%)	* MEAN ANGLE OF REPOSE (°)
DC5	1.77	54.72±0.40
DC6	2.64	53.98±0.79
DC7	3.48	53.21±0.62
DC8	4.30	51.71±0.94

* Individual values for 3 replicate determinations are shown in Appendix 92.

It becomes evident from Table 5.5, that there was an improvement in powder flow, and hence, a decrease in the angle of repose as the Aerosil® 200 concentration was increased. However, suitable flow properties were still unattainable, even at the relatively high concentrations of Aerosil® 200 used. The recommended concentration of Aerosil® 200 for use as a glidant is in the range 0.5-1% (Harpaz, 1994). Therefore, further attempts to improve the flow properties of the powder blend, by increasing the concentration of Aerosil® 200, were considered unfeasible.

5.2.1.1.2.1.2 *Diluents*

Direct compression as a means of tablet manufacture has many merits. The technique has also gained extreme popularity due to the availability of direct compression tablet excipients (Patel *et al.*, 1994). Therefore, the use of microcrystalline cellulose and dicalcium phosphate as diluents was also investigated, in an attempt to improve the flow properties of the powder blend. The repose angles of Batches DC9 and DC10 are indicated in Table 5.6, while the drug release data from Batches DC9 and DC10 are presented in Table 5.7 and Figure 5.4.

Table 5.6: Mean repose angles of Batches DC9 and DC10

BATCH	* MEAN REPOSE ANGLE (°)
DC9	33.05±0.92
DC10	67.51±1.05

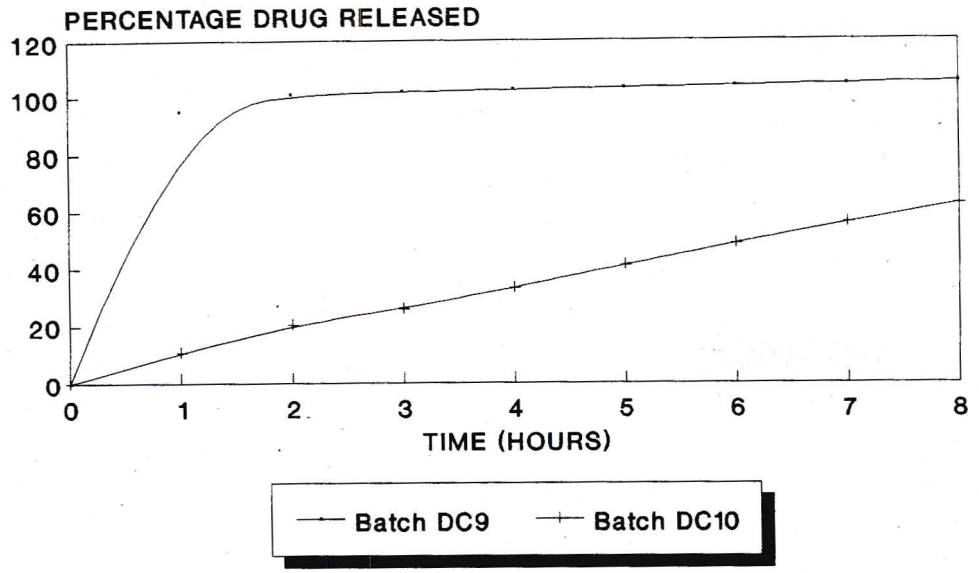
* Individual values for 3 replicate determinations are shown in Appendix 92.

Table 5.7: Mean cumulative drug release data of diclofenac sodium from Batches DC9 and DC10

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD	
	BATCH DC9	BATCH DC10
0.5	81.45±3.30	7.48±0.48
1	95.02±3.95	10.77±0.32
1.5	100.38±0.33	15.45±0.79
2	101.05±0.14	20.44±0.91
3	101.80±0.24	25.87±0.91
4	102.48±0.45	33.18±1.48
5	103.04±0.47	40.79±2.09
6	103.69±0.42	48.53±2.62
7	104.28±0.48	55.85±2.43
8	104.84±0.46	62.37±2.84

* Individual values for 3 replicate determinations are shown in Appendices 14 and 15 respectively.

Figure 5.4: Drug release profiles of diclofenac sodium from Batches DC9 and DC10



The use of microcrystalline cellulose (Batch DC9) resulted in an improved flow rate (mean repose angle = 33.05±0.92°), while there was no advantage in using dicalcium phosphate over lactose anhydrous, as far as the flow properties were concerned. The mean repose angle obtained for Batch DC10 was 67.51±1.05°. However, with microcrystalline cellulose, the tablet disintegrated on contact with the dissolution medium, releasing almost the entire dose in one and a half hours. A formulation displaying such drug release characteristics can lead to 'dose dumping' *in vivo*. Batch DC10 led to more retarded drug release, with only 62.37±2.84% of the drug being released in 8 hours. Hence, the use of both microcrystalline cellulose and dicalcium phosphate, as a means of improving the flow properties, was considered unsuitable.

In general, powders with angle of repose <25° have excellent flow properties, while powders with angle of repose between 25-30° have good flow properties. On the other hand, powders with angle of repose between 30-40°C have flow properties that are satisfactory, and can be improved by the addition of a glidant, and powders that have angle of repose values >40° have very poor flow characteristics (Wells and Aulton, 1988).

Lin and Lin (1993) formulated direct compression tablet matrices using a mixture of Eudragit® RSPM and Eudragit® RLPM. The Aerosil® concentration was maintained at 1.5% in all formulations. These researchers did not report on any limitations as far as the flow properties of the powders were concerned. Efentakis *et al.* (1990) also formulated direct compression Eudragit® matrices. However, the formulations developed by these researchers did not include a glidant, and no problems with flow properties were reported. McGinity *et al.* (1983) on the other hand, used acrylic resins in the formulation of modified release tablets. Preliminary investigations included the incorporation of fumed silicon dioxide in the formulations. Excellent flow properties were observed with all the formulations in that study.

All the studies mentioned above in which Eudragit® polymers were used, supported the use of the direct compression technique; however, the problems encountered with the use of this technique may not have been unique to the present study. Alvarez *et al.* (1991), Abdel-Rahman *et al.* (1992) and Fernandez-Arevalo *et al.* (1993) formulated modified release tablets using Eudragit® polymers. The formulations developed in these studies were based on the granulation technique, and produced the desired modified release characteristics.

It was thus decided that the wet granulation technique be investigated in an attempt to overcome the problems associated with the direct compression method encountered in the preliminary studies.

5.2.2 *WET GRANULATED MATRICES*

5.2.2.1 Optimisation Of Processing Conditions For The Granulation

The processing conditions for the granulation technique were optimised, to ensure the integrity of the matrices produced. This included optimising the drying time and temperature; a suitable granule size range and tablet hardness.

5.2.2.1.1 Optimal drying temperature and time

Prior to the commencement of the study, preliminary investigations were conducted on the Eudragit® RLPO and Eudragit® RSPO polymers to determine the glass transition temperatures of the respective Eudragit® polymers. The temperature at which a glassy polymer becomes rubbery on heating and a rubbery polymer reverts to a glassy one on cooling is called the glass transition temperature (Martin *et al.*, 1993).

The Eudragit® polymers were subjected to differential scanning calorimetric (DSC) analysis, as described in section 4.3.2.1.1. In general, the thermal methods involve heating a sample under controlled conditions and observing the changes that occur. These methods measure a number of different properties e.g. melting point, heat capacity, heats of reaction, kinetics of decomposition and changes in the flow properties of materials (Martin *et al.*, 1993). The thermograms obtained for the Eudragit® RLPO and RSPO polymers are illustrated in Figures 5.5 and 5.6 respectively.

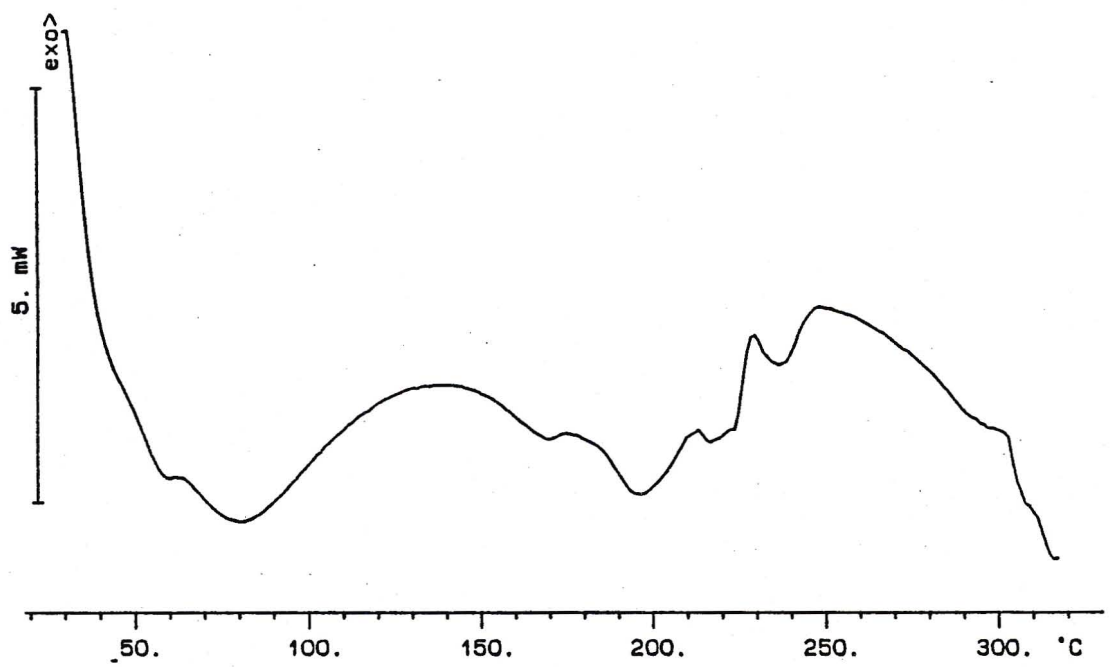


Figure 5.5: DSC thermogram of Eudragit® RLPO

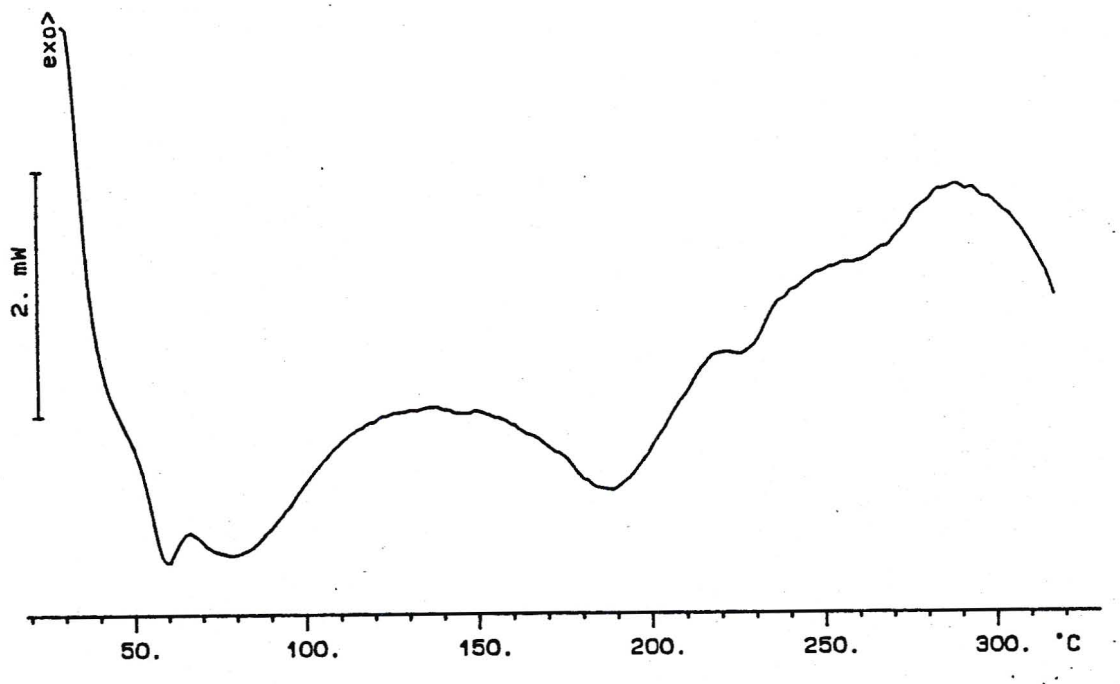


Figure 5.6: DSC thermogram of Eudragit® RSPO

The thermograms displayed endothermic peaks at 60°C for both the Eudragit® RLPO and RSPO polymers. Consequently, a drying temperature above 60°C was avoided, and drying temperatures of 30, 40 and 55°C were selected for investigation in the present study. The moisture content of the samples was determined at set time intervals, as reflected in Table 5.8.

Jenquin *et al.* (1990) reported glass transition temperatures of 55.1°C and 52.1°C for the Eudragit® RLPM and Eudragit® RSPM polymers respectively. Fernandez-Arevalo *et al.* (1993) on the other hand showed that Eudragit® RS exhibited an endothermic peak at 62°C. However, Durig and Fassihi (1993) and Perumal (1996) showed the absence of endothermic peaks for the Eudragit® RL and RS polymers.

Table 5.8: Moisture content assessment of samples tested at various times and temperatures

TEMPERATURE (°C)	TIME (MINUTES)	MOISTURE CONTENT (%)
30	20	11.98
	40	11.74
	60	10.84
40	20	10.96
	40	10.14
	60	9.96
55	20	6.85
	40	6.10
	60	5.24

NB. Initial moisture content was 15.13%.

The initial moisture content of the granules prior to commencement of drying was 15.13%. Temperatures of 30°C and 40°C over a period of 60 minutes showed the inability of these drying temperatures to significantly decrease the moisture content of the granules. Compression of the granules also led to picking and sticking of the granules to the punch and die surfaces, due to the excessive moisture content of the granules.

On the other hand, a temperature of 55°C was able to significantly decrease the moisture content of the granules, after 20 minutes. These granules also displayed excellent compression characteristics. However, drying times of 40 and 60 minutes produced granules that were very friable. Compression of these granules produced tablets that were more friable (1.76%) compared to tablets compressed from granules that were dried over a period of 20 minutes (0.93%).

Hence in subsequent investigations, a drying temperature of 55°C over a period of 20 minutes was used.

5.2.2.1.2 Optimal granule size range

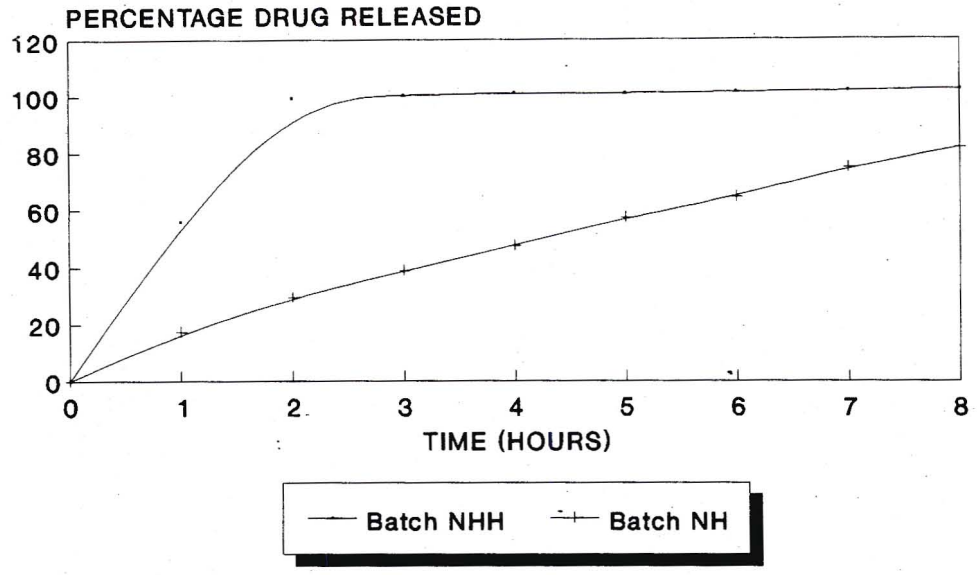
The formulation presented in Table 4.6 was used to prepare granules according to the wet granulation method. Preliminary investigations to compress the granules resulted in an unacceptably wide variation in tablet mass. The granules were then separated into two size fractions: 0-250 μm and 251-710 μm. Approximately 60% of the granules was in the 251-710 μm granule size range. These granules were compressed to form tablets of Batch NH, while the granules in the range 0-250 μm were compressed to produce tablets of Batch NHH. Separation of the granules into the different granule size ranges led to a more uniform mass of the tablets. The tablets from Batches NHH and NH were then subjected to dissolution testing in 0.2 M phosphate buffer pH 6.8. The dissolution data for the tablets of Batches NHH and NH are depicted in Table 5.9 and Figure 5.7.

Table 5.9: Mean cumulative drug release data for diclofenac sodium from tablets prepared with granules of different size ranges

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD	
	BATCH NHH	BATCH NH
0.5	30.12±3.91	12.85±0.21
1	55.96±2.49	17.29±1.29
1.5	87.32±4.70	20.73±0.55
2	99.47±0.13	29.37±1.31
3	100.31±0.17	38.85±2.03
4	101.20±0.36	47.64±2.02
5	100.97±0.07	57.26±2.59
6	101.46±0.08	64.35±3.04
7	101.82±0.17	74.43±2.51
8	102.42±0.32	81.80±1.23

* Individual values for 3 replicate determinations are shown in Appendices 16 and 17 respectively.

Figure 5.7: Effect of granule size on the drug release characteristics of diclofenac sodium from Eudragit® matrices



The drug release data showed that tablets from Batch NHH were unable to release diclofenac sodium slowly, with the complete dose being released in about 2 hours. Batch NH on the other hand was shown to retard drug release, and released diclofenac sodium in a controlled manner throughout the test. The faster release of drug from Batch NHH compared to that of Batch NH was due primarily to the difference in the size of the granules used in the respective batches. The larger granules may have resulted in more effective retardation of drug release due to greater bonding and consolidation of the drug particles with the Eudragit® polymer.

Therefore, based on the observations from the dissolution study, it was concluded that granules in the range 251-710 μm be selected for further investigations.

5.2.2.1.3 Optimal tablet hardness

Four lots of Batch NH were prepared and compressed to different hardnesses on an Erweka EKO tabletting machine. Tablet hardness was measured using the Pharma Test PTB tablet hardness tester. Tablet friability was determined as described in section 4.3.2.1.3 The friability values for the different lots of Batch NH are presented in Table 5.10.

Table 5.10: Friability of tablets of various lots of Batch NH compressed to different hardnesses

LOT PREPARATION OF BATCH NH	TABLET HARDNESS RANGE (Kp)	FRIABILITY (%)
NH (a)	3-4	1.73
NH (b)	4-5	0.93
NH (c)	6-7	0.77
NH (d)	9-10	0.59

The upper limit of acceptability of tablet friability was set at 1.5%. It is thus evident from Table 5.10 that compression of the tablet matrices to hardnesses below the range 4-5 Kp was not feasible, due to increased tablet friability. Therefore, in subsequent investigations, unless otherwise stated, all tablets were compressed to a hardness in the range 4-5 Kp.

5.3 IN-PROCESS QUALITY CONTROL TESTS

5.3.1 *DRUG CONTENT UNIFORMITY*

The USP XXIII (1995) limits for drug content uniformity are in the range 85-115% of the labelled claim. The drug content of all batches produced were within 15% of the theoretical drug content. It was therefore concluded that the drug was uniformly distributed within the tablet batches. The mean drug content as determined for each batch is reflected in Appendix 93.

5.3.2 *UNIFORMITY OF MASS*

The USPXXIII (1995) limits for weight variation are in the range 85-115%. All the tablets produced were within an acceptable mass range. The mean weight of ten tablets produced from each batch is presented in Appendix 94.

5.3.3 *FRIABILITY*

The friability of ten tablets from each batch is recorded in Appendix 95. The values were shown to be acceptable.

5.3.4 *UNIFORMITY OF TABLET THICKNESS, DIAMETER AND HARDNESS*

The thickness, diameter and hardness values for the various batches are recorded in Appendices 96.1, 96.2 and 96.3 respectively. All values were within an acceptable range.

5.4 INFLUENCE OF EUDRAGIT® POLYMER ON DRUG RELEASE

5.4.1 *INFLUENCE OF DIFFERENT TYPES OF EUDRAGIT® POLYMERS*

In order to determine the effects of the various types of Eudragit® polymers on drug release, they were added individually to tablet formulations. Tablets from each batch were subjected to dissolution testing. The drug release data from the dissolution studies are presented in Tables 5.11 and 5.12 and Figures 5.8 and 5.9 respectively.

Table 5.11: Mean cumulative drug release data for diclofenac sodium from tablets prepared with different types of Eudragit® polymers

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD				
	BATCH NRL	BATCH NRS	BATCH NL	BATCH NS	BATCH NN
0.5	14.10±0.90	10.45±0.87	49.17±3.67	74.52±4.17	93.58±2.45
1	20.80±1.18	13.82±0.92	86.11±2.99	99.35±0.48	99.43±0.79
1.5	26.95±1.19	18.56±1.40	98.45±0.21	99.99±1.20	100.69±0.05
2	34.24±2.04	22.82±1.04	99.11±0.33	100.85±1.23	100.97±0.22
3	46.18±1.69	27.58±1.33	98.97±0.33	101.47±0.08	101.43±0.20
4	58.30±1.57	33.41±1.63	99.73±0.01	101.89±0.18	101.90±0.06
5	68.39±1.90	38.27±1.61	100.11±0.30	102.59±0.26	102.50±0.21
6	78.16±1.47	43.99±1.48	100.96±0.37	103.07±0.14	102.72±0.29
7	83.05±1.88	49.85±1.48	101.52±0.12	103.25±0.37	103.04±0.25
8	88.13±2.39	54.87±1.52	102.03±0.15	103.91±0.11	103.56±0.09

* Individual values for 3 replicate determinations are shown in Appendices 18, 19, 20, 21 and 22 respectively.

Table 5.12: Mean release rates of diclofenac sodium from tablets prepared with different types of Eudragit® polymers

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)				
	BATCH NRL	BATCH NRS	BATCH NL	BATCH NS	BATCH NN
1	20.80±1.18	13.82±0.92	86.11±2.99	99.35±0.48	99.43±0.79
2	13.43±1.10	9.01±0.30	13.00±3.13	1.50±1.71	1.54±0.58
3	11.94±0.69	4.76±0.54	-0.13±0.12	0.63±1.26	0.46±0.41
4	12.12±0.41	5.83±0.30	0.75±0.33	0.42±0.12	0.47±0.19
5	10.09±0.83	4.86±0.13	0.39±0.29	0.70±0.44	0.60±0.21
6	9.77±0.84	5.71±0.82	0.84±0.33	0.47±0.25	0.22±0.48
7	4.89±0.73	5.86±0.54	0.56±0.28	0.18±0.27	0.32±0.05
8	5.08±0.99	5.02±0.43	0.51±0.19	0.66±0.38	0.52±0.17

* Individual values for 3 replicate determinations are shown in Appendices 68, 69, 70, 71 and 72 respectively.

Figure 5.8: Effect of different types of Eudragit® polymers on the drug release characteristics of diclofenac sodium

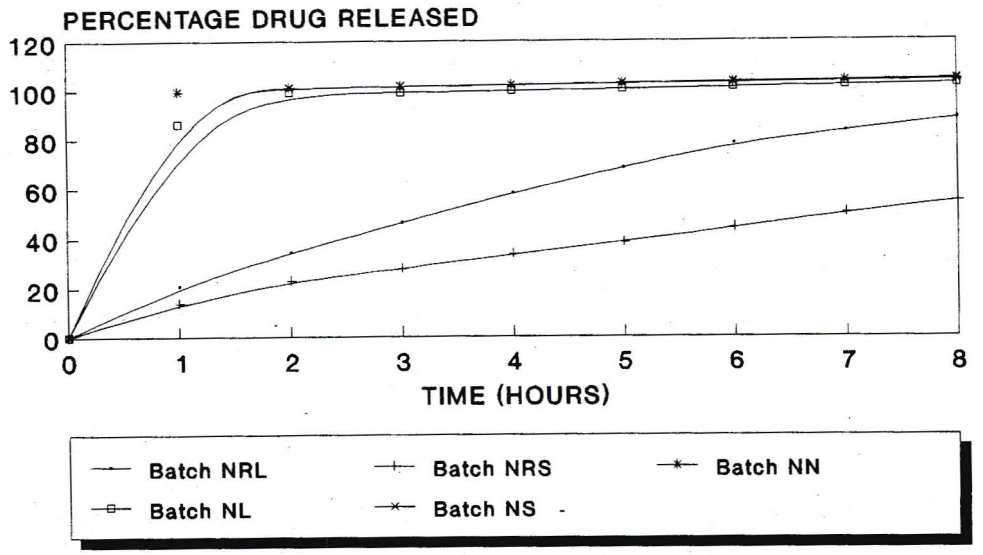
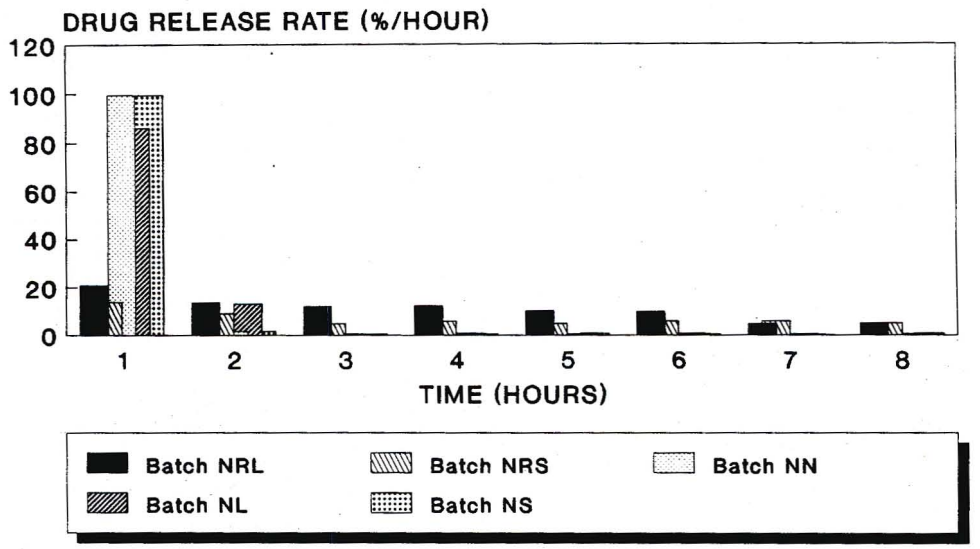


Figure 5.9: Release rates of diclofenac sodium from tablets containing different types of Eudragit® polymers



During the first hour, Batch NRS displayed an initial fast release of drug. The mean cumulative amount of drug released at the end of the second hour was 22.82±1.04%. From the second hour onwards however, drug release became slower, and remained so until the end of the test. Batch NRL also presented with an initial fast release of drug, 20.80±1.18% in one hour, followed by slower release until six hours. After the sixth hour, there was a further decline in drug release rates. A comparison of the drug release profiles of Batch NRL and Batch NRS showed that slower drug release was observed from the latter.

With Batch NL, 86.11±2.99% of the drug was released in the first hour, with almost the entire dose being released in one and a half hours. Drug release from Batch NS occurred even faster, with almost the entire dose being released in one hour. Batch NN showed even faster drug release, with more than 90% of the drug being released in thirty minutes.

From the above observations it was evident that the effect of polymer type on the retardation of drug release occurred in the following order:
Eudragit® RS > Eudragit® RL > Eudragit® L > Eudragit® S > Eudragit® NE.

The use of water soluble polymers (Eudragit® L, Eudragit® S and Eudragit® NE) resulted in water penetration of the matrix, hydration, and dissolution of the polymer and drug. In contrast, the water swellable polymers (Eudragit® RL and Eudragit® RS) retarded drug release. The retarding effect was more pronounced with Eudragit® RS due to its slightly permeable nature, compared to Eudragit® RL, which is freely permeable.

The greater retardant effect demonstrated by Eudragit® RS was attributed to the lower content of hydrophilic groups compared to Eudragit® RL, that contains a higher content of hydrophilic groups, thus rendering it highly permeable. Similar findings were reported by El-Fattah *et al.* (1984) for the release of pheniramine aminosalicylate from solid dispersions.

Although Eudragit® S and Eudragit® L have similar structural and solubility properties, Eudragit® L is more permeable than Eudragit® S (Table 2.11). However, matrices prepared with Eudragit® S (Batch NS) displayed faster drug release characteristics than matrices

prepared with Eudragit® L (Batch NL). These results are in keeping with those reported by Akbuga (1989), who demonstrated that formulations containing the Eudragit® S polymer released drug faster than formulations containing Eudragit® L. On the other hand, McGinity *et al.* (1983) and Alvarez *et al.* (1991) showed that Eudragit® L matrices had the ability to release drug faster than Eudragit® S matrices. They also demonstrated that Eudragit® RL matrices did not retard drug release to the same extent as the Eudragit® RS matrices.

Cameron and McGinity (1987) formulated matrix tablets using a combination of Eudragit®L and Eudragit® RS. The loss of retardant effect in basic media (phosphate buffer pH 7.4) was attributed to the higher solubility (above pH 6), of the Eudragit® L polymer. The dissolution of the Eudragit® L polymer resulted in a porous matrix which broke apart more readily upon agitation, with the net result being a faster release of drug than observed for Eudragit® RS.

Based on the above investigations, and with reference to a review of the literature, it was concluded that the permeability and solubility characteristics of the various types of Eudragit® polymers are the determining factors in controlling drug release.

5.4.2 *INFLUENCE OF EUDRAGIT® RL AND EUDRAGIT® RS CONCENTRATIONS*

A comparison of the drug release data from studies conducted with formulations containing different concentrations of Eudragit® RL and Eudragit® RS polymers is presented in Tables 5.13 and 5.14 and Figures 5.10 and 5.11 respectively.

Table 5.13: Mean cumulative drug release data for diclofenac sodium from tablets prepared with different concentrations of Eudragit® RL and Eudragit® RS

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD				
	BATCH RLRS21	BATCH RLRS12	BATCH NH	BATCH NRL	BATCH NRS
0.5	13.46±0.68	15.80±1.40	12.85±0.21	14.10±0.90	10.54±0.87
1	20.69±0.99	19.32±0.80	17.29±1.29	20.80±1.18	13.82±0.92
1.5	29.47±1.58	25.82±1.77	20.73±0.55	26.95±1.19	18.56±1.40
2	36.69±1.85	30.22±1.73	29.37±1.31	34.24±2.04	22.82±1.04
3	46.95±2.20	39.86±1.71	38.85±2.03	46.18±1.69	27.58±1.33
4	55.69±2.14	49.52±1.80	47.64±2.02	58.30±1.57	33.41±1.63
5	62.44±1.98	57.60±1.80	57.26±2.59	68.39±1.90	38.27±1.61
6	70.72±1.72	64.93±2.27	64.35±3.04	78.16±1.47	43.99±1.48
7	76.49±2.06	71.31±2.60	74.34±2.51	83.05±1.88	49.85±1.48
8	82.64±1.84	76.31±2.14	81.80±1.23	88.13±2.39	54.87±1.52

* Individual values for three replicate determinations are shown in Appendices 23, 24, 17, 18 and 19 respectively.

Figure 5.14: Mean release rates of diclofenac sodium from tablets prepared with different concentrations of Eudragit® RL and Eudragit® RS

TIME (HOURS)	* MEAN DRUG RELEASE RATES (%/HOUR)				
	BATCH RLRS21	BATCH RLRS12	BATCH NH	BATCH NRL	BATCH NRS
1	20.69±0.99	19.32±0.80	17.29±1.29	20.80±1.18	13.82±0.92
2	15.99±1.08	10.90±0.96	12.08±0.77	13.43±1.10	9.01±0.30
3	10.27±0.45	9.64±0.55	9.48±1.85	11.94±0.69	4.76±0.54
4	8.74±0.37	9.67±0.25	8.80±0.48	12.12±0.41	5.83±0.30
5	6.76±0.36	8.07±0.01	9.61±1.75	10.09±0.83	4.86±0.13
6	8.28±0.33	7.33±1.13	7.10±0.92	9.77±0.84	5.71±0.82
7	5.77±0.34	6.38±0.70	10.08±2.10	4.89±0.73	5.86±0.54
8	6.15±0.65	5.00±0.71	7.37±2.10	5.08±0.99	5.02±0.43

* Individual values for three replicate determinations are shown in Appendices 73, 74, 67, 68 and 69 respectively.

Figure 5.10: Effect of Eudragit[R]RL and RS concentrations on the drug release characteristics of diclofenac sodium

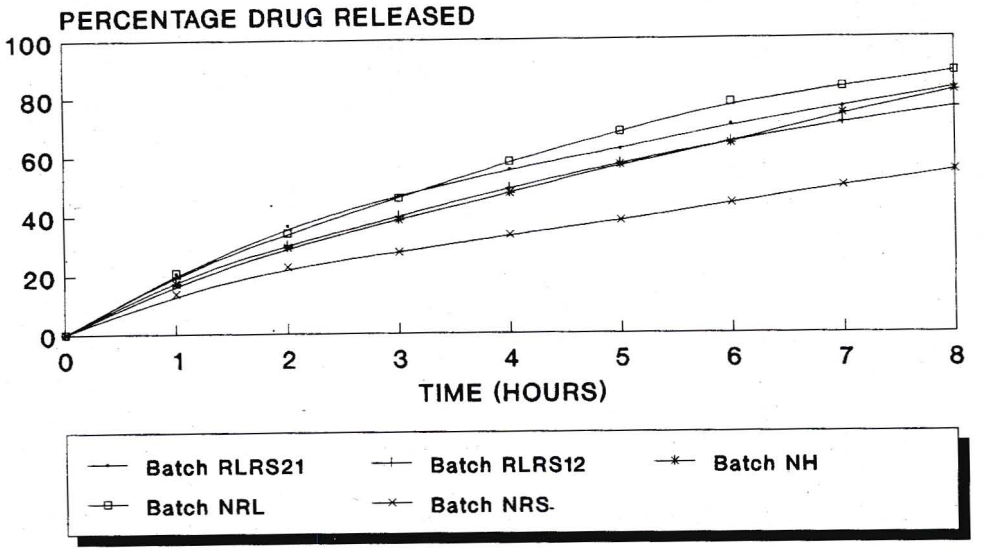
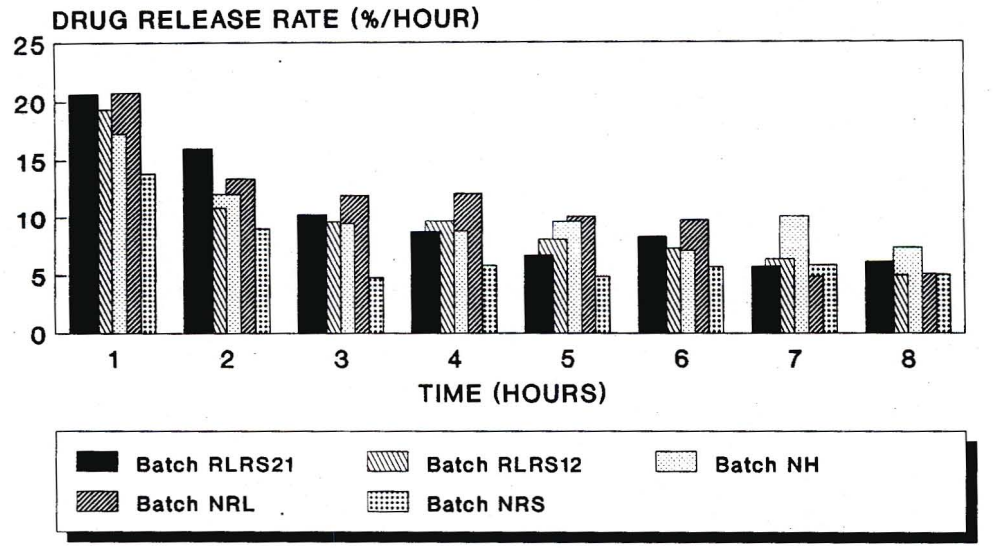


Figure 5.11: Release rates of diclofenac sodium from tablets with different concentrations of Eudragit[R]RL and RS



Batch RLRS21 was formulated to contain twice the concentration of Eudragit® RL as compared to Batch NH. The concentration of Eudragit® RS in both formulations was the same. Any differences in drug release between Batch RLRS21 and Batch NH were therefore justifiably attributed to Eudragit® RL. It is evident from the graphical representation of the dissolution data that faster drug release occurred from Batch RLRS21. On the other hand, a comparison of the profiles of Batch RLRS21 and Batch NRL showed that Batch NRL released diclofenac sodium even faster than Batch RLRS21. While Batch RLRS21 and Batch NRL were formulated to contain the same concentrations of Eudragit® RL, the difference in the formulation of these two batches was the absence of Eudragit® RS in Batch NRL. It was therefore argued that the differences in drug release between these two batches were due to the presence of Eudragit® RS in Batch RLRS21.

While Batch RLRS12 and Batch NH contained the same concentration of Eudragit® RL, Batch RLRS12 contained twice the concentration of Eudragit® RS than Batch NH. As anticipated, drug release from Batch NH occurred faster than from Batch RLRS12. Batch NRS contained no Eudragit® RL, but had the same concentration of Eudragit® RS as Batch RLRS12. Drug release from Batch NRS was shown to be markedly slower than drug release from Batch RLRS12.

Based on these findings, it was concluded that drug release from the tablets could be controlled by varying the concentrations of the Eudragit® RL and Eudragit® RS polymers. The increased release of diclofenac sodium from formulations containing increased concentrations of Eudragit® RL and the decrease in drug release from formulations containing increased concentrations of Eudragit® RS were due to the greater permeability of Eudragit® RL compared to Eudragit® RS. The Eudragit® RS-type polymer was reported to be less permeable to gastric juice than the Eudragit® RL-type, due to the lower content of quaternary ammonium groups of the latter (Efentakis *et al.*, 1990).

Alvarez *et al.* (1991) formulated matrix tablets with Eudragit® polymers. The findings of their study indicated that the high content of quaternary ammonium groups attached to the polymer backbone made the matrix produced from Eudragit® RL too water sensitive to effectively control drug release, whereas Eudragit® RS markedly retarded drug release.

Oth and Moës (1989) formulated solid dispersions using Eudragit® polymers. They reported that a highly water-soluble polymer can be used to increase the permeability of Eudragit RS to water and to modify the release profiles. By changing the Eudragit® RL and Eudragit® RS concentrations, they were also able to manipulate drug release. An increase in Eudragit® RL content improved drug release. Similarly, Malamataris and Avgerinos (1990) demonstrated that modulation of drug release can be achieved by using Eudragit® RL in conjunction with Eudragit® RS.

An increase in Eudragit® RL concentration, with a subsequent increase in drug release, due to the highly permeable nature of Eudragit® RL, was also described by El-Fattah *et al.*, (1984) and Abdel-Rahman *et al.*, (1992).

In conclusion, the present study demonstrated that, within the chosen polymer concentration ranges, drug release was directly proportional to the concentration of Eudragit® RL and inversely proportional to the concentration of Eudragit® RS in the tablet matrix.

5.5 SELECTION OF A DICLOFENAC SODIUM EUDRAGIT® MATRIX FORMULATION

The reference standard used in the present study was Veltex® 100 CR. *In vitro* dissolution studies on Veltex® 100 CR indicated a first-order drug release profile, with 81.11±0.02% drug dissolved at the end of the 12 hour study. The amounts of drug released at the end of the first and eighth hours were 14.47±0.48 and 67.42±0.19% respectively.

In the present study, numerous formulations were considered for the preparation of various batches of diclofenac sodium Eudragit® matrix tablets. A multitude of drug release profiles were obtained from the *in vitro* dissolution studies that the different batches were subjected to. It was not the intention of the researcher to select a formulation that would simulate the drug release behaviour of Veltex® 100 CR, although it was initially selected for use as a reference, since drug release occurred very slowly from this commercially available preparation.

At the time of the study, there were no Compendial specifications on which to model the drug release behaviour of diclofenac sodium from modified release dosage forms. The dissolution parameters for the study were selected after an extensive literature review and careful consideration. The reference and test products were subjected to similar conditions, hence the selection of a particular batch was based on the percentage drug released at the end of the first and eighth hours, since all studies were conducted over a minimum period of 8 hours.

A review of the literature has indicated that researchers formulating modified release drug delivery systems aim to achieve between 20-30% and 80-90% drug release at the end of the first and eighth hours respectively. Pillay (1996) formulated a modified release calcium alginate drug delivery system that released 28±1.23% of the drug in the first hour, and more than 90% of the drug at eight hours, with total drug release being achieved at the end of the 12 hour period. Govender (1992) also formulated a modified release drug delivery system of salbutamol sulphate that released 22.45±1.55% and almost 80% of the drug at eight hours. Batch NH displayed drug release characteristics that were in keeping with the trend followed by these researchers. With Batch NH, 17.29±1.29% and 81.80±1.23% drug release was observed at the end of the first and eighth hours respectively.

The other factor that had to be taken into consideration when selecting a formulation was gastrointestinal transit time. The gastrointestinal tract presents some unusual features that are not present in the other routes of drug administration. The relatively brief transit time through the gastrointestinal tract, approximately 12 hours, constrains the length of prolongation that can be expected. The variability in stomach emptying time and the chemical conditions of the stomach are additional limiting factors in the choice of prolonging mechanisms for this route. The variable nature of the chemical environment throughout the length of the gastrointestinal tract and the variable absorbing surface are further constraints on dosage form design (Ballard, 1982). The mean transit time for a tablet from the mouth to the stomach is about 4-6 hours, and from the stomach to caecum about 3-4 hours (Davis *et al.*, 1984). The length of time the dosage form remains in the colon is influenced by defaecation, and can be as long as 20 hours. Absorption of substances does occur in the colon, but is limited due to the poor surface area characteristics of the region (Marriott,

1989). Some dosage forms (e.g. matrix tablets), that remain intact in the gastrointestinal tract, have an average effective absorption time of 9-12 hours after administration. The release rate of drug from the dosage form must therefore be programmed accordingly. Hence, slower release rates run the risk of poor bioavailability (Gibaldi, 1991).

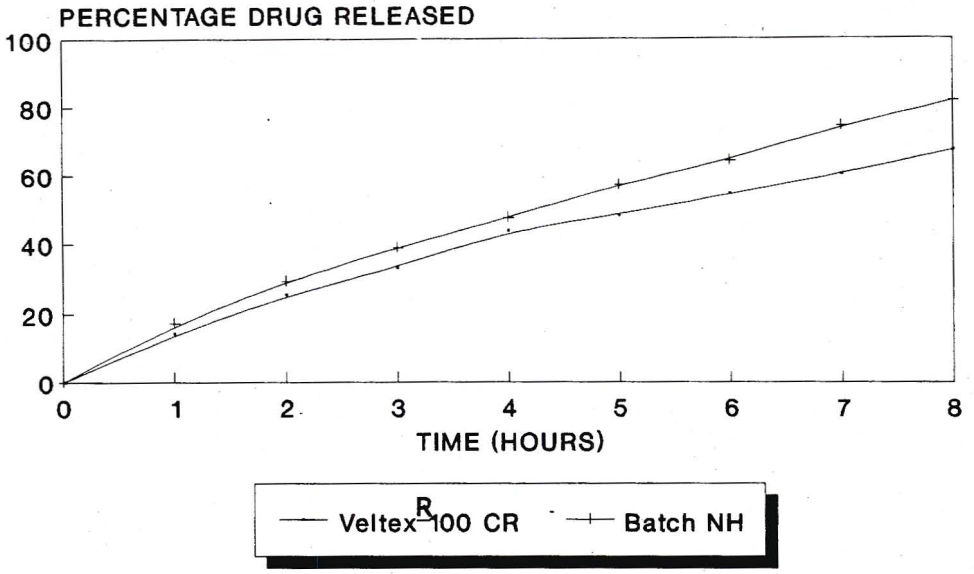
Since the oro-caecal transit time is short and is affected markedly only by gastric emptying, a formulation was selected that would ensure total drug release. Hence, no wastage of the drug in the dosage form would occur. However, controlled *in vivo* studies need to be undertaken to ensure that this would indeed occur with the dosage form selected for investigation in the present study.

Danckwerts and van der Watt (1995) formulated a novel oral core-in-cup drug delivery system that released drug at a zero-order rate for up to 18 hours. However, they realised that this is too long for an oral system, as gastrointestinal transit time is not much longer than 12 hours on average.

These studies further endorsed the researcher's efforts in the present study to formulate a product that would release drug at a faster, but predetermined, rate than the reference. Consequently, the formulation described for Batch NH was selected as the most appropriate for later use to investigate the integrity of the technique used in the present study.

The *in vivo* drug release data of Batch NH are presented in Table 5.9, while the data for Veltex® 100 CR are recorded in Table 5.1. A comparative illustration of the drug release characteristics from Batch NH and Veltex® 100 CR is presented in Figure 5.12.

Figure 5.12: Comparison of drug release from Veltex^{R}100 CR capsules and tablets of Batch NH



5.6 REPRODUCIBILITY STUDY

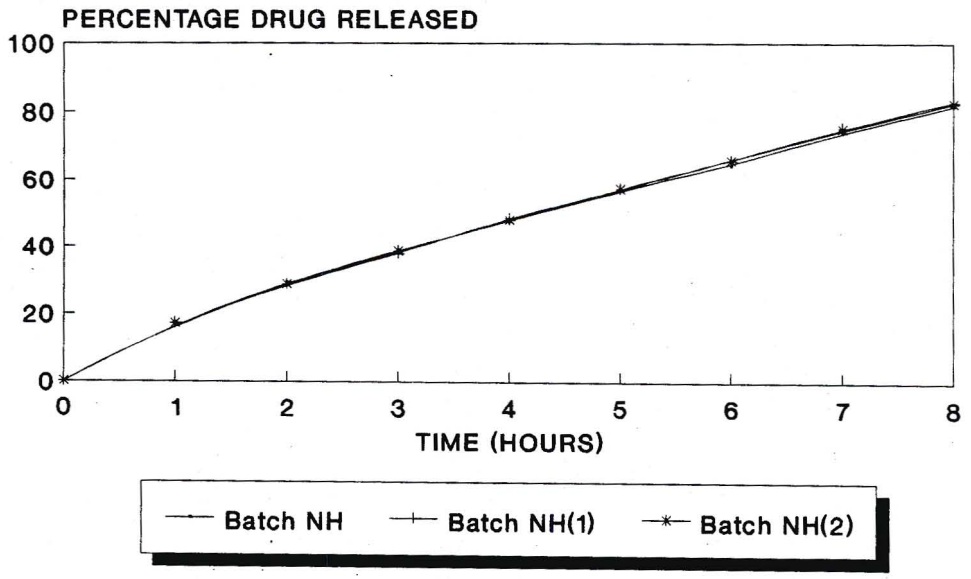
A reproducibility study was conducted on the lots of batches prepared as described by the formulation NH. The dissolution data of Lots NH(1) and NH(2) were compared to those of Batch NH, which served as a control. The dissolution data and profiles are outlined in Table 5.15 and Figure 5.13.

Table 5.15: Mean cumulative percentages of diclofenac sodium released from lots of Batch NH prepared for the reproducibility study

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	BATCH NH	BATCH NH(1)	BATCH NH(2)
0.5	12.85±0.21	12.63±0.50	12.97±0.38
1	17.29±1.29	17.24±1.27	17.23±0.98
1.5	20.73±0.55	20.76±0.98	21.18±1.00
2	29.37±1.31	28.73±2.14	28.80±2.20
3	38.85±2.03	37.94±1.84	38.60±1.80
4	47.64±2.02	48.58±2.19	48.01±1.83
5	57.26±2.59	57.47±2.41	57.43±2.13
6	64.35±3.04	65.90±3.33	65.87±2.83
7	74.43±2.51	75.52±2.63	75.12±2.53
8	81.80±1.23	83.05±1.65	82.53±1.69

* Individual values for three replicate determinations are shown in Appendices 17, 25 and 26 respectively.

Figure 5.13: Comparison of the drug release profiles of Batches NH(1) and NH(2) with the control, Batch NH



The dissolution data in Table 5.15 indicated the intra- and inter-batch variations to be within an acceptable range. Statistical analyses of the data (Appendix 97) using the Analysis of Variance (ANOVA) test revealed that the upper 95% confidence limit observed was below 5%. It was thus concluded that the differences among the preparations were within the maximum allowable limit of 5%. Such differences are considered to be statistically and pharmaceutically insignificant.

Therefore, by way of graphical and statistical analyses, it was concluded that the technique investigated in the present study was reproducible in its application.

5.7 *IN VITRO* DISSOLUTION STUDIES

5.7.1 *INFLUENCE OF DISSOLUTION METHODS*

The dissolution characteristics of diclofenac sodium from tablets of Batch NH were investigated using the rotating paddle, rotating basket and rotating bottle dissolution methods. The tests were conducted at 50 rpm so as to quantitatively assess and compare drug release using each of the different methods. The dissolution data obtained are presented in Tables 5.16 and 5.17 and Figures 5.14 and 5.15 respectively.

Table 5.16: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH using different dissolution methods

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	ROTATING PADDLE	ROTATING BASKET	ROTATING BOTTLE
0.5	14.34±1.08	8.75±0.29	78.94±2.20
1	18.07±1.17	11.35±1.12	83.09±2.68
1.5	22.89±1.13	14.51±0.52	85.81±2.32
2	26.32±1.01	18.64±0.44	89.64±1.03
3	30.73±1.56	22.72±0.70	96.00±1.01
4	35.67±1.69	26.76±1.31	99.98±0.60
5	39.52±1.56	30.10±1.53	100.72±0.51
6	42.80±1.16	33.41±1.09	101.49±0.18
7	47.86±0.97	35.74±1.07	101.61±0.22
8	51.73±1.59	40.18±1.62	101.72±0.08

* Individual values for 3 replicate determinations are shown in Appendices 27, 28 and 29 respectively.

Table 5.17: Mean drug release rates of diclofenac sodium from tablets of Batch NH using different dissolution methods

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	ROTATING PADDLE	ROTATING BASKET	ROTATING BOTTLE
1	18.07±1.17	11.35±1.12	83.09±2.68
2	8.25±0.37	7.10±0.90	6.55±3.62
3	4.41±0.70	4.27±0.52	6.36±0.90
4	4.94±0.44	4.04±1.18	3.99±1.09
5	3.85±0.17	3.34±1.16	0.74±0.49
6	3.27±0.42	3.31±0.93	0.77±0.68
7	5.06±0.36	2.33±0.36	0.11±0.12
8	3.87±0.62	4.44±1.01	0.11±0.14

* Individual values for 3 replicate determinations are shown in Appendices 75, 76 and 77 respectively.

Figure 5.14: Effect of different dissolution methods on the drug release characteristics of diclofenac sodium

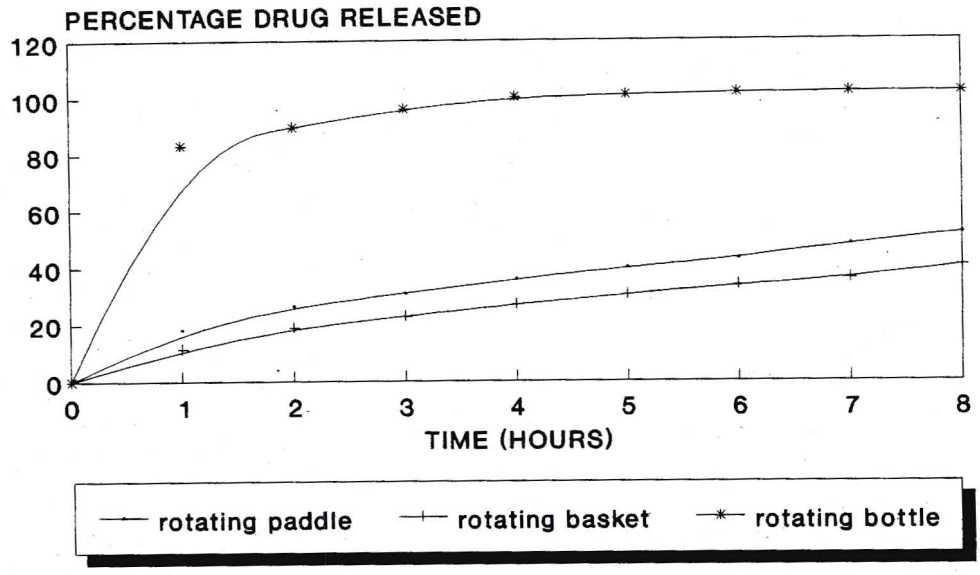
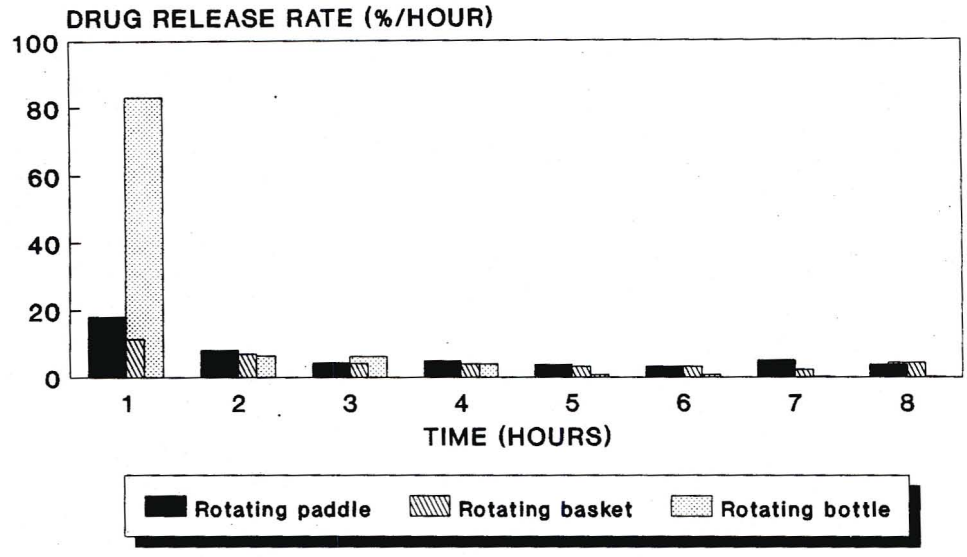


Figure 5.15: Release rates of diclofenac sodium from tablets of Batch NH using different dissolution methods



It was observed that the application of different dissolution methods produced significantly different drug release profiles at 50 rpm.

Drug release using the rotating bottle apparatus was significantly faster when compared with that of the rotating paddle and rotating basket methods. With the rotating bottle apparatus, approximately 80% drug release was observed in the first hour. On visual inspection, it was noted that the tablets had almost completely disintegrated in two hours. However, almost total drug dissolution was only observed at 4 hours. With the rotating paddle method, drug release during the first two hours occurred at a faster rate than in the remainder of the test. However, from the second hour onwards, drug release became slower and almost constant. A similar effect was observed with the rotating basket method. Drug release during the first two hours occurred at a faster rate than in the remainder of the test. However, a comparison of the release rates between the rotating paddle and rotating basket methods showed that in the first hour, drug release occurred at a faster rate with the rotating paddle method, but thereafter, the drug release rates were almost comparable.

The rotating bottle apparatus was considered an unsuitable method for assessing the drug release characteristics from the tablet matrices. The violent agitation afforded by the rotating bottle apparatus caused the tablets to break up into smaller fragments within two hours.

It was thus evident that drug release did not remain constant as the dissolution method was varied; and it was therefore concluded that the dissolution method employed would impact significantly on drug release. Drug release is therefore a function of the dissolution method.

5.7.2 *INFLUENCE OF AGITATION RATES*

The influence of various agitation rates using the rotating paddle and rotating basket dissolution methods was also investigated. The drug release data for the different agitation rates within each method are presented in Tables 5.18, 5.19, 5.20 and 5.21 and Figures 5.16, 5.17, 5.18 and 5.19 respectively.

Table 5.18: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH at different agitation rates using the rotating paddle apparatus

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	50 rpm	100 rpm	150 rpm
0.5	14.34±1.08	12.85±0.21	12.66±1.95
1	18.07±1.17	17.29±1.29	20.64±2.33
1.5	22.89±1.13	20.73±0.55	28.45±1.87
2	26.32±1.01	29.37±1.31	40.00±2.46
3	30.73±1.56	38.85±2.03	58.27±1.82
4	35.67±1.69	47.64±2.02	70.99±1.92
5	39.52±1.56	57.26±2.59	79.12±2.84
6	42.80±1.16	64.35±3.04	85.65±1.09
7	47.86±0.97	74.43±2.51	91.72±1.73
8	51.73±1.59	81.80±1.23	98.39±1.63

* Individual values for 3 replicate determinations are presented in Appendices 27, 30 and 31 respectively.

Table 5.19: Mean release rates of diclofenac sodium from tablets of Batch NH at different agitation rates using the rotating paddle apparatus

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	50 rpm	100 rpm	150 rpm
1	18.07±1.17	17.29±1.29	20.64±2.33
2	8.25±0.37	12.08±0.77	19.36±0.14
3	4.41±0.70	9.48±1.85	18.26±0.64
4	4.94±0.44	8.80±0.48	12.72±0.16
5	3.85±0.17	9.61±1.75	8.13±1.13
6	3.27±0.42	7.10±0.92	6.53±1.79
7	5.06±0.36	10.08±2.10	6.07±0.68
8	3.87±0.62	7.37±2.10	6.68±1.91

* Individual values for 3 replicate determinations are presented in Appendices 75, 78 and 79 respectively.

Table 5.20: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH at different agitation rates using the rotating basket apparatus

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	50 rpm	100 rpm	150 rpm
0.5	8.75±0.29	9.14±0.67	21.26±1.50
1	11.35±1.12	14.04±1.21	31.18±1.79
1.5	14.51±0.52	17.62±1.46	37.14±1.85
2	18.64±0.44	21.77±1.62	43.62±1.45
3	22.72±0.70	29.21±1.69	49.98±1.85
4	26.76±1.31	37.03±1.79	55.89±1.86
5	30.10±1.53	43.43±2.09	62.56±2.19
6	33.41±1.09	50.17±2.31	68.91±1.85
7	35.74±1.07	55.59±1.74	74.43±2.07
8	40.18±1.62	60.26±2.12	80.30±1.60

* Individual values for 3 replicate determinations are shown in Appendices 28, 32 and 33 respectively.

Table 5.21: Mean release rates of diclofenac sodium from tablets of Batch NH at different agitation rates using the rotating basket apparatus

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	50 rpm	100 rpm	150 rpm
1	11.35±1.12	14.04±1.21	31.18±1.79
2	7.10±0.90	7.73±0.90	12.44±0.34
3	4.27±0.52	7.44±0.97	6.36±0.41
4	4.04±1.18	7.82±0.39	5.91±0.02
5	3.34±1.16	6.39±0.41	6.67±0.84
6	3.31±0.93	6.75±0.22	6.35±1.20
7	2.33±0.36	5.41±0.60	5.52±0.96
8	4.44±1.01	4.68±0.46	5.88±0.60

* Individual values for 3 replicate determinations are shown in Appendices 76, 80 and 81 respectively.

Figure 5.16: Effect of the rotating paddle agitation rate on the release characterictics of diclofenac sodium

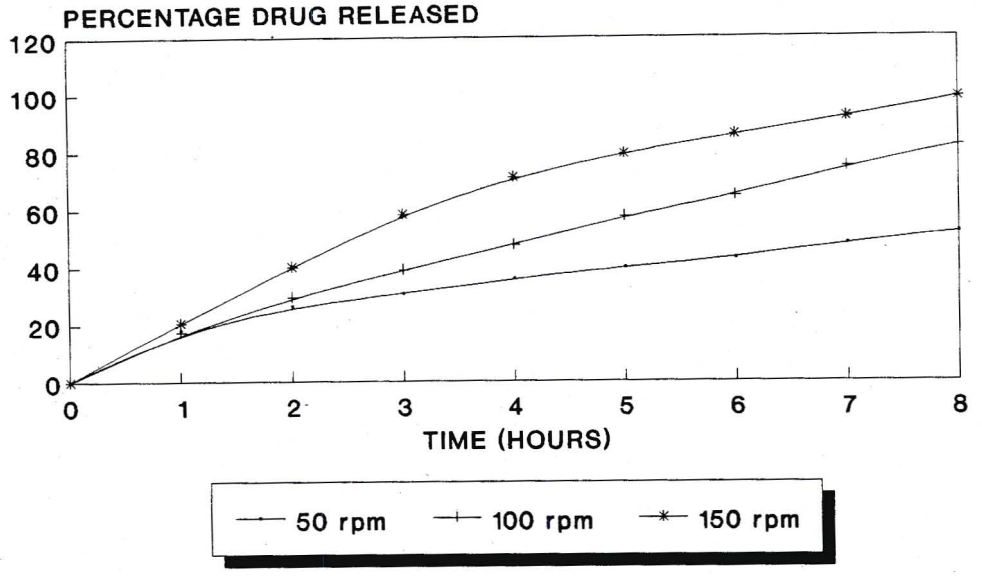


Figure 5.17: Release rates of diclofenac sodium from tablets of Batch NH using various rotating paddle agitation rates

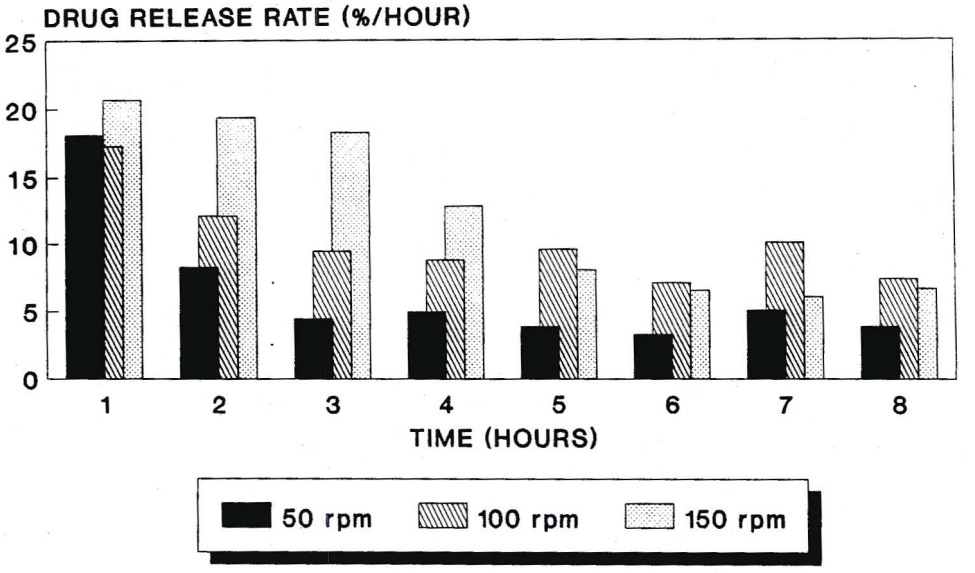


Figure 5.18: Effect of the rotating basket agitation rate on drug release characteristics of diclofenac sodium

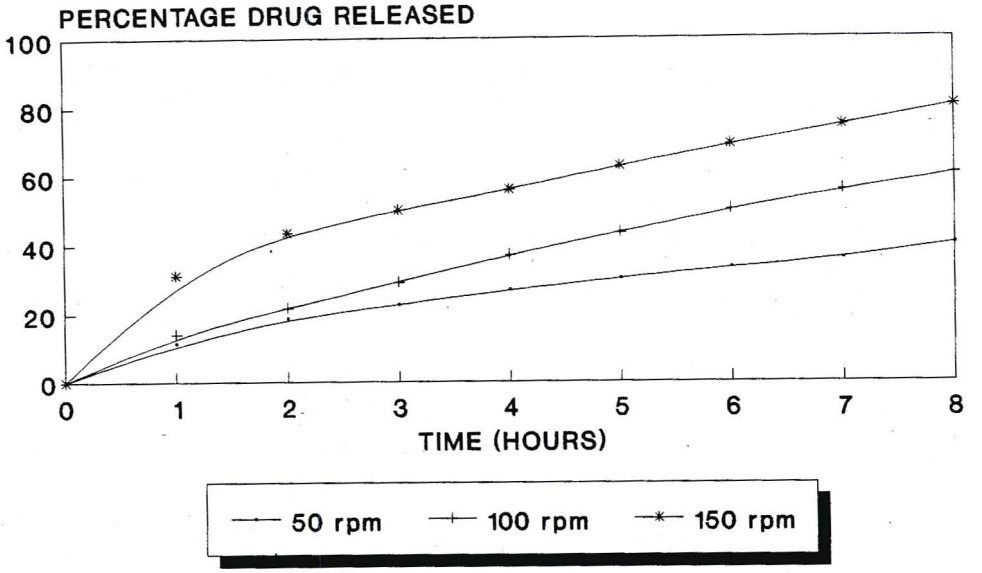
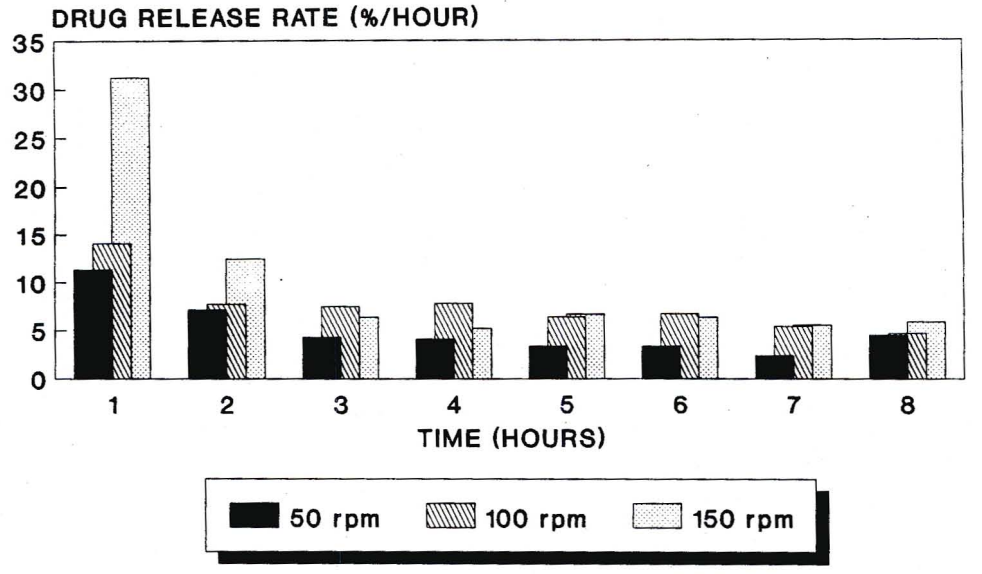


Figure 5.19: Release rates of diclofenac sodium from tablets of Batch NH using various rotating basket agitation rates



It was demonstrated that with an increase in agitation rate, there was an increase in drug release from tablets subjected to dissolution testing using the rotating paddle and rotating basket methods. A comparison of the drug release data from the tablets of Batch NH that were subjected to different rotating paddle agitation rates showed that there were very small differences in the amount of drug released at one hour. At two hours, the difference in the amount of drug released between the 50 and 100 rpm agitation rates was $3.05 \pm 2.32\%$, while the difference in drug release between 100 and 150 rpm at two hours was $10.63 \pm 3.34\%$. However, from the third hour onwards, drug release at 100 rpm occurred at a faster rate compared to drug release at 50 rpm. A comparison of the drug release rates at 100 rpm and 150 rpm showed that until the fourth hour, drug release occurred at a faster rate with the higher agitation rate, and thereafter, the drug release rates became slower and almost comparable to those at 100 rpm.

With the rotating basket apparatus, at the one hour and two hour sampling intervals, there was a $2.69 \pm 0.81\%$ and $3.32 \pm 1.33\%$ difference in drug release between the 50 and 100 rpm agitation rates respectively. From the third hour onwards, the differences in drug release became greater. With the 150 rpm agitation speed however, there was an almost two-fold increase in drug release at the first and second hour sampling intervals, compared to the 100 rpm agitation speed. At the end of the eighth hour, the difference in the amount of drug released between the agitation rates 50 and 100 rpm, and 100 and 150 rpm was approximately 20%.

Similar findings were reported by Bain *et al.* (1991) who observed that at high rotation speeds (200-250 rpm) diclofenac sodium wax matrix tablets bounced around inside the basket or moved about vigorously under the paddle, resulting in increased tablet surface erosion. A combination of diffusion of drug through tortuous pores (causing an increase in pore volume) with the erosion of the matrix surface (causing a shortening of diffusional path lengths) was offered as an explanation for the increased rate of drug release. On the other hand, Miyagawa *et al.* (1996), showed that drug release from diclofenac sodium wax matrix granules occurred independently of the agitation rate. Drug release within the range 50-200 rpm was shown to be constant with the rotating paddle method. It was found that introducing tablets into a basket during agitation can lead to the mesh acting as a

'cheesegrater', thereby leading to increased release rates through tablet erosion (Gould, 1983).

Lin and Lin (1993) studied the influence of agitation rates on the release of theophylline from Eudragit® matrix tablets. They observed that faster drug release occurred at higher agitation speeds.

Dissolution studies of spiramycin also showed that faster dissolution was observed at higher agitation rates (Veiga and Alvarez de Eulate, 1994). Similarly, Malamataris and Ganderton (1991) showed an increase in drug release with an increase in agitation rate.

The influence of agitation rate on the release of diclofenac sodium from hydroxypropyl methyl cellulose (HPMC) and wax tablets was studied by Chetty *et al.* (1994). They found that drug release from the HPMC tablets was not affected by changes in agitation, while drug release from the wax tablets was affected markedly at higher agitation rates (200 rpm) due to disintegration of the dosage form. Fassihi and Ritschel (1993) also demonstrated that drug release from multiple layer tablets occurred independently of the agitation rate. Bansal *et al.* (1993) also showed drug release to be independent of rotational speed.

Therefore, it was concluded that the increase in drug release with an increase in agitation rate for both the methods could be attributed to an increase in the rate of erosion of the matrix with a subsequent loss of matrix integrity:

- with the rotating paddle apparatus, the tablets moved about in the dissolution flask more vigorously as the agitation rate was increased, which led to increased erosion of the surface of the tablet resulting in more rapid drug release; and
- with the rotating basket apparatus, there was increased tablet erosion as the agitation rate was increased due to the mesh of the basket acting as a 'grater'. This was confirmed by a conical heap of powder (as a consequence of erosion from the tablet) that formed at the bottom of the vessel.

5.7.3 *INFLUENCE OF pH OF MEDIA*

The *in vitro* drug release characteristics of diclofenac sodium from the tablets of Batch NH were investigated in buffers of varying pH (hydrochloric acid buffer pH 1.5 and phosphate buffers pH 4.5; 6.2; 6.8; 7.5 and 8). The mean drug release data and the dissolution profiles obtained are presented in Table 5.22 and Figure 5.20 respectively. The drug release rate constant in each of the different media, according to zero-order release kinetics, is presented in Table 5.23 and a plot of the respective curves is shown in Figure 5.21.

Table 5.22: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH in buffer solutions of various pH levels

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD					
	pH 1.5	pH 4.5	pH 6.2	pH 6.8	pH 7.5	pH 8
0.5	0.41±0.05	0.51±0.05	5.73±0.46	12.85±0.21	19.58±2.52	27.50±1.77
1	0.25±0.10	0.52±0.06	6.34±0.21	17.29±1.29	31.50±2.58	40.09±1.90
1.5	0.40±0.08	0.62±0.03	7.27±0.05	20.73±0.55	41.68±2.21	53.62±2.62
2	0.44±0.02	0.78±0.04	8.44±0.25	29.37±1.31	51.95±2.45	65.30±2.60
3	0.76±0.25	0.88±0.03	11.52±0.55	38.85±2.03	66.71±3.57	85.66±2.77
4	0.89±0.19	1.18±0.04	14.88±0.46	47.64±2.02	81.38±2.97	97.56±2.06
5	0.95±0.11	1.15±0.02	17.77±0.18	57.26±2.59	88.08±1.91	101.33±0.16
6	0.95±0.08	1.17±0.01	20.47±0.36	64.35±3.04	95.81±1.78	101.94±0.17
7	0.93±0.07	1.32±0.13	23.40±0.38	74.43±2.51	101.12±0.31	102.44±0.26
8	0.97±0.03	1.37±0.04	25.57±0.42	81.80±1.23	101.88±0.24	102.93±0.08

* Individual values for 3 replicate determinations are shown in Appendices 34, 35, 36, 37, 38 and 39 respectively.

Table 5.23: Influence of pH on the zero-order drug release rate constant of diclofenac sodium from tablets of Batch NH

pH OF DISSOLUTION MEDIUM	RELEASE RATE CONSTANT (K) ($HOUR^{-1}$)	r^2
1.5	0.113	0.816
4.5	0.143	0.860
6.2	2.960	0.984
6.8	9.740	0.987
7.5	15.276	0.945
8.0	23.328	0.951

Figure 5.20: Effect of pH on the drug release characteristics of diclofenac sodium from tablets of Batch NH

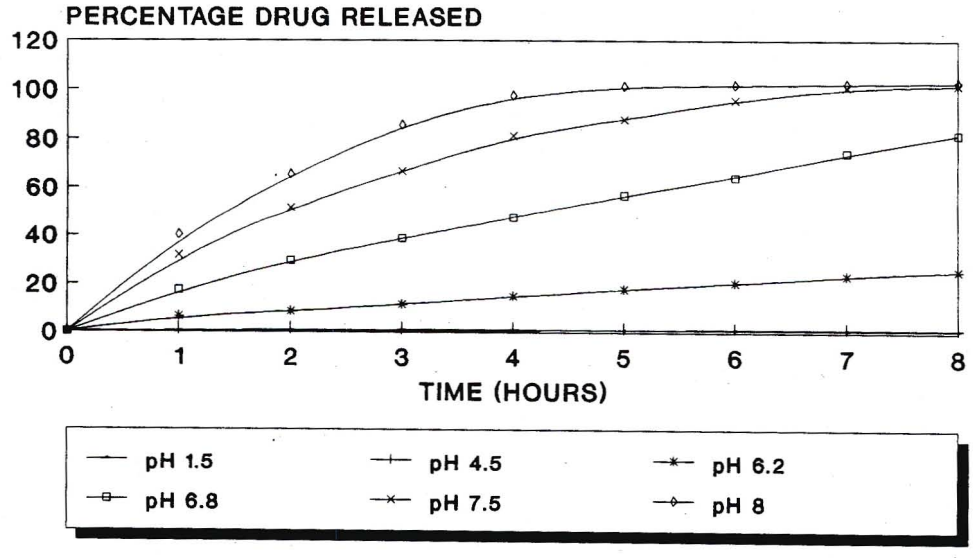
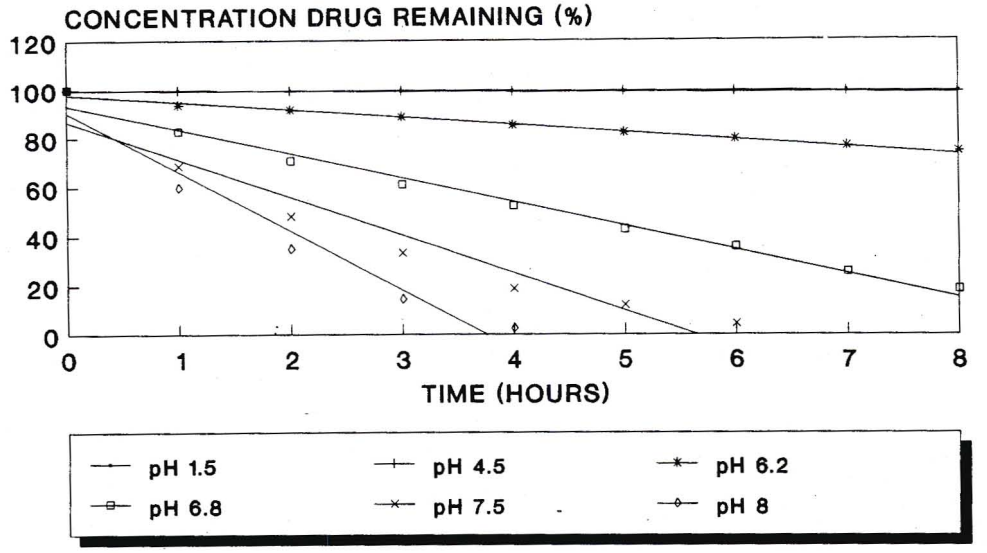


Figure 5.21: Determination of the zero-order rate constants of diclofenac sodium in different pH conditions



The dissolution data of the pH studies presented in Table 5.22 and Figure 5.20 demonstrated the influence of pH on drug release from the Eudragit® matrices. Hydrochloric acid buffer pH 1.5 markedly suppressed the release of diclofenac sodium from the tablets of Batch NH, with a total amount of 0.97 ± 0.03% drug released at the end of 8 hours. A similar effect was observed with the phosphate buffer pH 4.5, with a mean total of 1.37 ± 0.04% drug released in 8 hours. As the pH of the medium was further increased, markedly increased drug release patterns were observed. With phosphate buffer pH 6.2, approximately 25% of the drug was released in 8 hours, in comparison with the phosphate buffer pH 6.8, where the amount of drug released at the end of the eighth hour was more than three-fold, compared to that for the pH 6.2 buffer. A 0.6 difference in pH (i.e. between pH 6.2 and 6.8) produced markedly increased drug release characteristics. Drug release in phosphate buffer pH 8 and pH 7.5 was also increased, when compared to pH 6.8. Total drug release was observed at 5 and 7 hours with buffers at pH 8 and 7.5 respectively.

Both Eudragit® RL and Eudragit® RS possess permeability characteristics that are independent of the pH of the media (Table 2.11). Consequently, it was postulated that the

drug release behaviour from the tablets in the various media was due to the influence of pH on drug solubility.

Since the *in vitro* dissolution rate of a drug is a function of the drug solubility (Doherty and York, 1989), the improved drug release observed as the pH of the medium increased was due to the insolubility of diclofenac sodium at low pH levels. Diclofenac sodium has a pKa of 4 (section 3.2). The drug will thus become more soluble as the pH is increased beyond 4. Figure 3.2 depicts the solubility of diclofenac sodium as a function of pH. The pH dependent solubility of diclofenac sodium has been well documented. Chetty *et al.* (1994) reported similar changes in diclofenac sodium solubility with pH. These co-workers also concluded that the dissolution of diclofenac sodium is a function of its solubility at various pH levels.

The characterisation of a dosage form over the full range of physiological pH values has been regarded as essential (Skelly *et al.*, 1990). Numerous studies have reported on the influence of the pH of the dissolution media on drug release.

Van Wilder *et al.* (1991) evaluated drug release from modified release formulations containing diclofenac sodium in buffers of varying pH levels. Drug release was found to be strongly medium dependent, with faster dissolution at higher pH levels.

This type of drug release behaviour was further highlighted in a study showing an increase in the drug release rate constant with an increase in the pH of the dissolution media (Pillay, 1996). According to the Henderson-Hasselbalch equation (Martin *et al.*, 1993), the dissolution rate of weak acids increases as the pH increases, whereas the dissolution rate of weak bases decreases as the pH is reduced. This phenomenon is also evident from the modified version of the Nernst-Brunner equation (Hoener and Benet, 1990). Diclofenac sodium is a weak acid. This partially explains the increase in the zero-order drug release rate as the pH of the buffer is increased.

Fassihi and Ritschel (1993) developed a modified release drug delivery system containing theophylline. One of the polymers used was Eudragit® RS. Drug release was found to be

nearly independent of pH. The results also showed that for both the rotating basket and rotating paddle methods, pH variation of the dissolution medium did not affect drug release significantly.

Abdel-Rahman *et al.* (1992) investigated the influence of pH on the drug release characteristics from matrix tablets containing ibuprofen using three different types of Eudragit® polymers. Ibuprofen is a water insoluble drug with a pKa of 5.3. The data revealed that with both Eudragit® RLPM and Eudragit® RSPM, very little drug was released at low pH (1.5), while markedly improved release rates were observed at pH 7.5. Kislalioglu *et al.* (1991) also demonstrated pH dependent drug release characteristics from ibuprofen co-precipitates prepared with methacrylate polymers. Soltero *et al.* (1991) observed increased release rates of quinidine hydrochloride with an increase in the pH of the buffer medium. Solid dispersions of indomethacin prepared with Eudragit® RL and Eudragit® RS showed that the liberation of drug from the coevaporate containing both types of Eudragit® polymers was negligibly influenced by pH modifications of the media.

It was thus concluded that the pH dependent drug release characteristics of diclofenac sodium from Eudragit® matrices was not due to the influence of pH on the Eudragit® polymers used, but rather, to the pH dependent solubility characteristics of the drug.

5.7.3.1 Drug Release Behaviour Of Diclofenac Sodium From Eudragit® Matrices In Dissolution Media Simulating The Gastrointestinal Milieu

Due to the pH dependent drug release behaviour of the diclofenac sodium Eudragit® matrices, the subsequent phase of this investigation involved the determination of the drug release profiles in various dissolution media for different periods of time, so as to simulate the gastrointestinal milieu following oral administration (Table 4.13). The mean cumulative percentages of diclofenac sodium released from tablets of Batch NH in 0.2 M phosphate buffer pH 6.8, relative to the media of various pH gradients are presented in Table 5.24 and Figure 5.22, while the mean drug release rates are outlined in Table 5.25 and Figure 5.23.

Table 5.24: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH in 0.2 M phosphate buffer pH 6.8 relative to various dissolution media simulating the gastrointestinal milieu

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASE ± SD	
	0.2 M PHOSPHATE BUFFER pH 6.8	VARIOUS pH GRADIENTS
0.5	12.85±0.21	0.46±0.16
1	17.29±1.29	0.69±.011
1.5	20.73±0.55	1.15±0.07
2	29.37±1.31	1.24±0.08
3	38.85±2.03	9.32±1.15
4	47.64±2.02	18.41±1.89
5	57.26±2.59	28.42±2.28
6	64.35±3.04	61.80±4.05
7	74.43±2.51	78.13±4.72
8	81.80±1.23	87.75±6.02

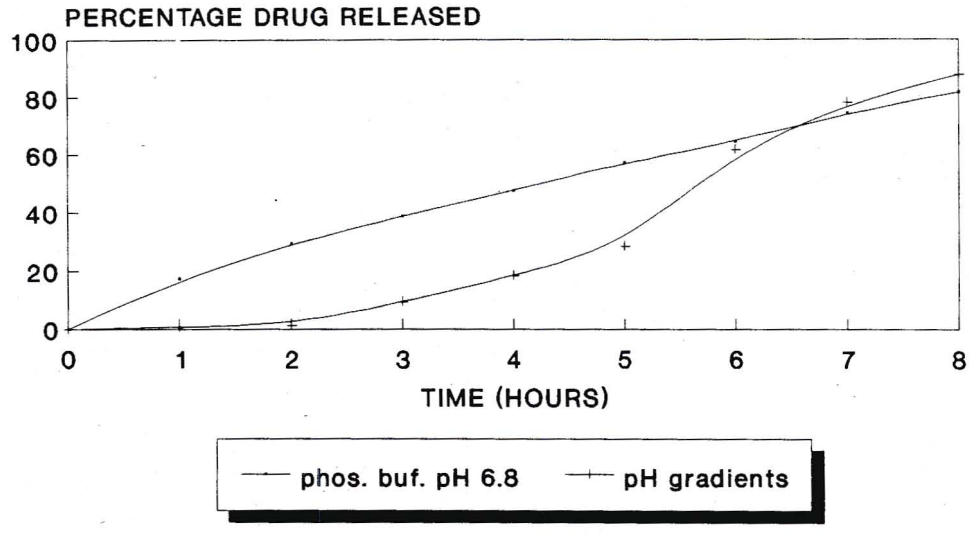
* Individual values for 3 replicate determinations are shown in Appendices 37 and 40 respectively.

Table 5.25: Mean release rates of diclofenac sodium from tablets of Batch NH in 0.2 M phosphate buffer pH 6.8 relative to various dissolution media simulating the gastrointestinal milieu

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)	
	0.2 M PHOSPHATE BUFFER pH 6.8	VARIOUS pH GRADIENTS
1	17.29±1.29	0.69±0.11
2	12.08±0.77	0.54±0.05
3	9.48±1.85	8.08±1.21
4	8.80±0.48	9.09±2.02
5	9.61±1.75	10.01±0.67
6	7.10±0.92	33.38±1.79
7	10.08±2.10	16.33±0.71
8	7.37±2.10	9.61±2.08

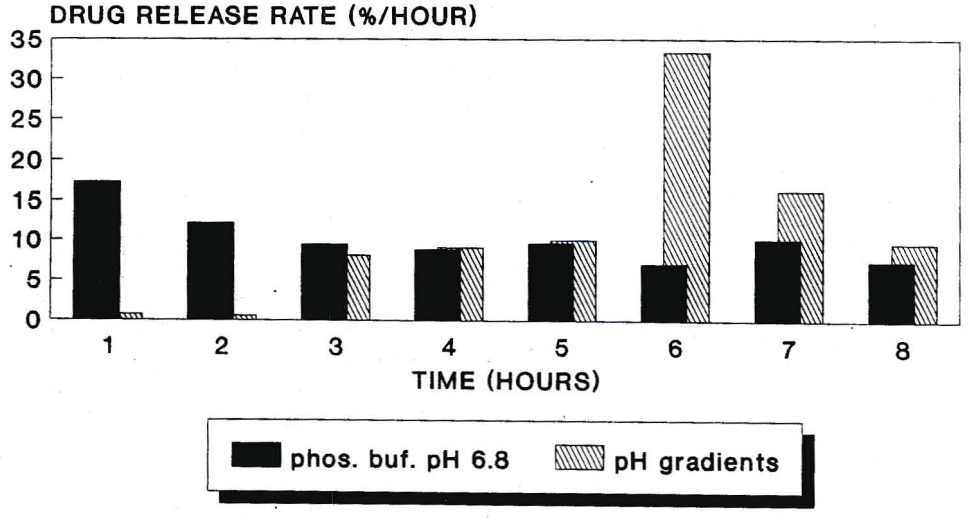
* Individual values for 3 replicate determinations are shown in Appendices 67 and 82 respectively.

Figure 5.22: Drug release patterns of diclofenac sodium in phos. buf. pH 6.8 relative to media simulating the GI mil.



phos. buf. pH 6.8 = 0.2 M phosphate buffer pH 6.8
GI mil. = gastrointestinal milieu

Figure 5.23: Release rates of diclofenac sodium in 0.2 M phosphate buffer pH 6.8 relative to media simulating the GI mil.



GI mil. = gastrointestinal milieu
phos. buf. pH 6.8 = 0.2 M phosphate buffer pH 6.8

In hydrochloric acid buffer (pH 1.5), the tablets remained almost unaffected, with only 0.69±0.11% of the drug being released at the end of the first hour. A similar effect was observed with the 0.2 M phosphate buffer pH 4.5. The tablets were subjected to this medium for a period of one hour, and the amount of drug released during this time was 0.54±0.05%. This slow drug release behaviour was also demonstrated in dissolution studies using the individual buffers. Slow drug release was also observed from the third to the fifth hour, when the tablets were subjected to 0.2 M phosphate buffer pH 6.8. The percentage drug released during this three hour period was 27.19±2.26%. In comparison, tablets that were subjected to 0.2 M phosphate buffer pH 6.8 released 38.85±2.03% in three hours. However, when the pH of the medium was further increased to 7.5, from the sixth hour onwards, very fast drug release rates were observed and 59.32±3.88% drug release was observed in that time period, with a total of 87.75±6.02% drug being released at the end of eight hours.

It was concluded that although the initial release rates of the drug were slow, an increase in pH resulted in faster drug release rates, especially from the sixth hour onwards.

A similar effect was observed by Van Wilder *et al.* (1991). Dissolution studies were conducted on modified release preparations of diclofenac sodium in a pH changing medium. Since diclofenac sodium is practically insoluble in acidic solutions, no dissolution occurred in 0.1 N HCl (pH 1). It was also reported that the acid digestion stage further delayed release when the pH of the medium was increased, compared to studies conducted in the absence of an initial low pH. This delay was explained by a low micro-environment pH of the formulations due to the acidic soaking stage.

On the other hand, Vandelli *et al.* (1995) also conducted dissolution studies in a pH changing medium on a novel drug delivery device for the immediate and controlled release of diclofenac sodium. Drug release was compared to dissolution data obtained from a modified release formulation of diclofenac sodium and a commercially available preparation, Voltaren Retard®. Almost no drug was in solution when the dissolution study was carried out at pH 1, for both the commercial product and the system. This was attributed to the insolubility of the drug in the medium. However, when the gastric simulated fluid (pH 1)

was replaced by the intestinal simulated fluid (pH 7.4), faster dissolution was observed from the system, compared to the commercial product. Drug release from the commercial product was scarcely affected by the different gastric pH values, while the amount of drug released from the system increased according to the increase in the drug solubility where the pH of the gastric medium changed from pH 1.1 to pH 3.9 and mostly to pH 5.

The findings of the present study clearly indicated the pH dependent release characteristics of diclofenac sodium. On the basis of the simulated study, it was concluded that a similar drug release profile can be expected in the changing pH environment of the gastrointestinal tract. Furthermore, the technique investigated in the present study for the formulation of the diclofenac sodium Eudragit® matrices was successful in modifying and extending drug delivery in the gastrointestinal tract. However, conclusive evidence to support the above conclusions can only be obtained from controlled *in vivo* studies.

5.7.4 *INFLUENCE OF MEDIA IONIC CONCENTRATION*

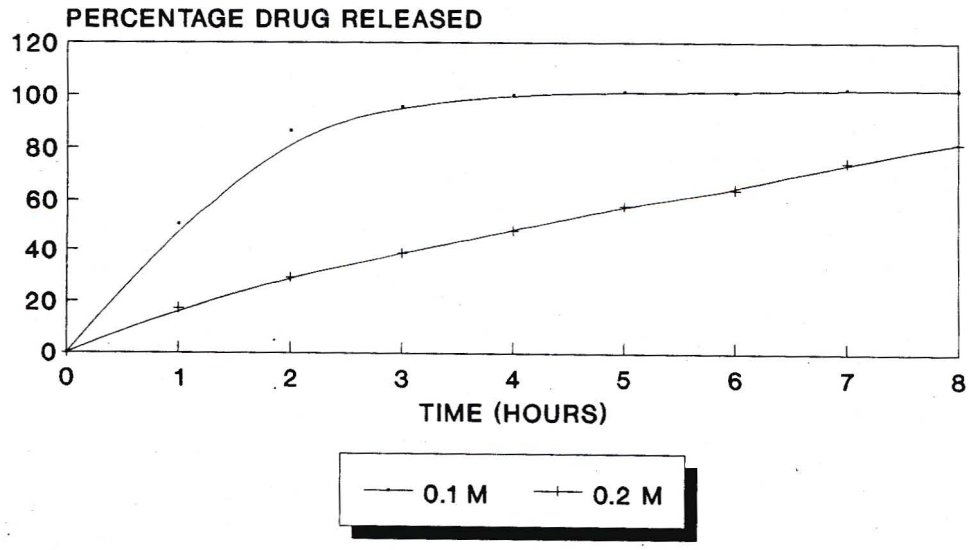
The ionic strength of the dissolution medium plays a significant role in the dissolution process (Bodmeier *et al.*, 1996). The presence of food in the stomach can induce the secretion of various chemicals in the gastrointestinal tract causing changes in the ionic strength of the gastrointestinal fluid. The presence of ions in food itself is also not unique, making it difficult to generalise the ionic strength of dissolution media used to test modified release dosage forms. This emphasises the importance of screening modified release formulations during developmental stages in dissolution media with various ionic strengths so that a proper evaluation of the developed formulation(s) can be made during *in vitro* studies in order to avoid any possible *in vivo* failures (Khan, 1996). The ionic strength of the dissolution medium was thus varied in the present study, to determine the effect of ions on drug release. The dissolution data from studies conducted with media of different ionic strengths are presented in Table 5.26 and are graphically illustrated in Figure 5.24.

Table 5.26: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices in 0.1 M and 0.2 M phosphate buffers

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD	
	0.1 M PHOSPHATE BUFFER	0.2 M PHOSPHATE BUFFER
0.5	43.99±1.98	12.85±0.21
1	50.14±2.76	17.29±1.29
1.5	72.28±2.30	20.73±0.55
2	86.13±2.23	29.37±1.31
3	95.56±2.46	38.85±2.03
4	100.09±0.19	47.64±2.02
5	101.16±0.36	57.26±2.59
6	100.96±0.15	64.35±3.04
7	102.17±0.33	74.43±2.51
8	102.02±0.21	81.80±1.23

* Individual values for 3 replicate determinations are shown in Appendices 41 and 37 respectively.

Figure 5.24: Effect of ionic concentration of the dissolution medium on the release of diclofenac sodium



0.1 ▪ 0.1 M phosphate buffer pH 6.8
0.2 ▪ 0.2 M phosphate buffer pH 6.8

It was observed that drug release was markedly increased in 0.1 M phosphate buffer pH 6.8. Approximately 50% of the drug was released in the first hour and drug release was complete in approximately four hours. In comparison, 0.2 M phosphate buffer pH 6.8 was able to retard drug release considerably, with 17.29±1.29 and 81.80±1.23% drug released at the end of the first and eighth hours respectively.

The influence of ionic strength of the dissolution media on drug release behaviour of modified release formulations which use hydrophillic gel forming polymers was extensively studied by Chetty *et al.* (1994); Fagan *et al.* (1989); Jalil and Ferdous (1993) and Rajabi-Saihboomi *et al.* (1994). Modified release diclofenac sodium tablets prepared in the form of HPMC matrices had significantly different release profiles in media of different ionic strengths. The dissolution rate was found to decrease as the ionic concentration was increased from 0.05 M to 0.2 M (Chetty *et al.*, 1994). These findings were similar to those of the present study.

Chetty *et al.* (1994) also reported on drug release from wax matrix tablets containing diclofenac sodium. The study showed that ionic concentration did not affect drug release.

It was thus concluded that the ionic concentration of the dissolution medium has a significant effect on the release of diclofenac sodium from Eudragit® matrices. The 0.2 M phosphate buffer was found to be a suitable dissolution medium, and drug release occurred in a controlled manner. A decrease in the ionic concentration resulted in drastically faster drug release, and it was postulated that a further decrease in ionic concentration could lead to even faster drug release patterns, and that in such an instance, a 'dose dumping' phenomenon could possibly be observed.

5.7.5 *INFLUENCE OF DISSOLUTION MEDIA*

Due to the absence of a drug dissolution monograph for modified release diclofenac sodium preparations, dissolution studies were conducted in various media to fully characterise the drug release behaviour from diclofenac sodium Eudragit® matrices. The media selected were

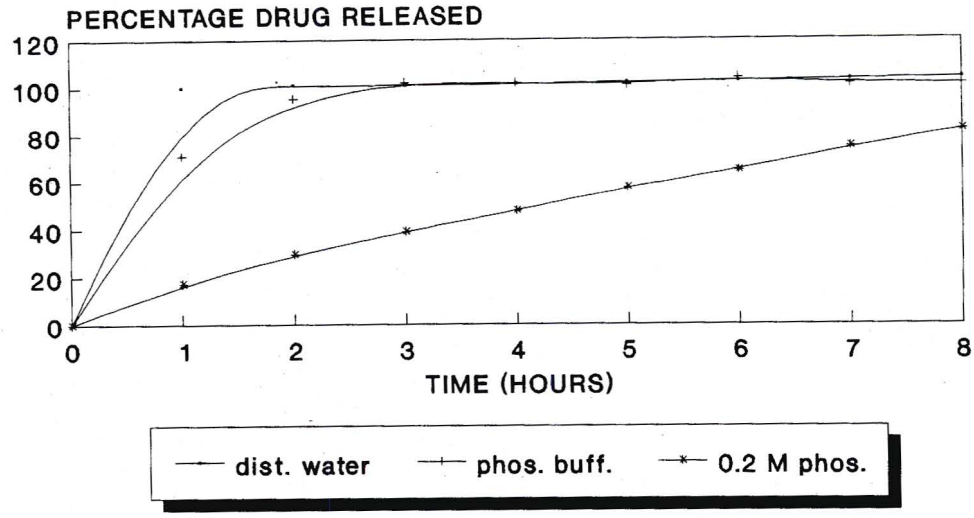
distilled water, USP phosphate buffer pH 6.8 and 0.2 M phosphate buffer pH 6.8. The drug release data are presented in Table 5.27 and Figure 5.25.

Table 5.27: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices in various media

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGES DRUG RELEASED ± SD		
	DISTILLED WATER pH 6.2	USP PHOSPHATE BUFFER	0.2 M PHOSPHATE BUFFER
0.5	97.16±1.48	34.83±3.79	12.85±0.21
1	100.10±0.07	71.02±2.37	17.29±1.29
1.5	100.53±0.18	90.63±3.54	20.73±0.55
2	101.20±0.18	95.46±2.28	29.37±1.31
3	101.02±0.12	102.02±0.34	38.85±2.03
4	101.43±0.13	101.72±1.13	47.64±2.02
5	102.08±0.14	101.03±0.05	57.26±2.59
6	102.45±0.15	103.58±1.27	64.35±3.04
7	103.14±0.26	101.24±0.37	74.43±2.51
8	103.60±0.16	101.28±0.58	81.80±1.23

* Individual values for 3 replicate determinations are shown in Appendices 42, 43 and 37 respectively.

Figure 5.25: Effect of dissolution media on drug release characteristics of diclofenac sodium



dist. water = distilled water
phos. buff. = USP phosphate buffer
0.2 M phos. = 0.2 M phosphate buffer

The data obtained revealed the inability of the formulation to maintain its integrity and to release diclofenac sodium in a controlled manner in distilled water and USP phosphate buffer pH 6.8. A 'dose dumping' effect was observed in dissolution studies with both these media.

A mean total of 97.16±1.48% of the drug was released in thirty minutes, with dissolution being complete within an hour, in distilled water. With the USP phosphate buffer pH 6.8, approximately 70% of the drug was released in one hour and almost 95% in two hours, with the remaining 5% being complete by three hours. Drug release in 0.2 M phosphate buffer pH 6.8, occurred in a more controlled manner throughout the study, with a mean total of 81.80±1.23% drug release in eight hours.

It has been postulated that drug release occurs rapidly in distilled water due to the highly soluble nature of diclofenac sodium, and to the presence of a high concentration of the water soluble diluent, lactose. The composition of the USP phosphate buffer pH 6.8, differed considerably from that of the 0.2 M phosphate buffer pH 6.8. The presence of the ions in the USP phosphate buffer may have been responsible for causing an interaction, thus

resulting in increased drug release.

Prasad *et al.* (1982) showed that buffer composition can have a significant effect on the dissolution rates of furosemide from tablet formulations. In another study, Prasad *et al.* (1983b) investigated the drug release characteristics of quinidine gluconate in various media. It was found that drug release varied significantly in different media.

It was thus concluded that the type of dissolution medium can significantly influence the drug release characteristics of diclofenac sodium. Since there is no Official dissolution method to model the drug release behaviour of diclofenac sodium from modified release dosage forms, the dissolution medium should be carefully selected when conducting *in vitro* dissolution studies.

5.8 INFLUENCE OF FORMULATION EXCIPIENTS

5.8.1 *INFLUENCE OF LACTOSE*

Amongst the excipients utilised in the pharmaceutical industry, lactose is the most widely used in tablet formulation, as it displays very good stability with most drugs and shows favourable release rates (Efentakis *et al.*, 1990). It was thus chosen as the diluent for the present study. To investigate the effect of lactose on the drug release patterns, its concentration was varied. The dissolution data of Batch NHL30, Batch NH and Batch NHL50 are presented in Tables 5.28 and 5.29 and Figures 5.26 and 5.27 respectively.

Table 5.28: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices containing different concentrations of lactose

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	BATCH NHL30	BATCH NH	BATCH NHL50
0.5	14.22±0.66	12.85±0.21	13.66±1.12
1	19.26±1.63	17.29±1.29	17.93±1.48
1.5	23.47±1.43	20.73±0.55	24.16±0.70
2	27.12±1.19	29.37±1.31	28.25±1.57
3	35.06±1.64	38.85±2.03	39.07±2.33
4	41.94±1.24	47.64±2.02	53.46±1.39
5	47.94±2.12	57.26±2.59	69.86±3.40
6	56.72±1.61	64.35±3.04	80.99±1.93
7	60.75±1.98	74.43±2.51	87.03±1.83
8	66.13±2.47	81.80±1.23	92.94±2.05

* Individual values for 3 replicate determinations are shown in Appendices 44, 17 and 45 respectively.

Table 5.29: Mean release rates of diclofenac sodium from tablets containing different concentrations of lactose

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	BATCH NHL30	BATCH NH	BATCH NHL50
1	19.26±1.63	17.29±1.29	17.93±1.48
2	7.86±0.57	12.08±0.77	10.32±0.26
3	7.94±0.46	9.48±1.85	10.82±0.82
4	6.88±0.44	8.80±0.48	14.39±1.10
5	5.99±0.93	9.61±1.75	16.41±2.02
6	8.78±0.53	7.10±0.92	11.13±1.50
7	4.03±1.08	10.08±2.10	6.03±0.63
8	5.38±1.34	7.37±2.10	5.92±0.50

* Individual values for 3 replicate determinations are shown in Appendices 83, 67 and 84 respectively.

Figure 5.26: Effect of lactose on the drug release characteristics of diclofenac sodium from Eudragit[R] matrices

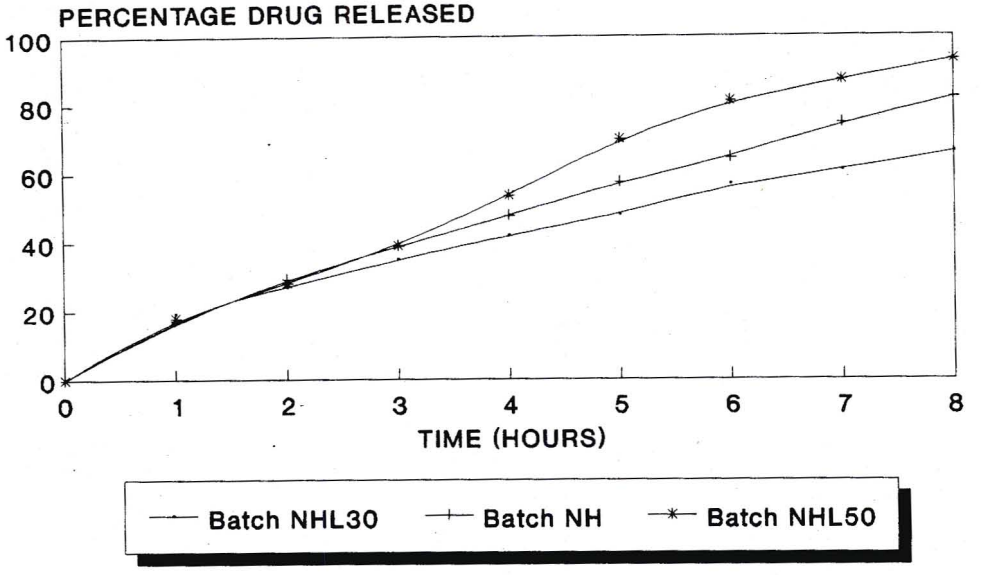
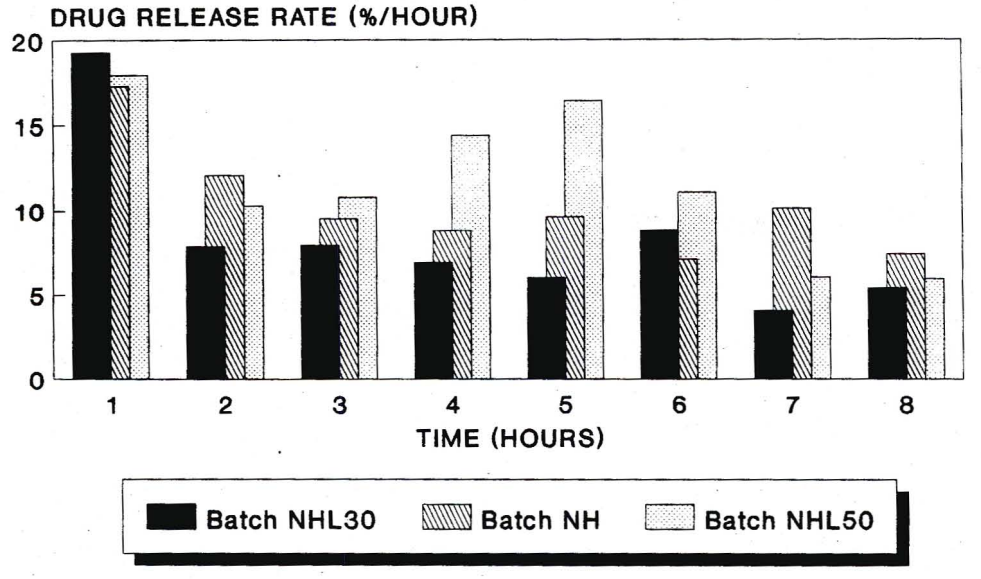


Figure 5.27: Release rates of diclofenac sodium from Eudragit[R] matrices containing different concentrations of lactose



The dissolution data indicated that the amount of drug released was markedly influenced by the concentration of lactose. An increase in the concentration of lactose led to an increase in drug release, while a decrease in lactose concentration led to a reduction in the total amount of drug released.

A comparison of the profiles in Figure 5.26 shows that the drug release from all these batches was almost equal at the 2 hours sampling interval. While Batch NHL50 continued to release drug at a faster rate than Batch NH until the sixth hour, Batch NHL30 released drug at a slower rate than Batch NH.

Since lactose is a water soluble diluent, it was anticipated that an increase in its concentration would provide faster release rates. In addition to increasing the drug release rates from the matrices, a faster rate of erosion of the matrix was also observed. Matrix erosion was more prominent at higher lactose concentrations due to the hydrophillic nature of lactose.

Similarly, Efentakis *et al.* (1990) observed increased release rates of drug with an increase in lactose concentrations.

It was thus concluded that the concentration of diluent present in the formulation can have a significant effect on drug release. In this instance, an increase in the water soluble diluent, lactose, led to an increase in drug release rates.

5.8.2 *INFLUENCE OF DIFFERENT TYPES OF DILUENTS*

The choice of a diluent can have a dramatic effect on the drug release characteristics. To demonstrate the effect of different types of diluents on the release behaviour of diclofenac sodium from Eudragit® matrices, in addition to lactose, the incorporation of dicalcium phosphate and microcrystalline cellulose as diluents was investigated. The drug release data are presented in Tables 5.30 and 5.31 and Figures 5.28 and 5.29 respectively.

Table 5.30: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices containing different types of diluents

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	BATCH NH	BATCH DCP	BATCH MCC
0.5	12.85±0.21	11.55±0.80	81.50±1.55
1	17.29±1.29	14.22±1.46	92.24±3.14
1.5	20.73±0.55	17.04±1.34	97.03±0.98
2	29.37±1.31	19.95±1.63	99.96±0.15
3	38.85±2.03	24.69±1.92	100.79±0.37
4	47.64±2.02	32.36±1.80	101.16±0.17
5	57.26±2.59	37.27±1.48	101.59±0.31
6	64.35±3.04	44.29±1.86	101.38±0.35
7	74.43±2.51	54.70±2.68	102.05±0.43
8	81.80±1.23	66.19±2.33	102.23±0.33

* Individual values for 3 replicate determinations are shown in Appendices 17, 46 and 47 respectively.

Table 5.31: Mean release rates of diclofenac sodium from Eudragit® matrices containing different types of diluents

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD %/HOUR)		
	BATCH NH	BATCH DCP	BATCH MCC
1	17.29±1.29	14.22±1.46	92.24±3.14
2	12.08±0.77	5.73±1.20	7.71±3.15
3	9.48±1.85	4.74±0.46	0.84±0.50
4	8.80±0.48	7.67±0.28	0.37±0.30
5	9.61±1.75	4.91±0.45	0.43±0.18
6	7.10±0.92	7.02±0.58	-0.21±0.48
7	10.08±2.10	10.42±1.04	0.67±0.54
8	7.37±2.10	11.48±0.83	0.17±0.76

* Individual values for 3 replicate determinations are shown in Appendices 67, 85 and 86 respectively.

Figure 5.28: Effect of diluents on the drug release characteristics of diclofenac sodium from Eudragit® matrices

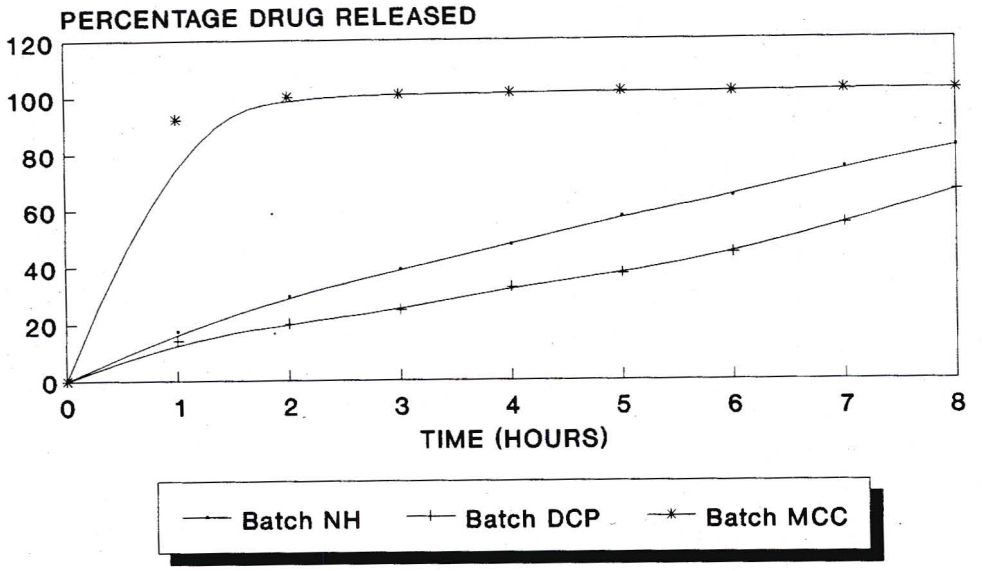
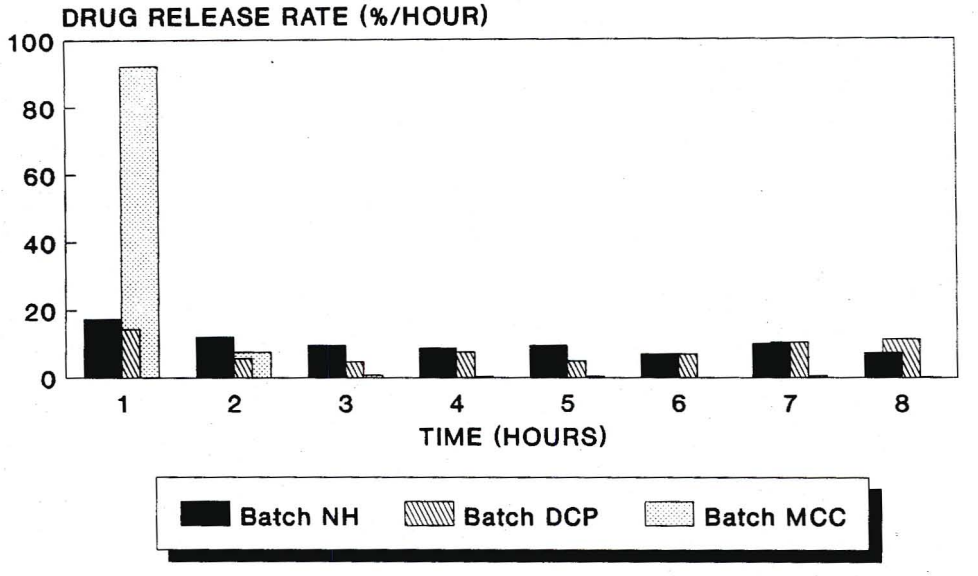


Figure 5.29: Release rates of diclofenac sodium from Eudragit® matrices containing different types of diluents



The data indicated the inability of microcrystalline cellulose (Avicel® pH 102) to retard the release of diclofenac sodium. More than 90% of the drug was released in the first hour, from Batch NH, with release being almost complete at the end of two hours. An insignificant amount, 2.28±0.44% was released over the remaining six hours. A comparison of the drug release data of Batch DCP with Batch NH showed that drug release from Batch DCP occurred at a slower rate than that from Batch NH, until five hours, after which the drug release rates became almost similar.

Lactose is a water soluble diluent. Dicalcium phosphate, on the other hand, is water insoluble, although it will dissolve in gastric acid (Parikh, 1994). The differences in drug release between Batches NH and DCP were thus attributed to the difference in the physical properties of the diluents used. In addition to being used as a diluent, microcrystalline cellulose also possesses disintegrant properties. The tablets of Batch MCC were observed to rapidly disintegrate when introduced into the dissolution medium. Drug release therefore occurred very rapidly.

A similar finding of drug release dependency on diluents was reported by Cameron and McGinity (1987), Lin and Lin (1993) and Fernandez-Arevalo *et al.* (1993).

The selection of a filler excipient was demonstrated to have a dramatic effect on the release properties of theophylline from matrix tablets containing an acrylic resin polymer as the retardant substance (Cameron and McGinity, 1987). The diluents investigated were sucrose, dextrose, spray-dried lactose, microcrystalline cellulose and calcium sulphate. In their study, the dissolution studies in acidic medium showed the most rapid drug release from tablets containing microcrystalline cellulose, while tablets containing calcium sulfate released drug at the slowest rate. Tablets containing the remaining excipients released drug at intermediate rates. The differences in drug release were attributed to the differences in porosity, dissolution or permeability of these materials. It was also interesting to note that drug release from the tablets was retarded by the acrylic resin (Eudragit® S100) despite the inherent disintegrant properties of microcrystalline cellulose. Though the tablets laminated within one hour of contact with the dissolution medium, four hours were required to release approximately 85% of the drug. This lamination was not evident with tablets containing the

other diluents, which released the drug by a slow erosion process of the matrix.

In the present study, tablets of Batch MCC also underwent a lamination process, which was followed by a rapid disintegration process, while tablets from Batches DCP and NH underwent a slow erosion process.

Lin and Lin (1993) also investigated the effect of diluents on the drug release behaviour of theophylline from tablets containing Eudragit® RLPM and Eudragit® RSPM. Numerous diluents were investigated. Tablets prepared from lactose showed delayed dissolution which was attributed to the granulation of lactose with polyvinyl pyrrolidine binder. In the present study, tablets prepared with lactose also demonstrated a similar effect, which can be attributed to the granulation of lactose with the Eudragit® polymers.

Fernandez-Arevalo *et al.* (1993) on the other hand demonstrated the inability of lactose to be used as a diluent for modified release formulations. An inert matrix could not be obtained as formulations prepared with lactose underwent a disintegration process due to their highly hydrophilic nature.

It was therefore concluded that the use of diluents with disintegrant properties led to extremely rapid drug release, with a 'dose dumping' effect being observed. In comparison, water insoluble diluents retarded drug release to a greater extent than water soluble diluents.

5.8.3 *INFLUENCE OF STARCH CONCENTRATIONS*

Starch is one of the most widely used excipients in the manufacture of solid oral dosage forms and can be used as a filler, disintegrant or binder (Visavarungroj and Remon, 1992). In the present study, starch was incorporated into the tablets in an attempt to improve drug release. To further characterise the influence of starch on drug release, tablets containing various concentrations of starch were formulated and analysed. The drug release data from the different batches are presented in Tables 5.32 and 5.33 and Figures 5.30 and 5.31 respectively.

Table 5.32: Mean cumulative percentages of diclofenac sodium from Eudragit® matrices containing different concentrations of starch

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	BATCH NHS2	BATCH NH	BATCH NHS4
0.5	12.73±0.66	12.85±0.21	15.61±1.21
1	15.46±1.63	17.29±1.29	22.10±1.85
1.5	19.17±0.37	20.73±0.55	29.89±1.44
2	23.33±1.35	29.37±1.31	39.34±1.84
3	28.82±1.43	38.85±2.03	49.28±2.50
4	36.71±1.24	47.64±2.02	57.80±2.42
5	42.67±1.67	57.26±2.59	69.28±1.79
6	49.81±1.76	64.35±3.04	77.81±3.30
7	55.77±2.01	74.43±2.51	85.78±1.81
8	65.06±2.67	81.80±1.23	93.24±2.19

* Individual values for 3 replicate determinations are shown in Appendices 48, 17 and 49 respectively.

Table 5.33: Mean release rates of diclofenac sodium from tablets containing various concentrations of starch in 0.2 M phosphate buffer pH 6.8

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	BATCH NHS2	BATCH NH	BATCH NHS4
1	15.46±1.63	17.29±1.29	22.10±1.85
2	7.87±0.28	12.08±0.77	17.24±0.05
3	5.49±0.32	9.48±1.85	9.39±0.68
4	7.90±0.24	8.80±0.48	8.52±0.09
5	5.96±0.57	9.61±1.75	11.49±0.74
6	7.14±0.24	7.10±0.92	8.53±1.53
7	5.96±0.25	10.08±2.10	7.97±1.49
8	9.29±1.49	7.37±2.10	7.64±0.39

* Individual values for 3 replicate determinations are shown in Appendices 87, 67 and 88 respectively.

Figure 5.30: Effect of starch on the release characteristics of diclofenac sodium from Eudragit® matrices

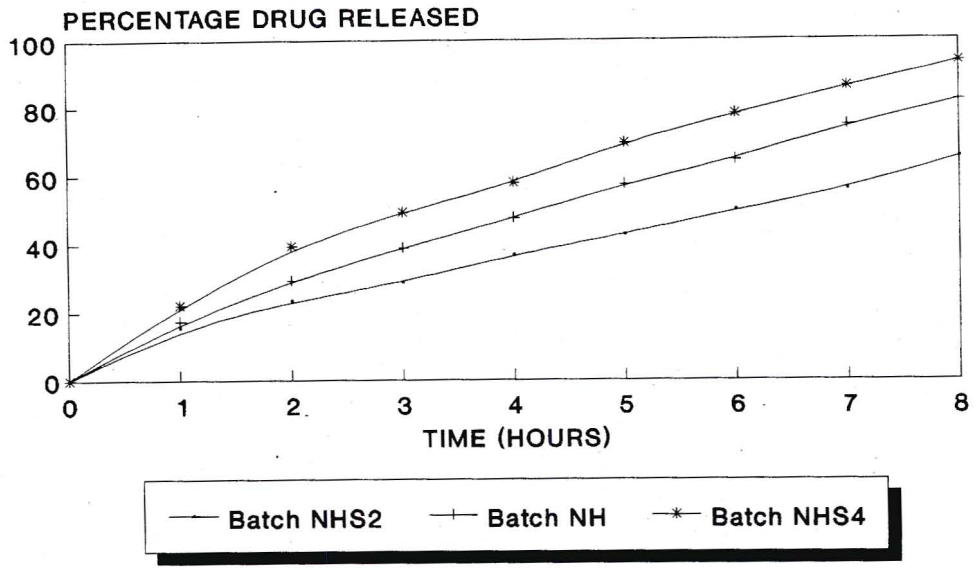


Figure 5.31: Release rates of diclofenac sodium from Eudragit® matrices containing different concentrations of starch

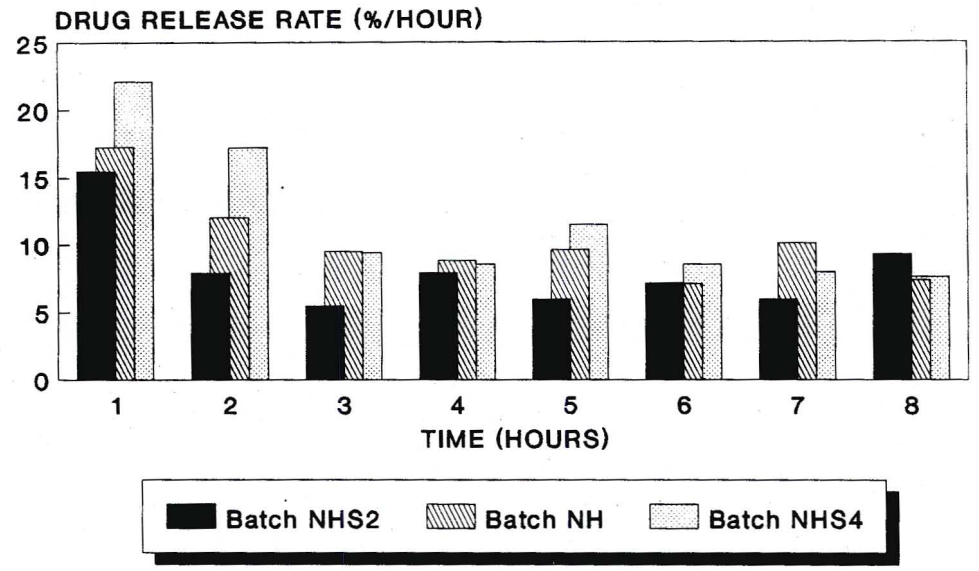


Figure 5.30 shows that as the concentration of starch was increased, there was a corresponding increase in drug release, with Batch NHS4 displaying the fastest drug release pattern. Due to the inherent disintegrant properties of starch, the amount of drug release was increased due to the swelling of the tablet matrices. The degree of swelling was dependent on the amount of starch present. The greater the content of starch, the more pronounced the swelling; hence the faster the release of drug. Although Batch NHS4 contained twice the amount of starch compared to Batch NHS2, the overall difference in drug release between these batches at eight hours was $28.36 \pm 0.91\%$.

It has been reported that starch is the most commonly used tablet disintegrant at concentrations between 3-15%. Unmodified starch does not compress well, and tends to increase tablet friability and capping if used in high concentrations (Farhadieh, 1994). The concentrations of starch that were investigated in the present study ranged between 3-6%. The friability values are reflected in Appendix 95, and were within the desired limit (i.e. $< 1.5\%$). All tablets that were produced had even, smooth surfaces, and no capping was observed. It was thus concluded that starch was a suitable excipient for use in the present study.

Generally, in granulated formulations, about half the total starch content is included in the granulation mixture, and the balance as part of the final blend with the dried granulation (Farhadieh, 1994). Since granules in the range 250-710 μm were used in tablet production, the entire quantity of starch that was used, was incorporated together with the binder, in the granulating liquid.

It was thus concluded that the selection of starch as an excipient, as well as the method of its incorporation in the present study was suitable.

5.8.4 *INFLUENCE OF MAGNESIUM STEARATE*

In solid dosage formulations the primary function of magnesium stearate, the most frequently used powder lubricant, is to reduce frictional forces during tablet formation. However,

including magnesium stearate in formulations may also cause deleterious changes in tablet crushing strength, disintegration time and drug dissolution. Because of its almost ideal lubrication properties and its notable disadvantages, magnesium stearate has been widely studied as a lubricant (Hussain *et al.*, 1988). The lubrication effect of magnesium stearate can be achieved in one of two ways, i.e. by an external addition or an internal addition process. In the internal addition process, the magnesium stearate is added to the powder blend prior to granulation, while in the external addition process, the magnesium stearate is added after the granulation process. In the present study, release of diclofenac sodium from the matrices incorporating magnesium stearate as an internal lubricant (Batch NHM) was compared to drug release from formulations incorporating magnesium stearate as an external lubricant (Batch NH). The drug release data are presented in Tables 5.34 and 5.35 and Figures 5.32 and 5.33 respectively.

Table 5.34: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices containing magnesium stearate as an internal and external lubricant

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD	
	BATCH NH	BATCH NHM
0.5	12.85±0.21	14.45±1.16
1	17.29±1.29	23.91±1.45
1.5	20.73±0.55	27.19±1.67
2	29.37±1.31	31.40±1.77
3	38.85±2.03	44.45±1.52
4	47.64±2.02	51.22±2.10
5	57.26±2.59	59.73±2.24
6	64.35±3.04	69.13±1.75
7	74.43±2.51	77.12±2.03
8	81.80±1.23	85.73±1.98

* Individual values for three replicate determinations are shown in Appendices 17 and 50 respectively.

Table 5.35: Mean release rates of diclofenac sodium from Eudragit® matrices containing magnesium stearate as an internal and external lubricant

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)	
	BATCH NH	BATCH NHM
1	17.29±1.29	23.91±1.45
2	12.08±0.77	7.50±0.93
3	9.48±1.85	13.05±3.28
4	8.80±0.48	6.76±0.76
5	9.61±1.75	8.52±0.65
6	7.10±0.92	9.40±1.27
7	10.08±2.10	8.08±0.32
8	7.37±2.10	8.52±0.38

* Individual values for three replicate determinations are shown in Appendices 67 and 89 respectively.

Figure 5.32: Effect of magnesium stearate on the drug release characteristics of diclofenac sodium

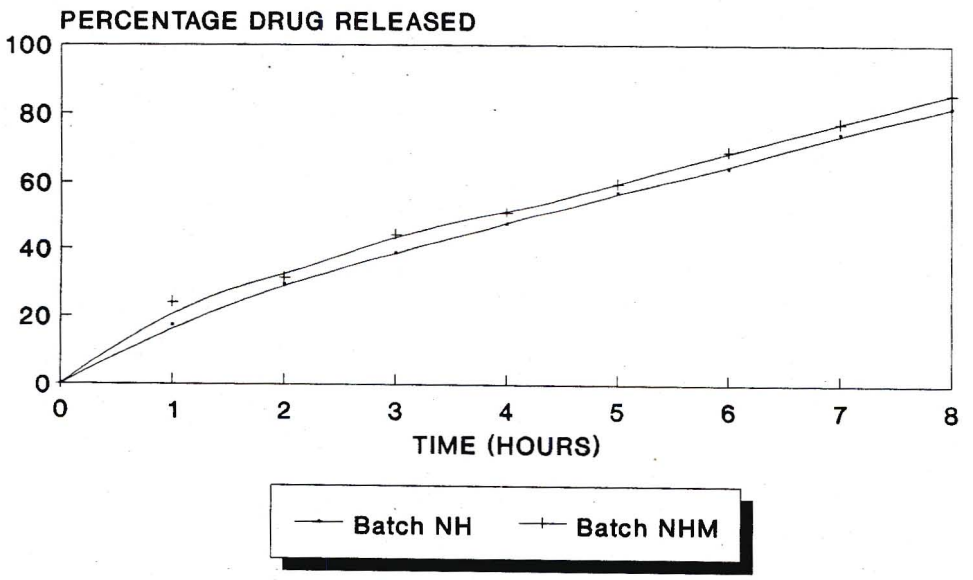
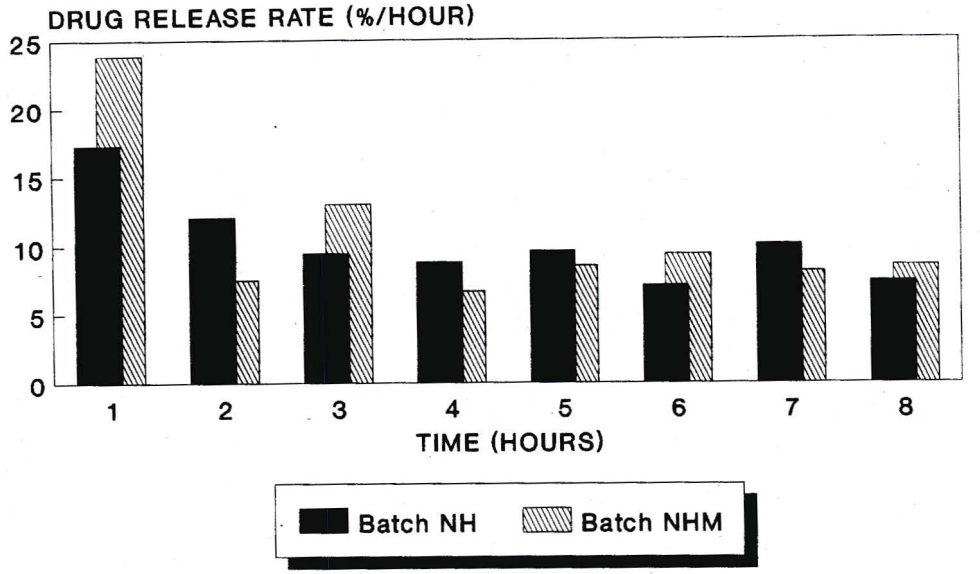


Figure 5.33: Effect of magnesium stearate on the release rates of diclofenac sodium from Eudragit® matrices



The results showed that the overall amounts of drug released from the tablets of Batch NH and Batch NHM at the end of the study were almost similar. Drug release occurred at a faster rate from tablets of Batch NHM during the first hour, compared to tablets of Batch NH. The drug release profiles of these two batches, as depicted in Figure 5.32 were similar, with the only difference being an almost constant difference in the amount of drug released at each time interval between the two batches.

The tablets of Batch NHM were more friable than the tablets of Batch NH. The friability values are recorded in Appendix 95. Tablets of Batch NHM were also observed to be prone to sticking and picking during compression.

It was reported that a decrease in the dissolution rate was observed when magnesium stearate was blended with the tablet granulation, and that magnesium stearate may increase tablet friability (Allen and Luner, 1994). An increase in tablet friability was observed in the internal addition process, and granulation of the drug with magnesium stearate caused increased release rates of the drug. Hwang and Parrott (1993) reported that although

lubricants enhance the structural homogeneity of a compressed tablet, they may reduce the mechanical strength of a compressed tablet by interfering with the bonding between particles.

According to Rowe (1988), when anhydrous lactose is compacted with magnesium stearate, the strong adhesive interactions will cause a film to be formed over the excipient. This film is extensive since continued shearing of the system will cause the magnesium stearate to spread further, until a monomolecular film is formed. This will decrease the number of strong cohesive interactions between the excipient particles causing a decrease in tablet strength.

It was therefore concluded that formulating tablets incorporating magnesium stearate as an external lubricant proved to be a better means of providing tablet lubrication, compared to formulating tablets containing magnesium stearate as an internal lubricant.

5.9 INFLUENCE OF PROCESSING VARIABLES

5.9.1 *INFLUENCE OF TABLET HARDNESS*

This study involved the comparison of drug release data generated from dissolution studies with tablets compressed to different hardnesses. Since the dissolution conditions as well as the composition of the formulation were identical, the differences in drug release could be solely attributed to the difference in tablet hardness. Tables 5.36 and 5.37 and Figures 5.34 and 5.35 depict the drug release data of the batches compressed at different hardnesses. The friability values of the different batches are presented in Appendix 95.

Table 5.36: Mean cumulative percentages of diclofenac sodium released from Eudragit® matrices compressed to different hardnesses

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD		
	BATCH HARD 34	BATCH NH	BATCH HARD 67
0.5	13.75±0.58	12.85±0.21	7.65±0.50
1	18.02±1.10	17.29±1.29	11.54±0.85
1.5	25.02±1.58	20.73±0.55	15.18±1.35
2	31.14±2.58	29.37±1.31	18.98±1.33
3	39.84±1.86	38.85±2.03	24.65±0.95
4	51.70±1.74	47.64±2.02	32.64±1.29
5	64.59±2.33	57.26±2.59	38.14±0.54
6	76.75±1.94	64.35±3.04	42.60±2.24
7	84.32±2.66	74.43±2.51	47.88±2.07
8	95.99±2.90	81.80±1.23	53.55±1.94

* Individual values for 3 replicate determinations are shown in Appendices 51, 17 and 52 respectively.

Table 5.37: Mean release rates of diclofenac sodium from Eudragit® matrices compressed at different hardnesses

TIME (HOURS)	* MEAN DRUG RELEASE RATES ± SD (%/HOUR)		
	BATCH HARD 34	BATCH NH	BATCH HARD 67
1	18.02±1.10	17.29±1.29	11.54±0.85
2	13.12±1.52	12.08±0.77	7.44±0.52
3	8.70±0.73	9.48±1.85	5.67±0.49
4	11.86±0.15	8.80±0.48	7.99±0.43
5	12.90±1.02	9.61±1.75	5.51±1.53
6	12.16±0.47	7.10±0.92	4.45±2.31
7	7.57±1.00	10.08±2.10	5.29±0.31
8	11.67±1.25	7.37±2.10	5.67±0.15

* Individual values for 3 replicate determinations are shown in Appendices 90, 67 and 91 respectively.

Figure 5.34: Effect of tablet hardness on the drug release characteristics of diclofenac sodium from Eudragit® matrices

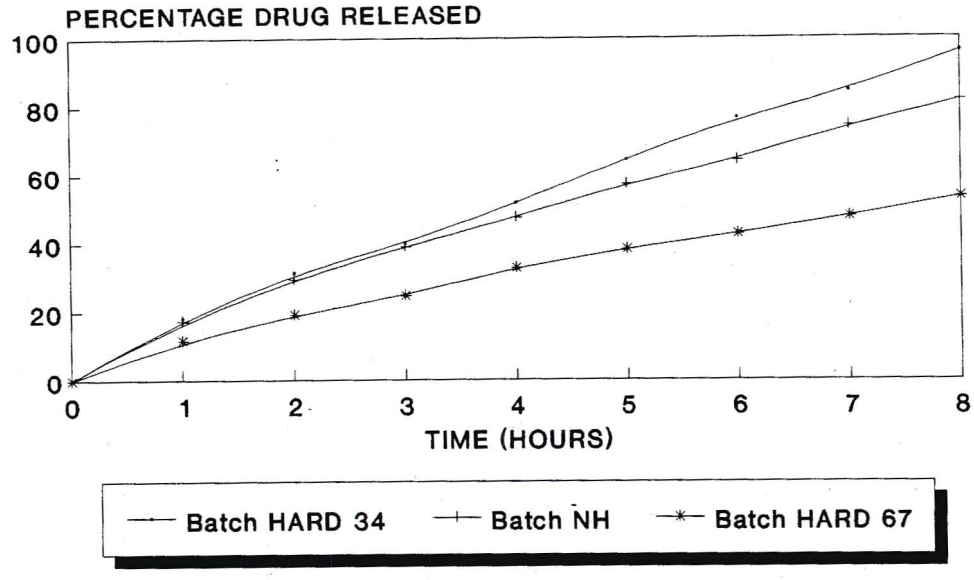
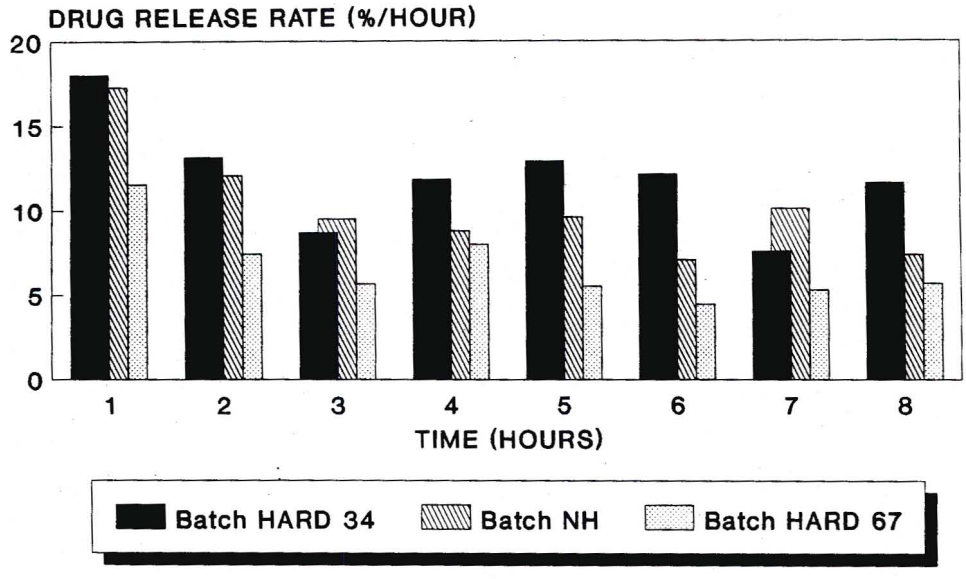


Figure 5.35: Release rates of diclofenac sodium from Eudragit® matrices compressed to different hardnesses



In the present study, tablet hardness was used as an indicator of compression force. The influence of compression force on the drug release characteristics of diclofenac sodium tablets is illustrated in Figure 5.34. Tablets compressed at lower compression pressures displayed increased release rates (Figure 5.35). Batch HARD 34 was compressed to a hardness in the range 3-4 Kp, while Batch NH was compressed to a range between 4-5 Kp. However, the slight increase in tablet hardness produced a notably significant decrease in drug release. The difference in the amount of drug released between these two batches at the end of the eight hour study was $14.18 \pm 4.12\%$. The release profiles of Batches HARD 34 and NH were similar until three hours, after which Batch HARD 34 continued to release drug at a faster rate than Batch NH. The release profile of Batch HARD 34 is almost consistent with that of a zero-order release profile (zero-order release constant = 11.452; $r^2 = 0.994$).

Batch HARD 67 was compressed to a hardness in the range 6-7 Kp. An initial increase in drug release was observed in the first hour. Thereafter, drug release proceeded at a somewhat slower and more constant rate. Although the friability of 0.77% (Appendix 95) for this Batch was well within the predetermined limit of acceptability ($< 1.5\%$ for this study), the significant decrease in drug release rates counteracted this potential advantage over Batch NH.

Similar to the findings of the present study, Katikaneni *et al.* (1995), Efentakis *et al.* (1990) and Cameron and McGinity (1987) also showed that the drug release patterns from tablets tend to decrease as the hardness is increased.

The study conducted by Katikaneni *et al.* (1995) involved the direct compression technique, using the polymer ethylcellulose. Efentakis *et al.* (1990) formulated direct compression tablet matrices using Eudragit® polymers. The study by Cameron and McGinity (1987) was similar to the study conducted by Efentakis *et al.* (1990) with respect to the technique and polymer, but in addition, the dry granulation technique was also investigated. Based on the findings of the present study, and a review of the literature, it was evident that the increase in tablet hardness with a concomitant decrease in drug release is independent of the polymer used in the particular study or the technique employed i.e. wet granulation, dry granulation

or direct compression.

On the other hand, Brossard *et al.* (1983) showed that while an increase in tablet hardness resulted in decreased release rates, wet granulated preparations were less sensitive to changes in tablet hardness.

While there appears to be a distinct trend for drug release characteristics to decrease with an increase in compression forces, Bansal *et al.* (1993) found that there was an insignificant effect of hardness on drug release from wax matrix tablets. This implied that the porosity and tortuosity of the wax matrix tablets remained practically unaltered, with an increase in compression pressure.

Foster and Parrott (1990) proposed that the decrease in the release rate with an increase in tablet hardness may be due to a decrease in porosity and a simultaneous increase in matrix tortuosity due to the formation of a continuous matrix at high applied forces. They argued that there was greater entrapment of drug within the matrix, and an increased difficulty for water to penetrate into the tablet to leach out the drug (Efentakis *et al.*, 1990).

The effect of compressional force on the deformation of granules within the tablet was visualised by means of scanning electron microscopy. It is evident from Figures 5.36, 5.37 and 5.38 that the porosity of a compressed tablet is decreased as the compressional force is increased. Similar findings were reported by Jarosz and Parrott (1983). As the compressional force was increased, the granules were fractured, and original granules could not be seen because consolidation had taken place.

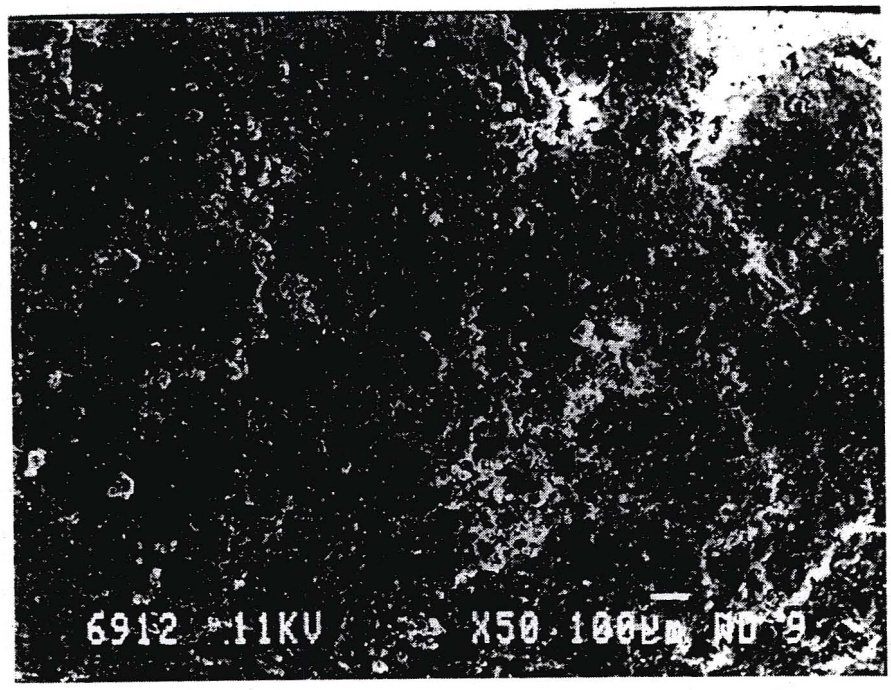


Figure 5.36: Surface morphology of a tablet of Batch HARD 34

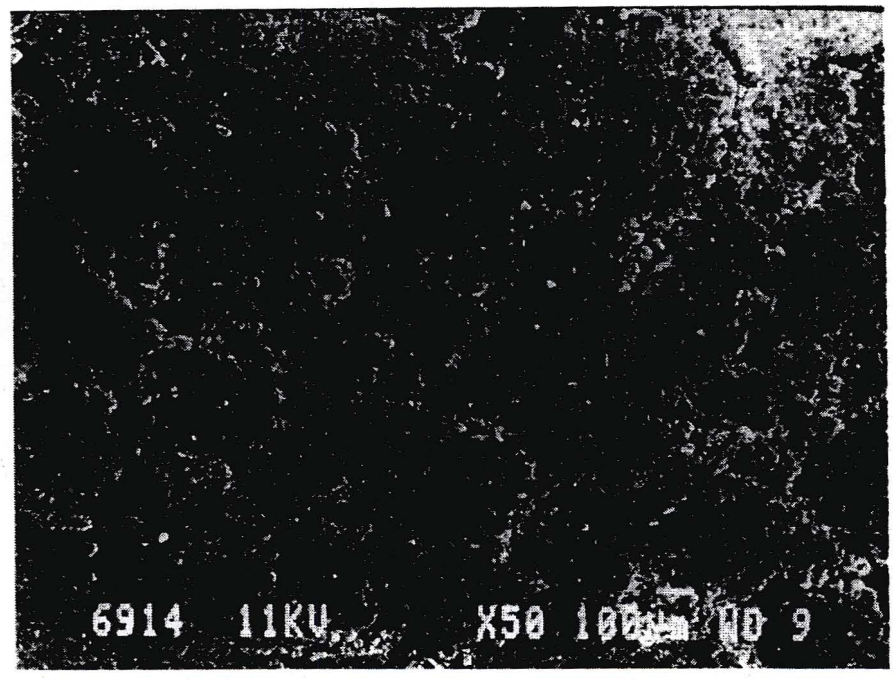


Figure 5.37: Surface morphology of a tablet of Batch NH

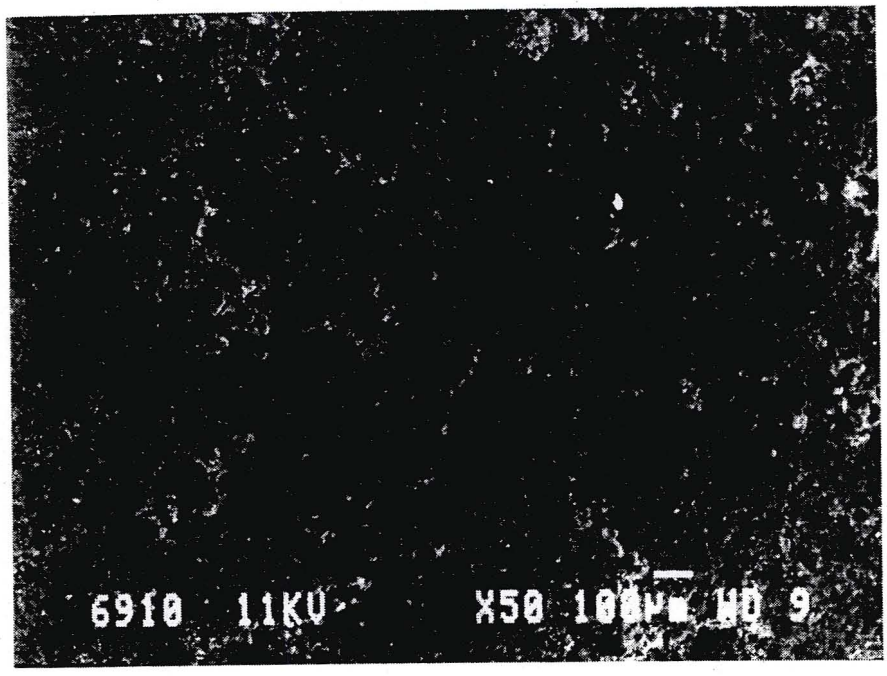


Figure 5.38: Surface morphology of a tablet of Batch HARD 67

5.10 ELECTRON MICROSCOPY

5.10.1 *SCANNING ELECTRON MICROSCOPY (SEM)*

SEM was performed on the diclofenac sodium Eudragit® matrix tablets of Batch NH. The surface, as well as cross-sectional morphological characteristics were obtained. The scanning electron micrographs are depicted in Figures 5.39, 5.40 and 5.41 respectively.

Figure 5.39: Surface morphology of a tablet of Batch NH

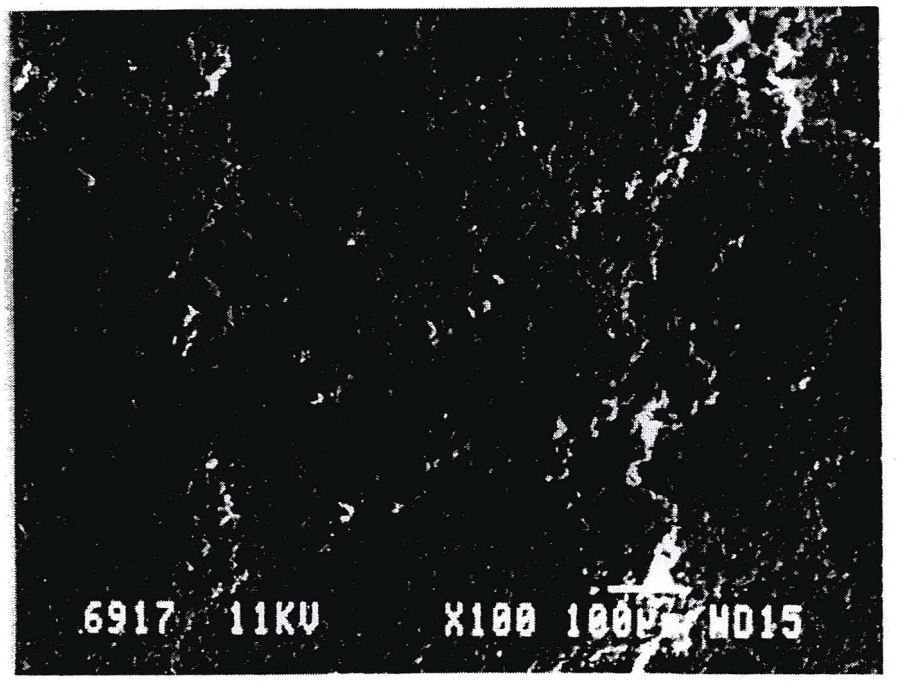


Figure 5.40: Vertical cross-section of a tablet of Batch NH

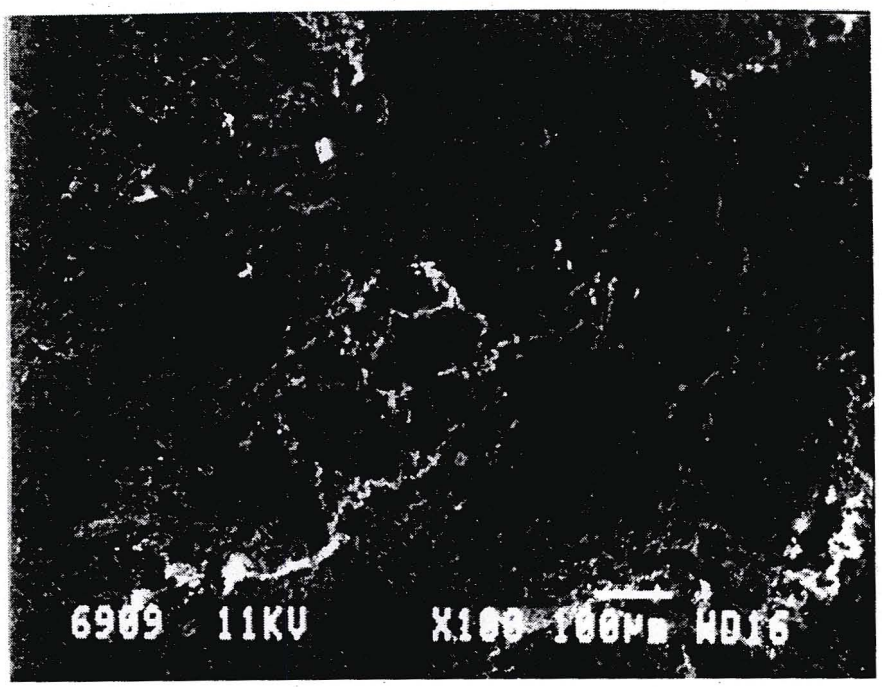
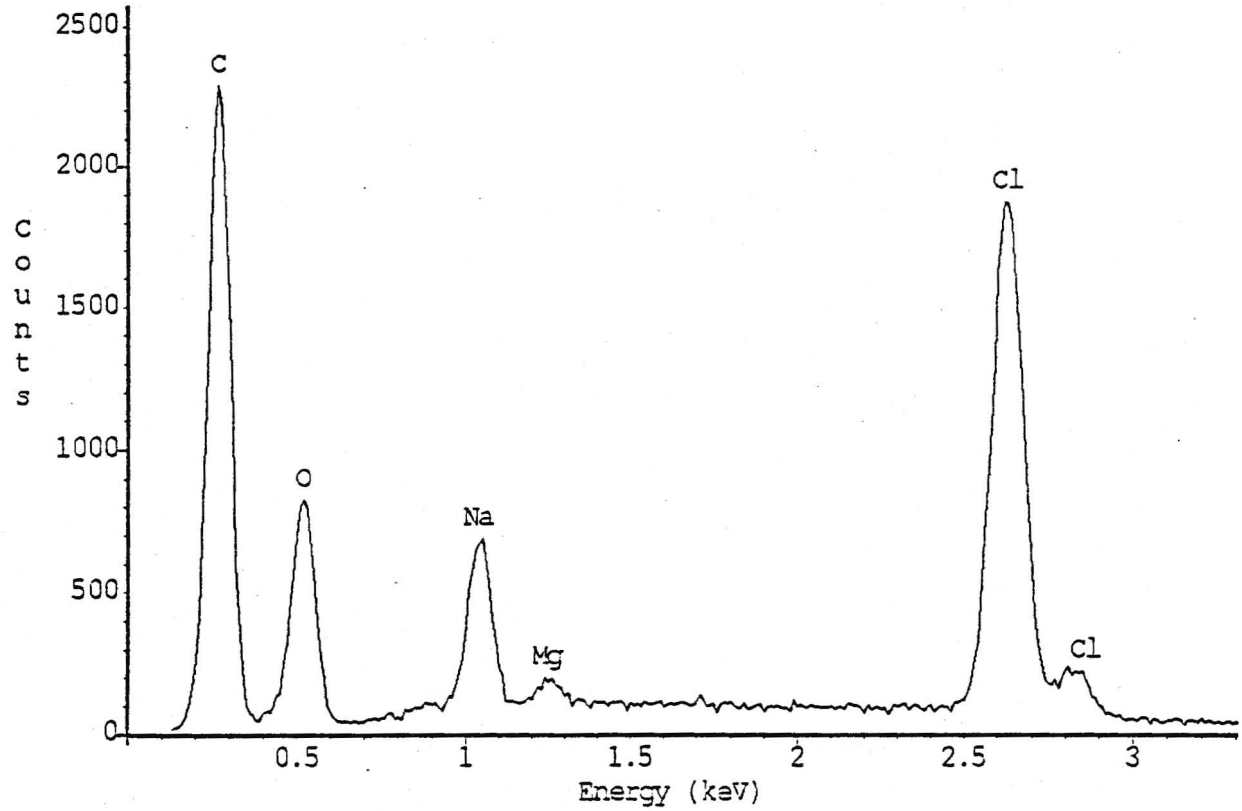


Figure 5.41: Horizontal cross-section of a tablet of Batch NH

Figure 5.39 shows that although the surface appeared cracked, the tablets had smooth and even surfaces. The so-called 'cracks' were evidence of the porous nature of the matrices. The vertical and horizontal sections as illustrated in Figures 5.40 and 5.41 also demonstrate the 'cracked' appearance, which further highlights the porous nature of the matrices.

5.10.2 *ENERGY DISPERSIVE X-RAY MICROPROBE ANALYSIS (EDX)*

The EDX spectrum of a tablet from Batch NH was obtained (Figure 5.42). This spectrum shows the elemental composition of the sample.



Chi-sqd = 2.48 Livetime = 60.0 Sec.

Standardless Analysis

Element	Relative k-ratio	Error (1-Sigma)	Net Counts	Error (1-Sigma)
C -K	---	---	19293 +/-	145
O -K	---	---	6737 +/-	131
Na-K	0.15362 +/-	0.00408	5042 +/-	134
Cl-K	0.83361 +/-	0.00905	22653 +/-	246
Mg-K	0.01277 +/-	0.00268	611 +/-	128

Adjustment Factors	K	L	M
Z-Balance:	0.0000	0.0000	0.0000
Shell:	1.0000	1.0000	1.0000

PROZA Correction Acc.Volt.= 15 kV Take-off Angle=30.98 deg
Number of Iterations = 5

Element	k-ratio (calc.)	ZAF	Atom %	Element Wt %	Wt % Err. (1-Sigma)
Na-K	0.13364	1.568	28.80	20.96	+/- 0.56
Cl-K	0.72516	1.064	68.78	77.18	+/- 0.84
Mg-K	0.01111	1.674	2.42	1.86	+/- 0.39
Total			100.00	100.00	

Tablet - Batch NH - average analysis

Figure 5.42: EDX spectrum of a tablet of Batch NH

The qualitative data that accompanies Figure 5.42 is expressed in two forms. One approach quantitates the elemental composition of the sample in terms of the skeleton elements, carbon and oxygen, while the other approach excludes this skeleton. Therefore, the latter is the more appropriate method to interpret the results.

The composition of the sodium ions was 20.96% $^{wt}/_{wt}$, while that of the chloride ions was 77.18% $^{wt}/_{wt}$. These elements are present in diclofenac sodium, hence they were detected in large quantities. Magnesium on the other hand was present in a total amount of 1.86% $^{wt}/_{wt}$. The presence of magnesium was due to the presence of the lubricant, magnesium stearate. Since the lubricant was present as 1% of the total mass of the tablets, a low concentration of the ions was detected.

Therefore, in terms of the predictability of the elemental composition of the drug delivery device, it can be noted that the theoretical predictions complement the observed chemistry.

5.11 POWDER X-RAY DIFFRACTION

X-ray diffraction was used as a qualitative method to analyse and elucidate any possible effects the processes of granulation or compression had on the crystal structures of the constituents of the tablet. X-ray diffraction patterns of diclofenac sodium, lactose, Eudragit® RLPO, Eudragit® RSPO, starch and magnesium stearate were obtained. These diffractograms were obtained to create a library of diffraction patterns so that the individual peaks in the physical mixture, granules and tablet diffractograms could be identified and characterised. In addition, x-ray diffraction patterns of the granulated Eudragit® polymers, RLPO and RSPO, were also obtained to determine the influence, if any, of granulation and drying on the respective Eudragit® polymers. The x-ray diffractograms of diclofenac sodium, lactose, Eudragit® RLPO, Eudragit® RSPO, granulated Eudragit® RLPO, granulated Eudragit® RSPO, starch, magnesium stearate, physical mixture, granules and tablets are illustrated in Figures 5.43, 5.44, 5.45, 5.46, 5.47, 5.48, 5.49, 5.50, 5.51, 5.52 and 5.53 respectively.

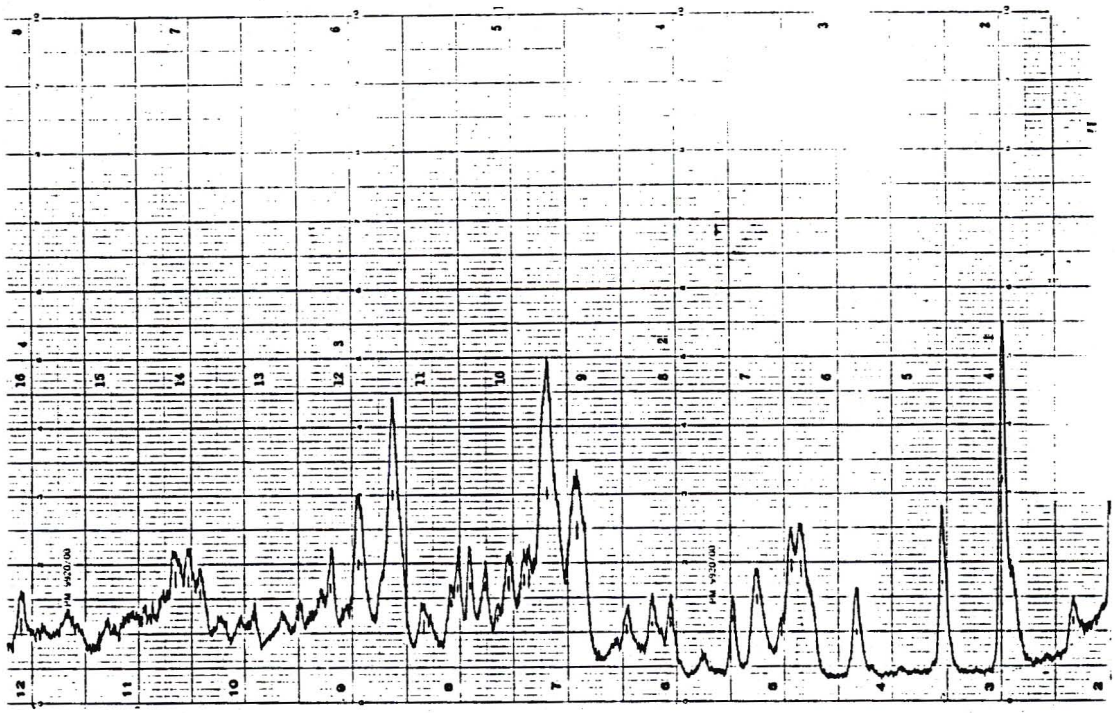


Figure 5.43: X-ray diffractogram of diclofenac sodium

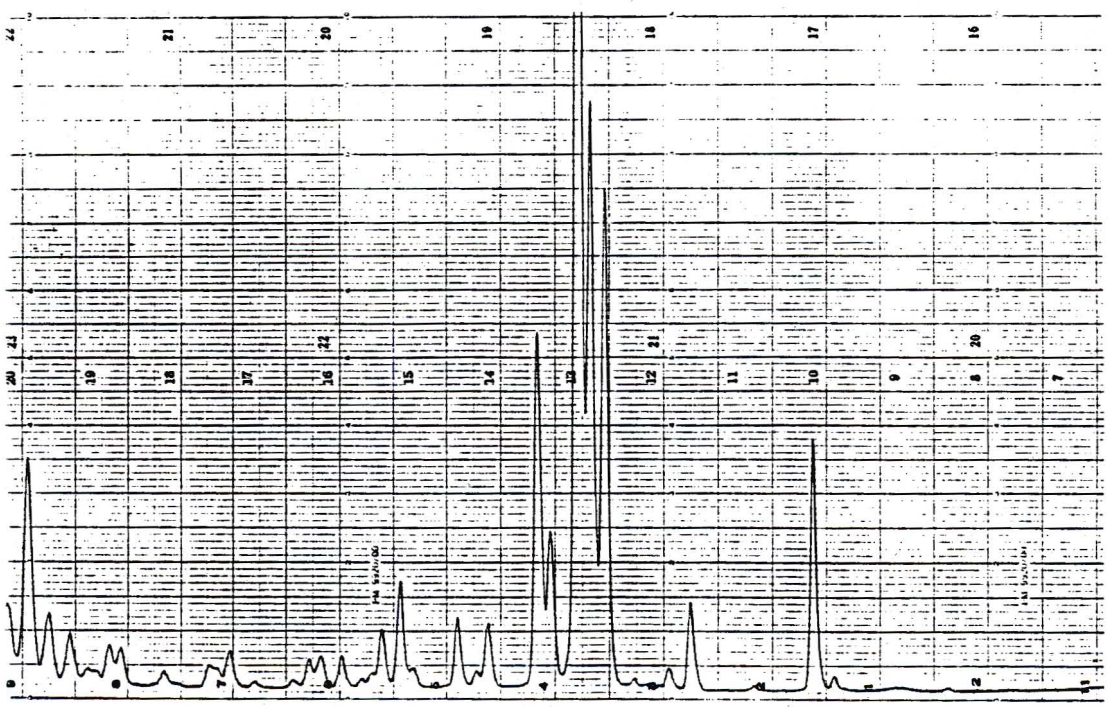


Figure 5.44: X-ray diffractogram of lactose

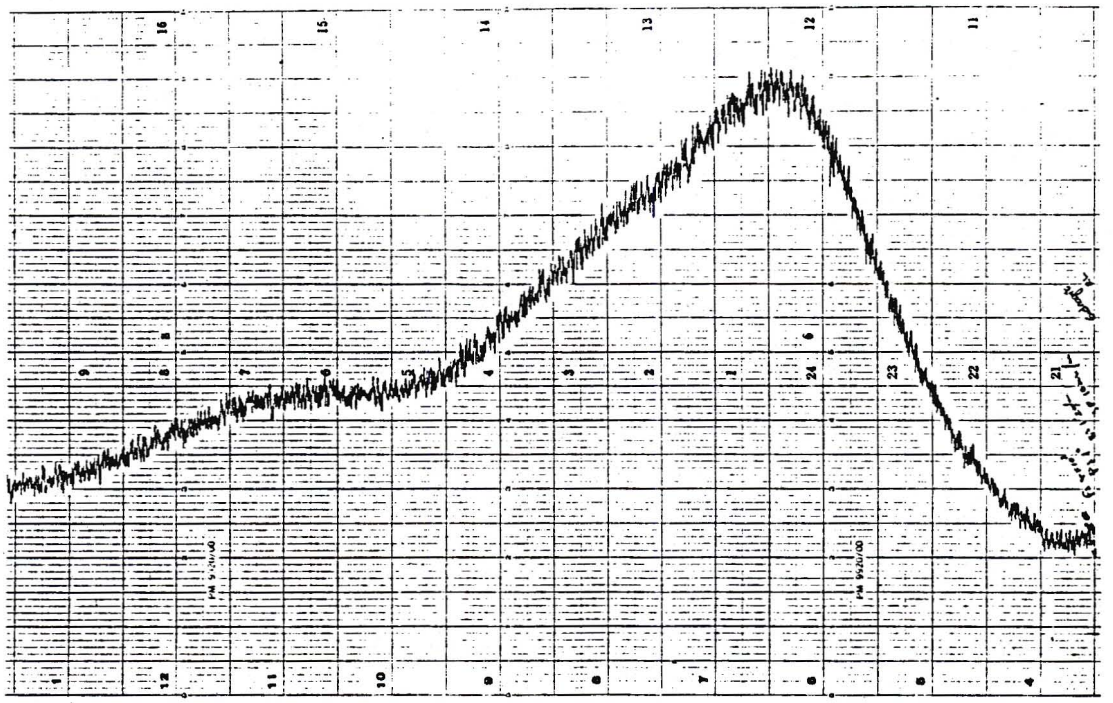


Figure 5.45: X-ray diffractogram of Eudragit® RLPO 4°2θ

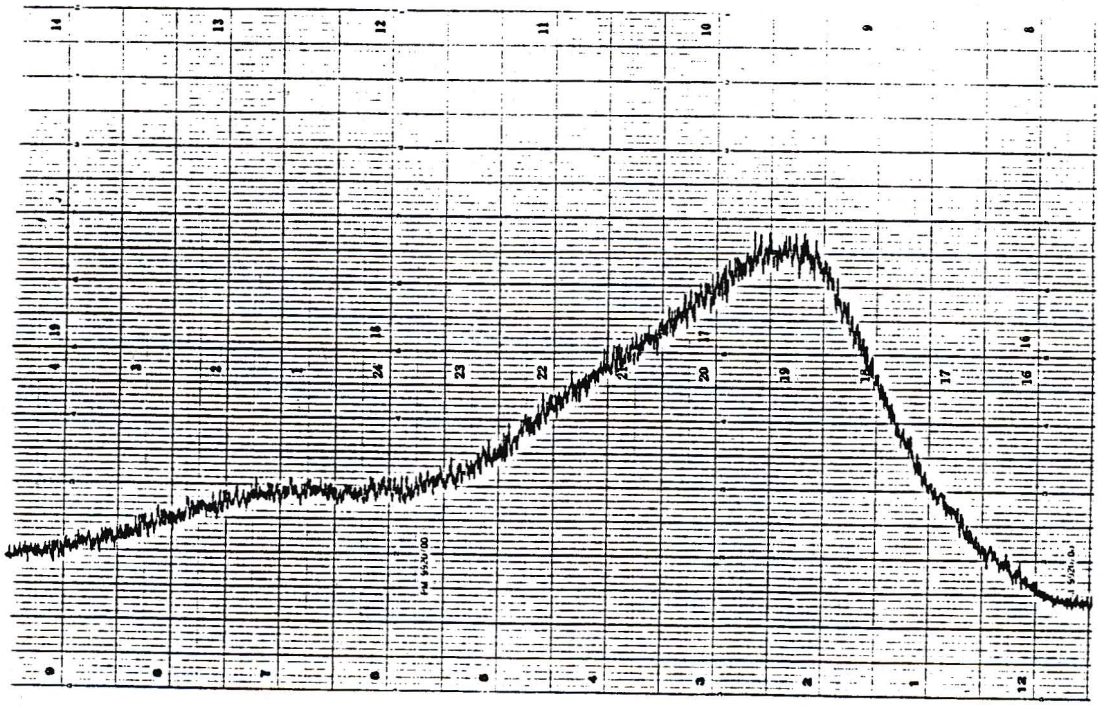


Figure 5.46: X-ray diffractogram of Eudragit® RSPO 4°2θ

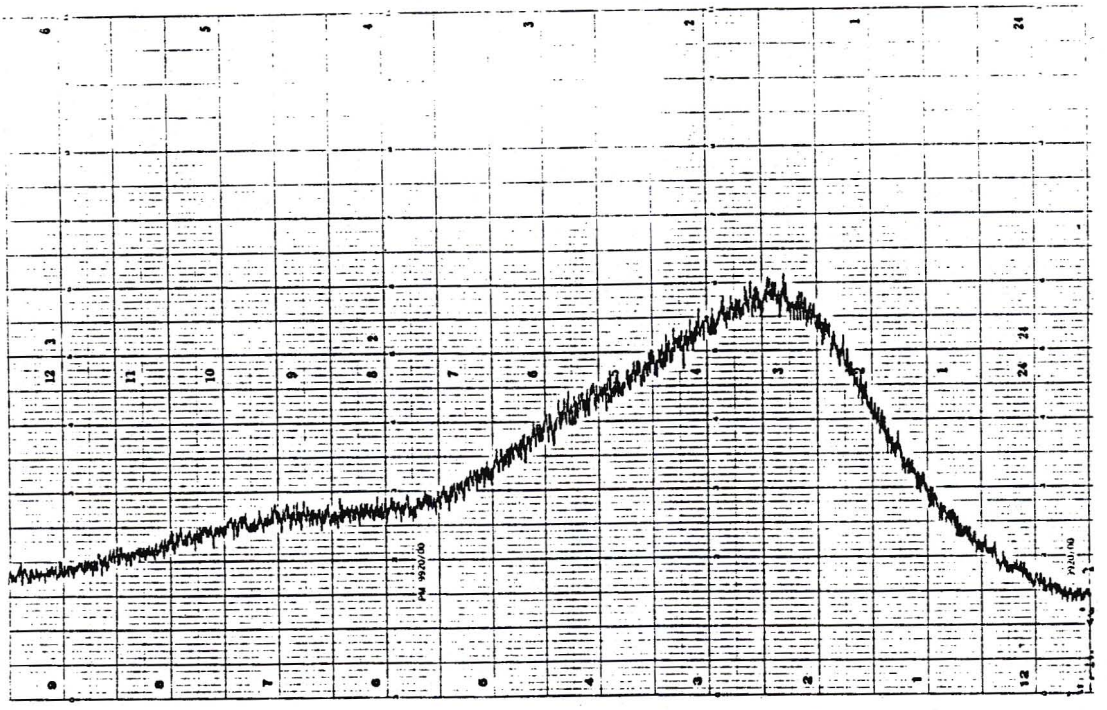


Figure 5.47: X-ray diffractogram of granulated Eudragit® RLPO 4°2θ

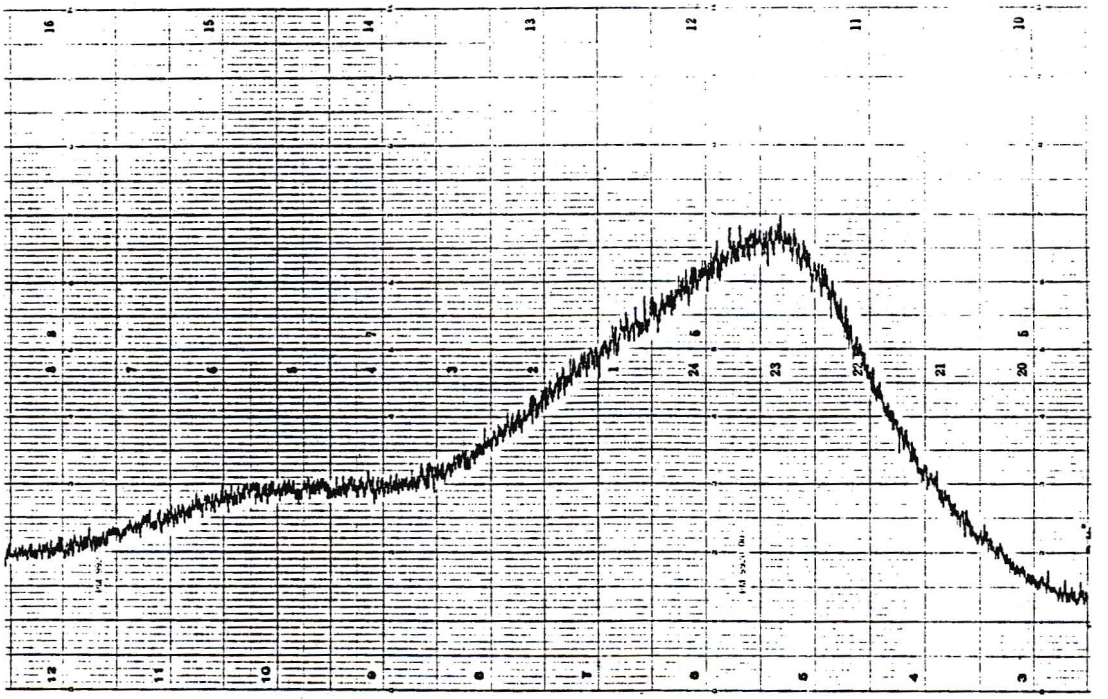


Figure 5.48: X-ray diffractogram of granulated Eudragit® RSPO 4°2θ

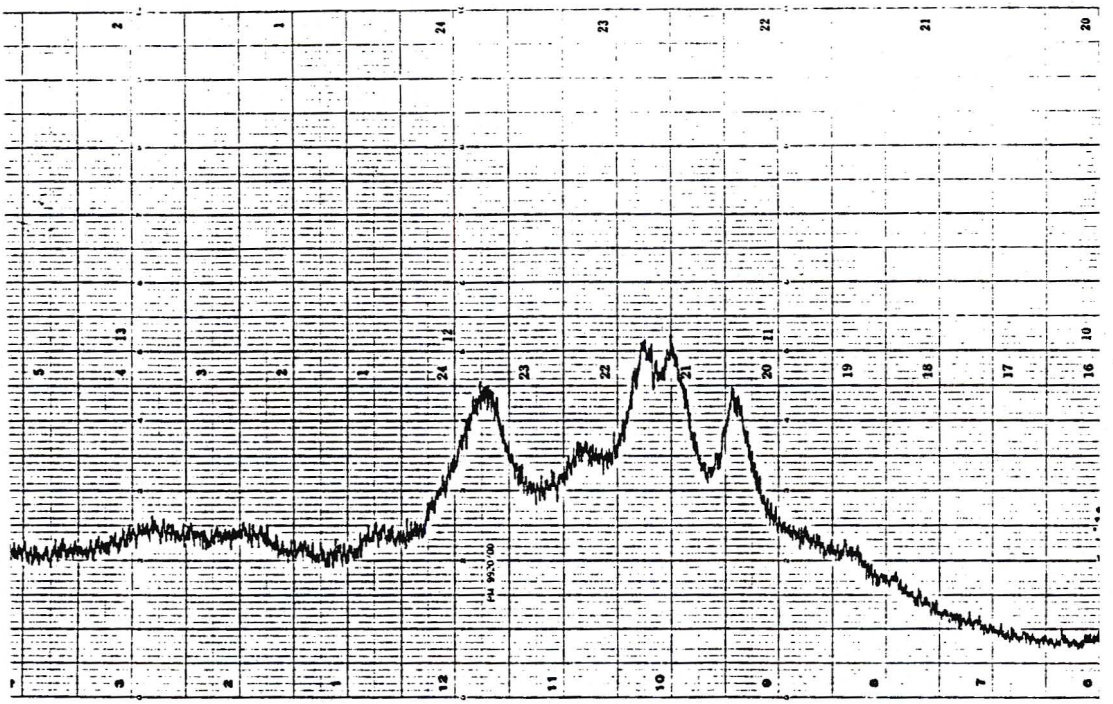


Figure 5.49: X-ray diffractogram of starch

4°2θ

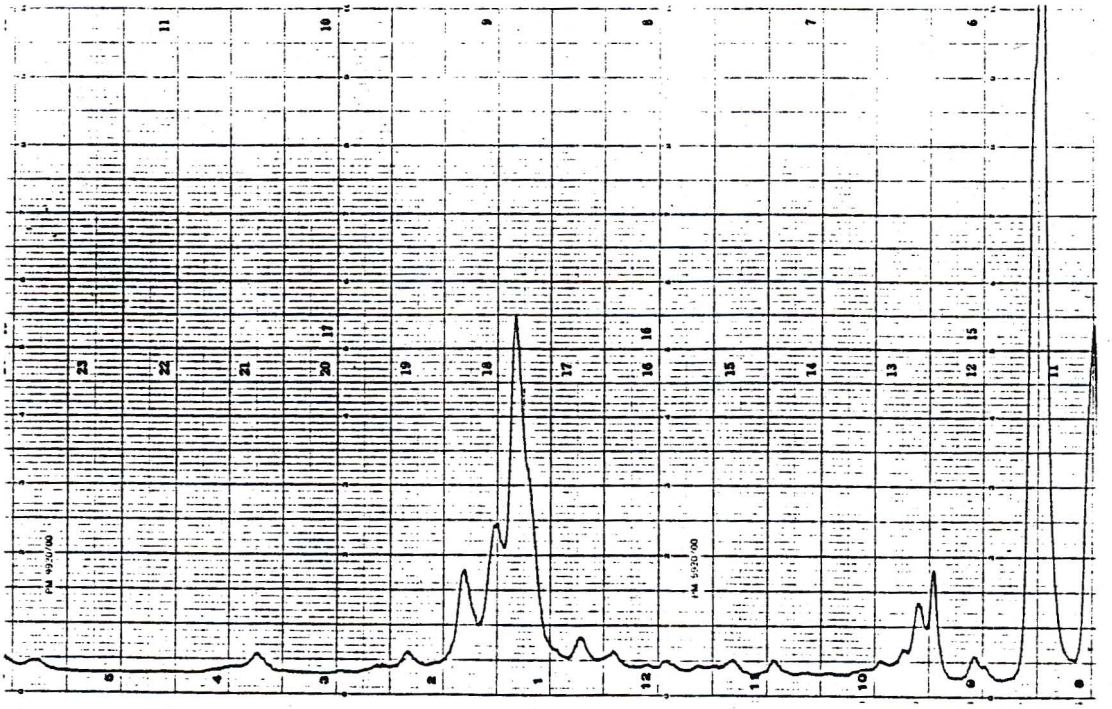


Figure 5.50: X-ray diffractogram of magnesium stearate

4°2θ

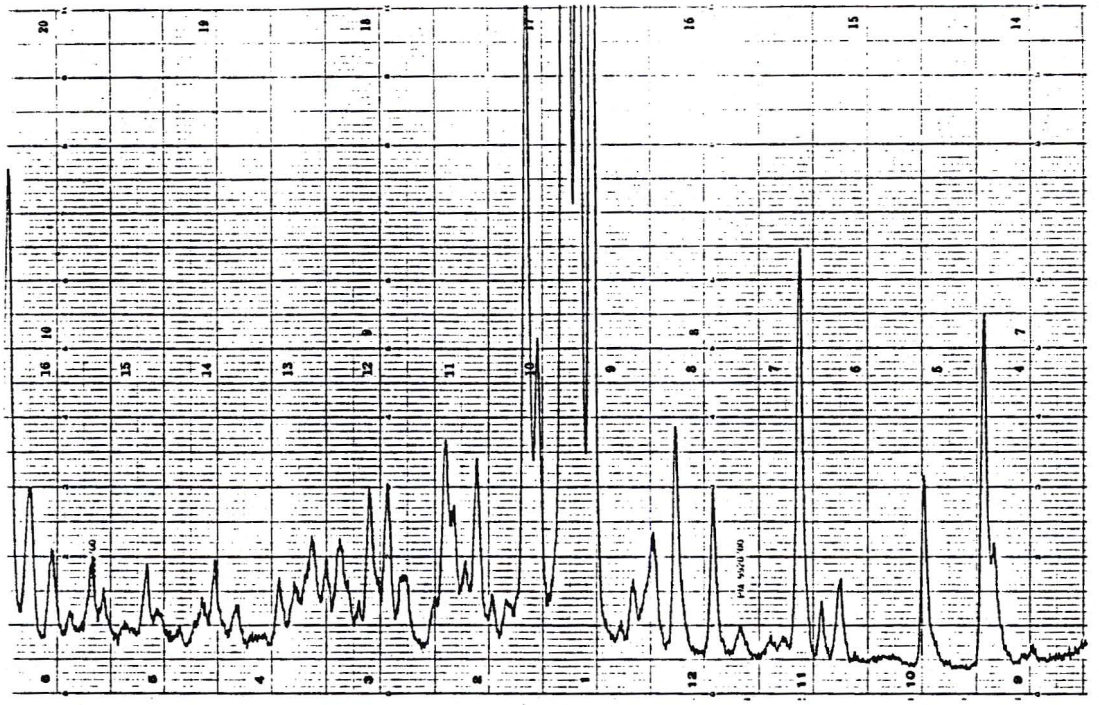


Figure 5.51: X-ray diffractogram of the physical mixture of Batch NH 4°2θ

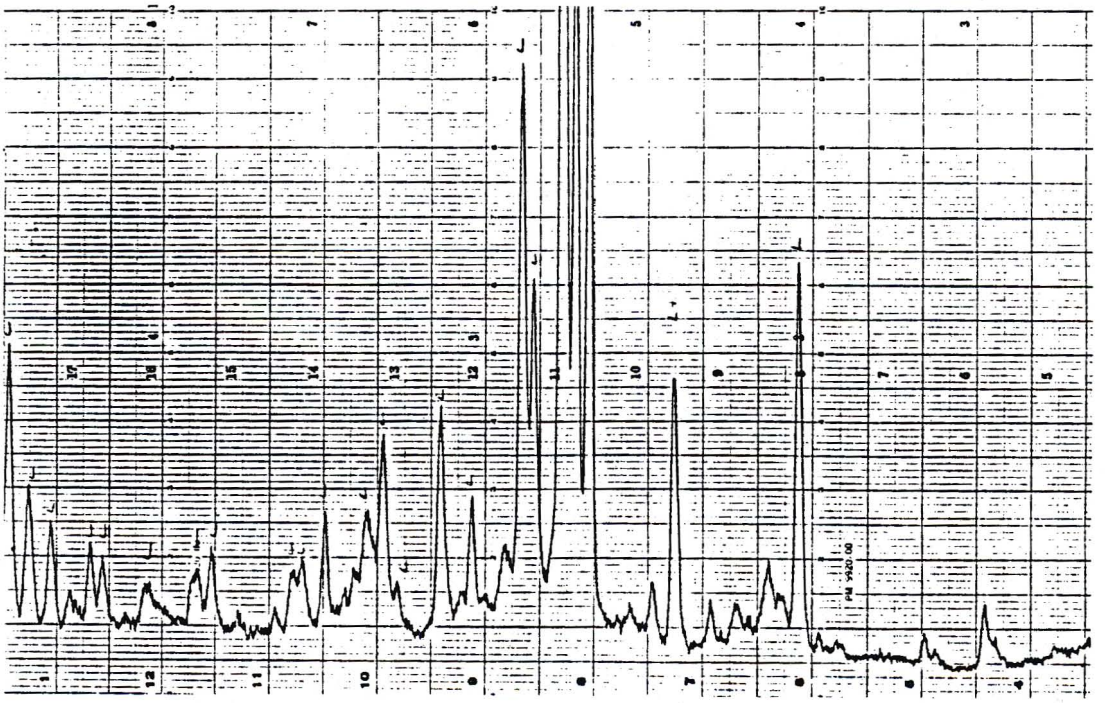


Figure 5.52: X-ray diffractogram of the granules of Batch NH 4°2θ

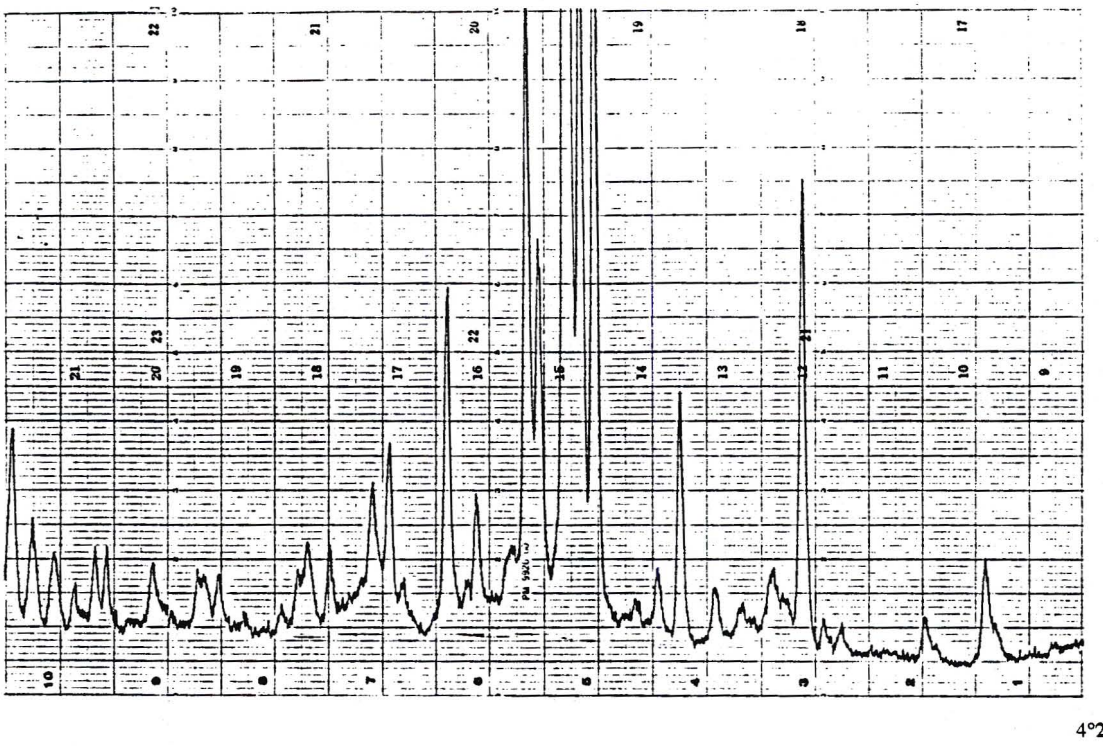


Figure 5.53: X-ray diffractogram of the tablets of Batch NH

The diffraction pattern of diclofenac sodium was found to be representative of a crystalline compound. Likewise, lactose was shown be a very crystalline compound. On the other hand, the Eudragit® polymers RLPO and RSPO displayed typical bell-shaped diffraction patterns. Such patterns are characteristic of amorphous compounds. The diffraction patterns of the granulated Eudragit® polymers also revealed bell-shaped patterns. There were no unaccounted for peaks, which indicated that no crystalline changes occurred after granulation. This therefore provided conclusive evidence that the Eudragit® polymers were amorphous in nature, and remained so even after the granulation process. The diffraction patterns of starch revealed it to be a very poorly crystalline, almost amorphous compound. Magnesium stearate was also found to be crystalline in nature.

A comparison of the diffractograms of the physical mixture with the granules showed that the peaks were essentially the same, with the only difference being a change in the intensity of some of the peaks. The diclofenac sodium peak occurred at a higher intensity in the mixture than in the granulation. This phenomenon can be explained on the basis of the

following:

- the presence of moisture in the granules (not all the moisture had been removed during drying);
- a possible coating effect of the lactose molecules by diclofenac sodium; or
- lactose could be porous in nature, which could have caused the incorporation of diclofenac sodium into it.

Likewise, a comparison of the diffractograms of the tablet and granulation showed that with the exception of slight changes in the intensities of some of the peaks, they were essentially the same. These changes in intensities may have been due to the preferred orientation of the molecules after compression. The lactose peaks were the dominant peaks, due to their high concentration (57.14%) in the formulation, while the diclofenac sodium peaks were clearly distinguishable at 8 and 10.2° 2Θ.

The usual detection limit for magnesium stearate is 2-3%. The concentration of magnesium stearate (1%) used in the present study was diluted to such an extent, that the strongest peak could only just be detected in the physical mixture, granulation and tablets. The concentration of starch in the formulation was also just at detection limits (4.29%). The peaks were in a difficult area for identification as they were crowded by other peaks. However, an enhancement of the background in the region of the peaks of starch was present.

Hence, it can be concluded that the processes of granulation and compression did not result in any atomic re-arrangement of the drug or any of the excipients.

5.12 STABILITY STUDIES

The potency, moisture content, tablet hardness, drug release profiles and surface morphology of tablets of Batch NH were examined prior to and after specific time intervals of storage under various temperature and humidity conditions.

5.12.1 *POTENCY DETERMINATION*

Potency determinations (HPLC) of all stored samples at different conditions over a 12 week period revealed that for each storage condition, a mean assay of greater than 90% of the mean potency of the tablets was obtained (Table 5.38). Since no additional peaks were observed on the chromatograms, it was concluded that no chemical degradation of the drug had occurred during storage under the various conditions. A typical chromatogram is depicted in Figure 5.54. Due to the absence of chemical degradation under the storage conditions investigated, it was not feasible to extrapolate the stability of the drug by an Arrhenius plot.

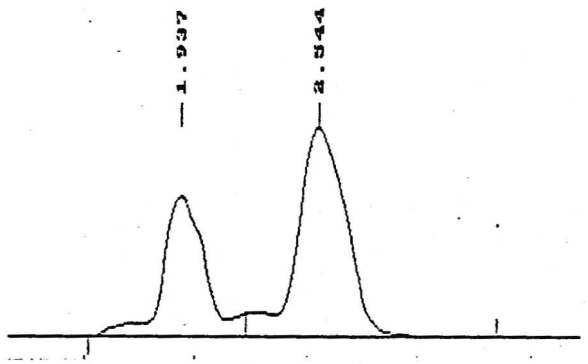


Figure 5.54: Typical HPLC chromatograms of para-nitrobenzoic acid (retention time of 1.937 minutes) and diclofenac sodium (retention time of 2.544 minutes) respectively

Table 5.38: Influence of storage on the drug content of tablets of Batch NH

STORAGE PERIOD (WEEKS)	* AVERAGE DRUG CONTENT (%) AFTER STORAGE			
	RT	5°C	37°C	40°C
0	91.6	91.6	91.6	91.6
4	91.3	90.0	94.6	91.1
8	94.2	90.0	91.3	93.1
12	106.8	105.5	101.4	99.5

* Individual values for 2 replicate determinations are presented in Appendices 6.2, 6.3, 6.4 and 6.5. respectively.

RT = room temperature

37°C = 37°C with 80% relative humidity

5.12.2 *MOISTURE CONTENT DETERMINATION*

The moisture content of the tablets as determined prior to and after storage under the various conditions, is outlined in Table 5.39.

Table 5.39: Influence of storage on the moisture content of tablets of Batch NH

STORAGE PERIOD (WEEKS)	* MEAN MOISTURE CONTENT AFTER STORAGE			
	RT	5°C	37°C	40°C
0	6.91±0.04	6.91±0.04	6.91±0.04	6.91±0.04
4	7.95±0.35	8.90±0.34	9.47±0.27	9.56±0.27
8	6.89±0.65	7.94±0.04	7.94±0.28	8.70±0.89
12	7.41±0.06	7.99±0.04	8.68±0.46	8.38±0.34

* Individual values for 3 replicate determinations are shown in Appendix 98.

RT = room temperature

37°C = 37°C with 80% relative humidity

There was a modest increase in the moisture content of the samples after storage. However, the moisture content of the samples did not contribute to any instability of the dosage form. Also, diclofenac sodium is hygroscopic in nature, and will absorb moisture, hence, an increase in the moisture content of the samples would occur.

5.12.3 *TABLET HARDNESS*

The hardness of the tablets was determined prior to and after storage under various temperature and humidity conditions. The mean hardness of 5 tablets is presented in Table 5.40.

Table 5.40: Influence of storage on the hardness of tablets of Batch NH

STORAGE PERIOD (WEEKS)	* MEAN TABLET HARDNESS (Kp) AFTER STORAGE AT			
	RT	5°C	37°C	40°C
0	4.68±0.13	4.68±0.13	4.68±0.13	4.68±0.13
4	4.52±0.16	4.52±0.08	5.28±0.08	5.20±0.22
8	4.68±0.24	4.30±0.16	5.88±0.19	5.96±0.22
12	4.52±0.24	4.08±0.08	6.56±0.18	6.32±0.15

* Individual values for 5 replicate determinations are shown in Appendix 99.

RT = room temperature

37°C = 37°C with 80% relative humidity

It is clear from Table 5.40, that the tablets stored at room temperature (22±1°C) and low temperature (5±1°C) did not undergo a change in hardness, whereas tablets stored at 37°C with 80% relative humidity and 40°C hardened considerably. The factors that are responsible for an increase in the hardness of tablets during storage have been extensively reviewed by Follonier and Doelker (1993).

Therefore, it can be concluded that the tablets stored at room temperature and low temperature remained stable with respect to tablet hardness.

5.12.4 *DRUG RELEASE EVALUATION*

5.12.4.1 Storage At Room Temperature (21±1°C)

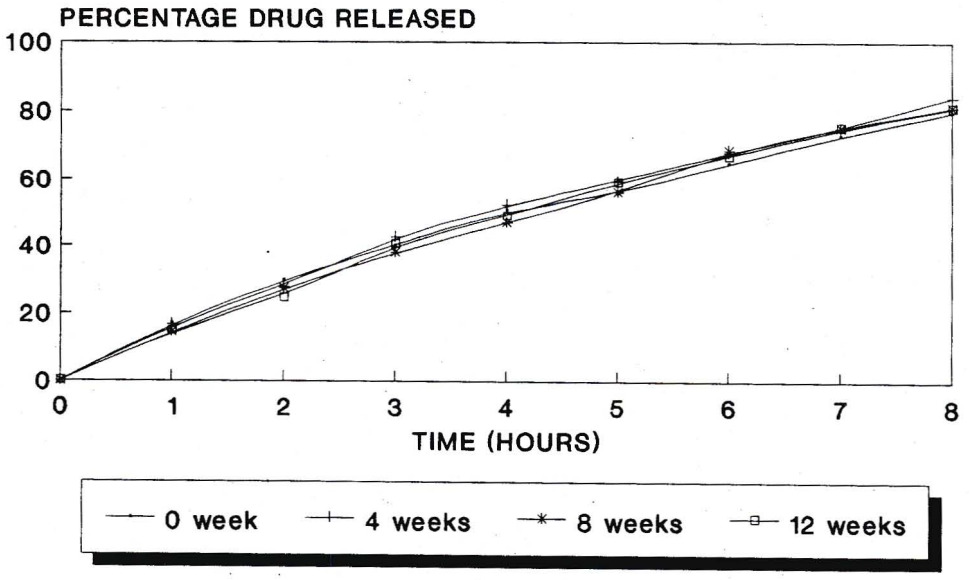
The mean cumulative percentages of diclofenac sodium released initially (0 weeks) and at 4, 8 and 12 weeks after storage at 21±1°C are presented in Table 5.41 and Figure 5.55.

Table 5.41: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH stored at room temperature (21±1°C)

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD			
	0 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	12.05±0.49	12.53±0.31	10.86±0.97	10.84±0.29
1	17.09±1.05	16.84±1.51	14.53±1.23	14.92±1.12
1.5	23.74±0.89	21.28±1.33	20.32±1.18	19.68±1.12
2	29.98±1.80	27.72±1.88	27.35±1.82	24.52±1.58
3	40.19±1.82	42.64±2.20	38.08±2.61	40.57±1.73
4	51.00±2.26	52.54±1.88	46.93±1.89	49.22±1.99
5	55.91±1.57	59.67±1.83	56.32±2.49	59.25±2.57
6	64.19±2.19	68.18±2.38	68.72±2.45	66.90±1.83
7	73.07±1.82	75.16±2.03	75.46±1.48	75.35±2.39
8	79.93±1.61	84.16±1.54	81.32±1.19	81.07±0.87

* Individual values for 3 replicate determinations are shown in Appendix 53, 54, 55 and 56 respectively.

Figure 5.55: Effect of storage at room temperature (21±1°C) on the release profile of diclofenac sodium (Batch NH)



The data presented in Table 5.41 and Figure 5.55 indicate that the tablets stored at room temperature (21±1°C) did not display any appreciable change in the drug release characteristics during the 12 week period of the investigation. It was thus inferred that the tablets were stable at room temperature conditions (21±1°C) with regard to their drug release characteristics.

5.12.4.2 Storage At Low Temperature (5±1°C)

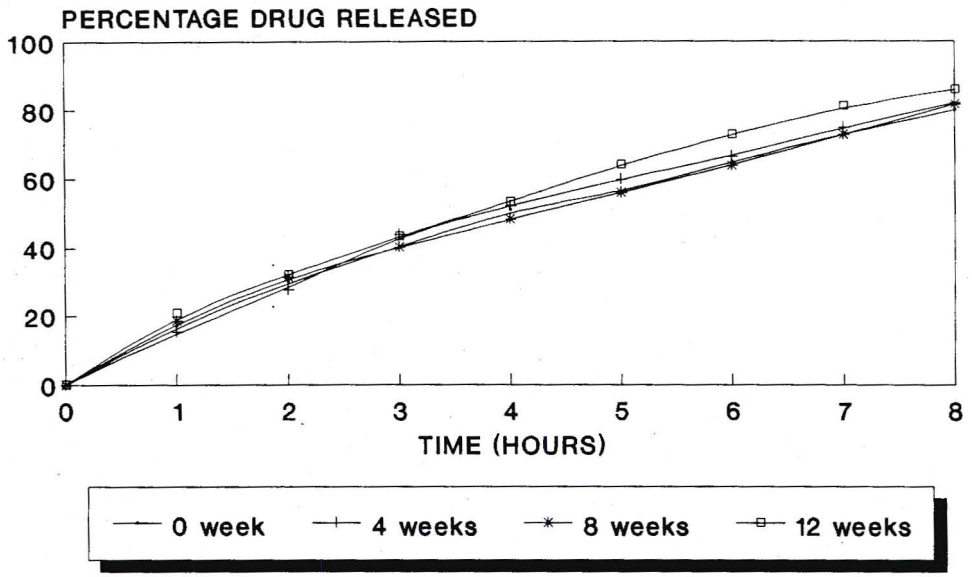
The mean cumulative percentages of diclofenac sodium released from tablets initially (0 weeks) and at 4, 8 and 12 weeks after storage at 5°C are presented in Table 5.32 and Figure 5.56.

Table 5.42: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH stored at 5±1°C

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGES DRUG RELEASED ± SD			
	0 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	12.05±0.49	11.90±0.92	11.77±1.01	15.04±0.99
1	17.09±1.05	15.22±0.48	18.47±1.23	20.80±1.69
1.5	23.74±0.98	21.45±1.39	23.39±0.97	26.74±1.71
2	29.98±1.80	27.59±1.78	31.50±2.25	32.02±1.35
3	40.19±1.82	44.00±1.59	40.09±2.38	43.39±1.59
4	51.00±2.26	52.20±2.25	48.35±2.58	53.41±0.93
5	55.91±1.57	59.84±0.87	56.04±1.51	64.01±2.89
6	64.19±2.19	66.46±1.69	63.73±2.04	72.81±2.02
7	73.07±1.82	74.84±2.77	72.75±2.56	81.11±1.98
8	79.93±1.61	82.03±1.12	81.58±1.24	85.92±0.75

* Individual values for 3 replicate determinations are shown in Appendices 53, 57, 58 and 59 respectively.

Figure 5.56: Effect of storage at low temperature (5+1°C) on the release profile of diclofenac sodium (Batch NH)



The data presented in Table 5.42 and Figure 5.56 do not show a considerable change in the dissolution characteristics of the stored tablets. The profiles of the tablets stored for 4 and 8 weeks yielded a release profile that was virtually identical and superimposable on the initial dissolution profile. The sample stored for 12 weeks however, showed enhanced drug release when compared to the initial sample (0 weeks). However, this profile appeared to be similar to the dissolution characteristics of the overall sample of Batch NH. Therefore the tablets of Batch NH were considered stable at 5 ± 1°C for the short term period of testing.

5.12.4.3 Storage At 37°C With 80% Relative Humidity

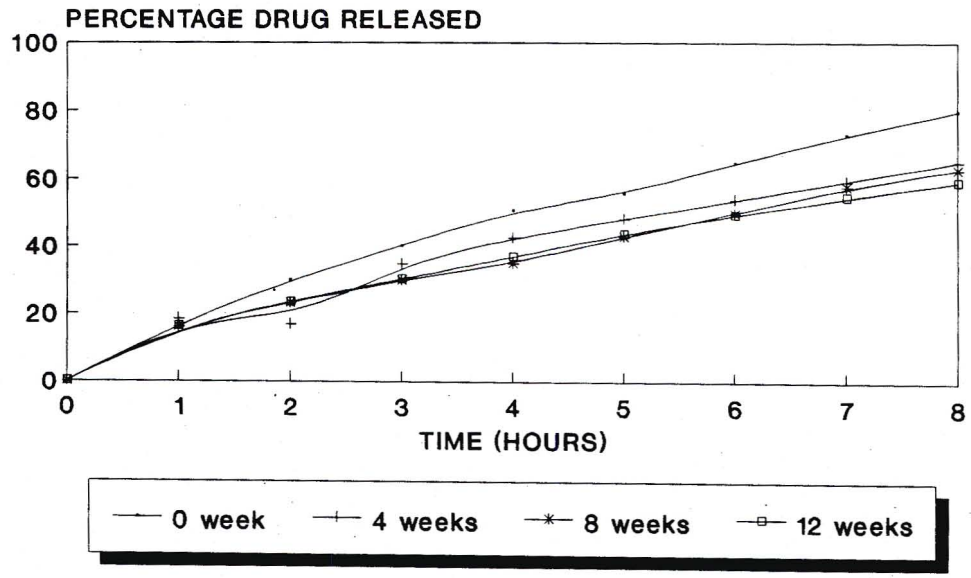
In order to demonstrate the effect of elevated temperature and humidity conditions on the tablets of Batch NH, the drug release behaviour of the tablets was evaluated at 37°C with 80% relative humidity over a 12 week period. The mean cumulative percentages and drug release profiles obtained are depicted in Table 5.43 and Figure 5.57.

Table 5.43: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH stored at 37°C with 80% relative humidity

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD			
	0 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	12.05±0.49	13.46±0.15	13.47±0.43	12.41±0.37
1	17.09±1.05	18.49±1.17	16.27±0.73	16.30±0.23
1.5	23.74±0.89	23.76±1.62	19.08±1.09	19.60±0.12
2	29.98±1.80	26.89±1.21	23.29±1.23	23.51±0.88
3	40.19±1.82	34.92±0.93	29.95±1.88	30.25±0.82
4	51.00±2.26	42.58±1.43	35.10±1.68	36.99±0.64
5	55.91±1.57	48.29±0.66	43.02±1.18	43.82±0.28
6	64.19±2.19	54.22±0.85	50.10±2.18	49.59±0.81
7	73.07±1.82	59.59±1.11	58.14±1.67	54.94±1.57
8	79.93±1.61	65.22±0.94	63.06±1.63	59.34±1.29

* Individual values for 3 replicate determinations are shown in Appendices 53, 60, 61 and 62 respectively.

Figure 5.57: Effect of storage at 37°C with 80% relative humidity on the release of diclofenac sodium (Batch NH)



The results presented in Table 5.43 and Figure 5.57 show that drug release was drastically decreased when the tablets were subjected to a storage condition of 37°C with 80% relative humidity. While there was a considerable decrease in drug release between the initial and four weeks samples, the differences between the 4, 8 and 12 week samples were not as great. It can therefore be concluded that the tablets stored at elevated temperatures and humidities showed dramatic changes in the drug release characteristics after a period of time.

5.12.4.4 Storage At 40°C

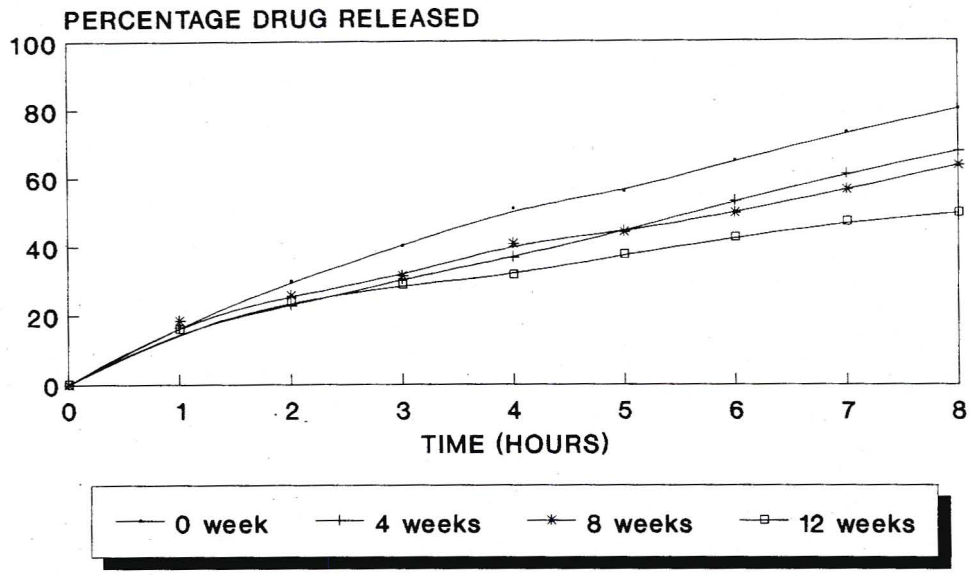
The mean cumulative percentage and drug release profiles obtained initially (0 weeks) and at 4, 8 and 12 weeks after storage are shown in Table 5.44 and Figure 5.58 respectively.

Table 5.44: Mean cumulative percentages of diclofenac sodium released from tablets of Batch NH stored at 40°C

TIME (HOURS)	* MEAN CUMULATIVE PERCENTAGES DRUG RELEASED ± SD			
	0 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	12.05±0.49	13.48±0.41	14.02±0.90	13.86±0.55
1	17.09±1.05	16.49±1.44	18.47±0.89	16.00±0.16
1.5	23.74±0.89	20.07±1.10	22.16±1.05	21.09±0.18
2	29.98±1.80	22.78±1.74	25.63±0.80	24.11±0.96
3	40.19±1.82	30.45±2.03	31.45±1.69	28.67±0.73
4	51.00±2.26	36.78±1.65	40.71±0.41	31.64±0.86
5	55.91±1.57	44.32±1.84	44.19±1.76	37.43±1.18
6	64.19±2.19	53.21±1.44	49.74±2.02	42.37±1.32
7	73.07±1.82	60.88±1.65	56.28±1.80	46.95±1.04
8	79.93±1.61	67.63±1.02	63.47±1.56	49.54±1.13

* Individual values for 3 replicate determinations are shown in Appendices 53, 63, 64 and 65 respectively.

Figure 5.58: Effect of storage at 40°C on the release profile of diclofenac sodium (Batch NH)



The results presented in Table 5.44 and Figure 5.58 show that the drug release profile of the tablets stored at 40°C markedly differed from that of the initial sample (0 weeks). There was a considerable decrease in the drug release characteristics between the initial sample and the 4 week sample. Drug release continued to decrease from the 4th to the 8th week.

Mathir (1991), Govender (1992) and Perumal (1996) also reported similar drug release characteristics for chlorpheniramine, salbutamol sulphate and ibuprofen respectively, for samples stored at 40°C over a period of 8 weeks. This slower drug release was attributed to spreading of the polymer as a film over the exposed sharp-edged surface crystals (Perumal, 1996), or as the result of coalescence of polymeric spheres at elevated temperatures (Govender, 1992).

The results therefore suggest that the integrity of the matrices, as well as their drug release characteristics, could not be maintained at high temperatures (40°C).

5.12.5 *SURFACE MORPHOLOGY STUDIES*

The surface morphology of the tablets prior to and after storage at the various conditions were examined by means of scanning electron microscopy (SEM). The SEM pictures of the tablets prior to and after storage are presented in Figures 5.59, 5.60, 5.61, 5.62 and 5.63.

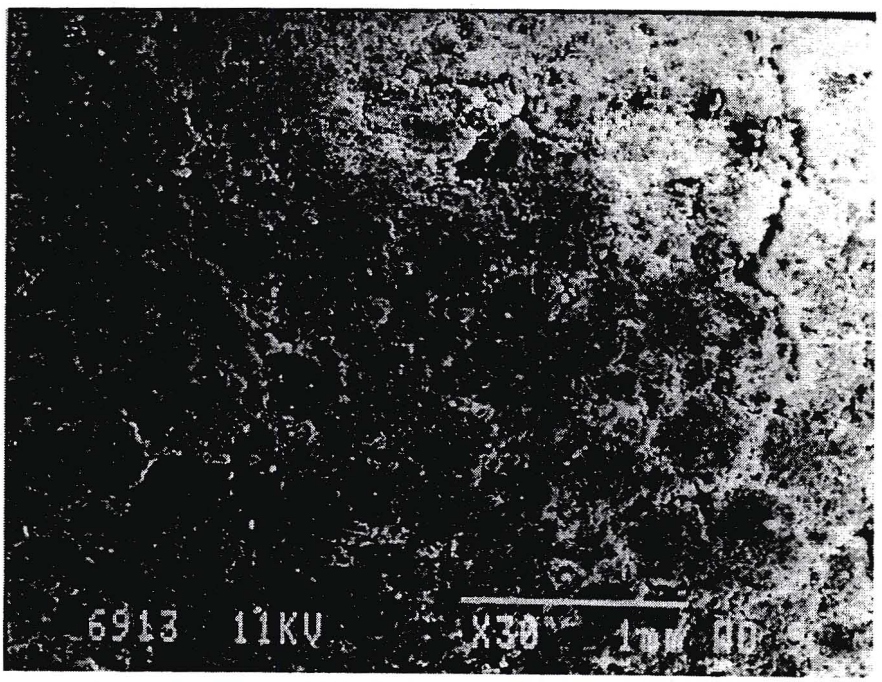


Figure 5.59: Surface morphology of a tablet of Batch NH prior to storage

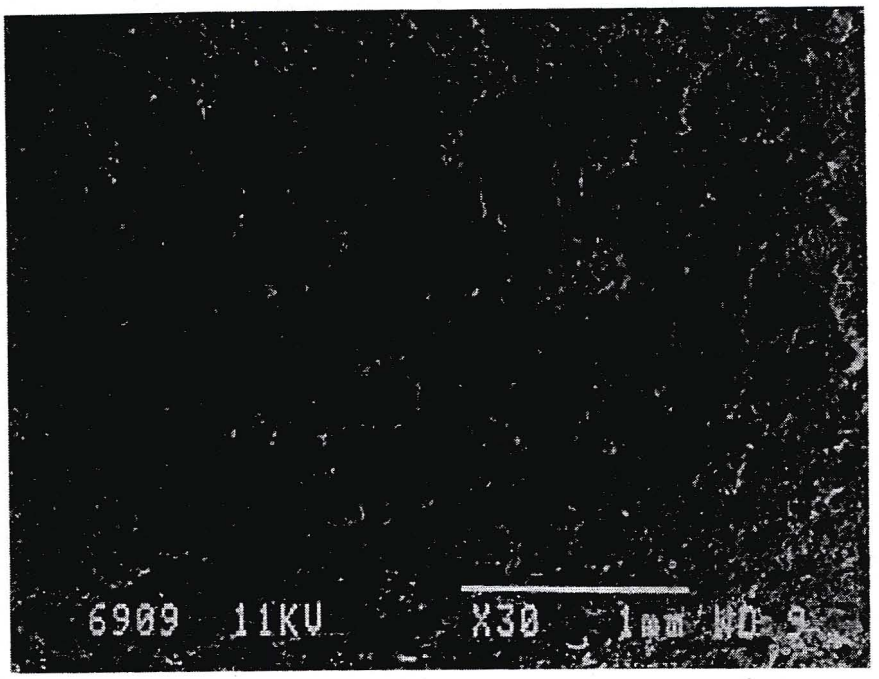


Figure 5.60: Surface morphology of a tablet of Batch NH after 12 weeks of storage at room temperature

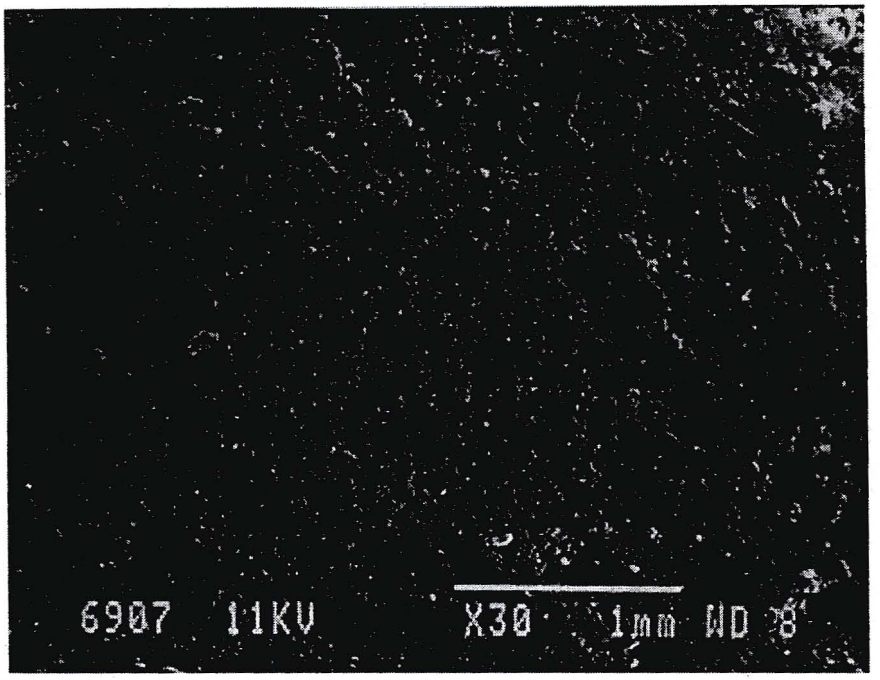


Figure 5.61: Surface morphology of a tablet of Batch NH after 12 weeks of storage at 5±1°C

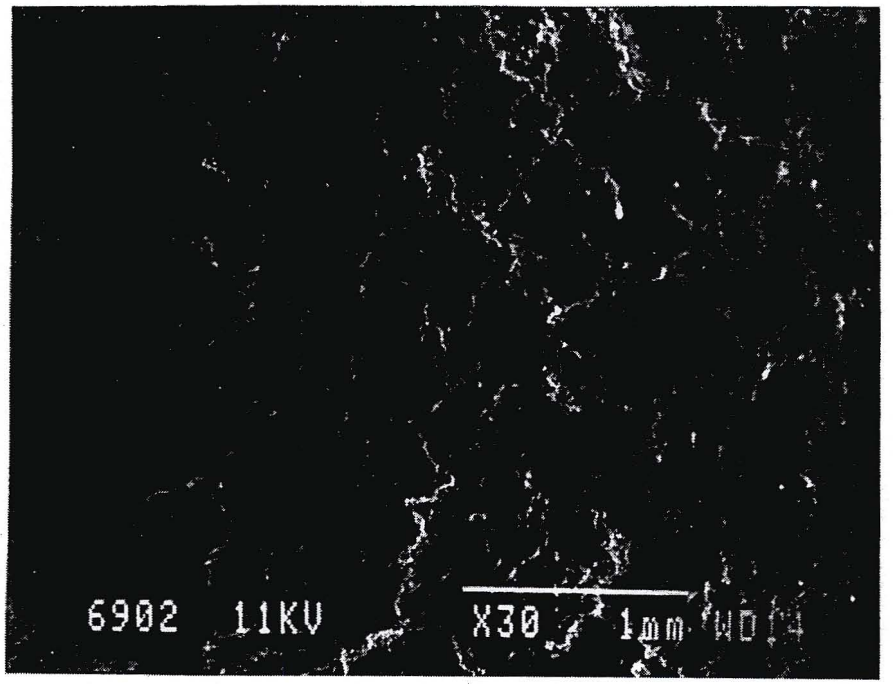


Figure 5.62: Surface morphology of a tablet of Batch NH after 12 weeks of storage at 37°C with a relative humidity of 80%

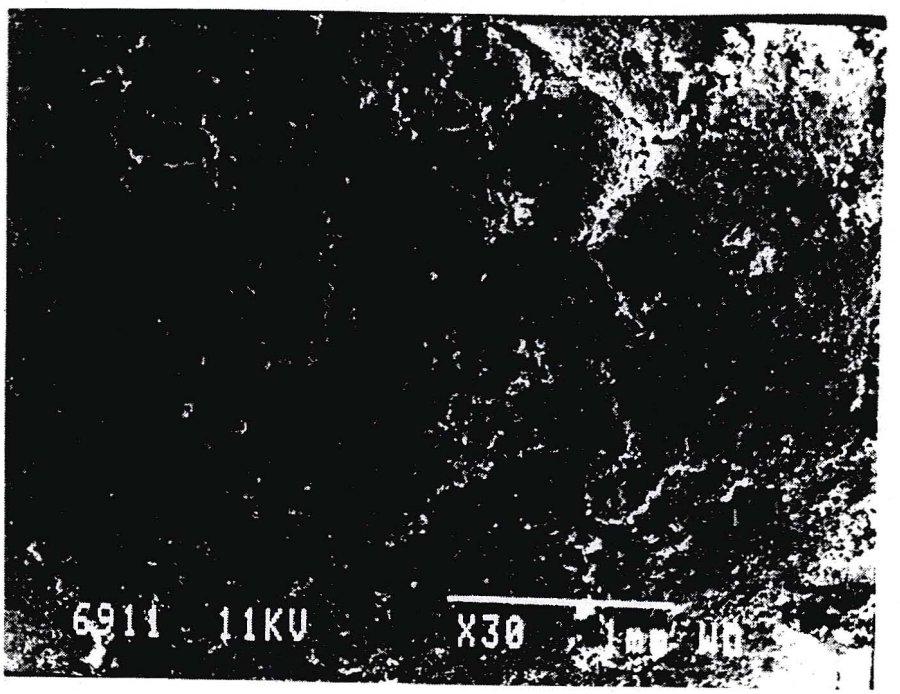


Figure 5.63: Surface morphology of a tablet of Batch NH after 12 weeks of storage at 40°C

The surface morphology of all the stored samples was similar to that of the initial sample. Therefore, on the basis of the surface morphological evaluation, it can be concluded that the tablets from each of the different storage conditions remained unchanged.

5.13 DETERMINATION OF DRUG RELEASE MECHANISM FROM DICLOFENAC SODIUM EUDRAGIT® MATRICES

The dissolution data from Batch NH in 0.2 M phosphate buffer pH 6.8 was used to model the drug release characteristics of diclofenac sodium from the tablet matrices, and the mechanism of drug release was analysed by fitting the dissolution data to each of the following models:

- zero-order kinetics (Malamataris and Averginos, 1990)
- first-order kinetics (Malamataris and Averginos, 1990)
- Higuchi equation (Malamataris and Averginos, 1990)
- Power law expression (Peppas, 1985)

5.13.1 APPLICATION OF KINETIC MODELS

The dissolution data of Batch NH in 0.2 M phosphate buffer pH 6.8 that was utilized in the determination of the drug release characteristics from the matrices are presented in Table 5.45. Model equations used for the drug release plots and subsequent determinations of the dissolution rate constants are tabulated in Table 5.46.

Table 5.45: Dissolution data of tablets of Batch NH for characterisation of drug release

TIME (HOURS)	TIME$^{1/2}$ (HOURS$^{1/2}$)	LOG TIME	% DRUG RELEASED	LOG % DRUG RELEASED	% DRUG REMAINING	LOG %DRUG REMAINING
0	0	-	0	-	100	2
0.5	0.71	-	12.85	1.11	87.15	1.94
1	1.00	0	17.29	1.24	82.71	1.92
1.5	1.23	0.18	20.73	1.32	79.27	1.90
2	1.41	0.30	29.37	1.47	70.63	1.85
3	1.73	0.48	38.85	1.59	61.15	1.79
4	2.00	0.60	47.64	1.68	52.36	1.72
5	2.24	0.70	57.26	1.76	42.74	1.63
6	2.45	0.78	64.35	1.81	35.65	1.55
7	2.65	0.84	74.43	1.87	25.57	1.41
8	2.83	0.90	81.80	1.91	18.20	1.26

Table 5.46: Parameters of the release kinetic models obtained for dissolution data of tablets of Batch NH

RELEASE MODEL	RELEASE EQUATION	RELEASE RATE CONSTANT	r^2
zero-order	$100 - M = K_0 t$	9.740	0.989
first-order	$\ln M = -K_1 t$	0.197	0.976
square root of time	$100 - M = K_2 t^{1/2}$	29.968	0.967
power law	$100 - M = K_3 t^n$	0.765	0.995

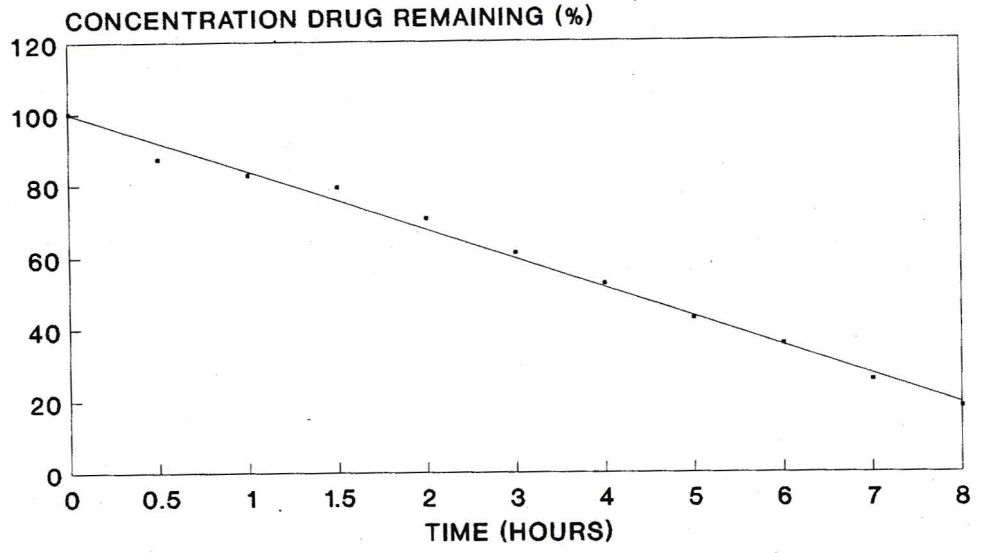
M is the percentage of undissolved drug;

t is the dissolution time;

n is the kinetic exponent; and

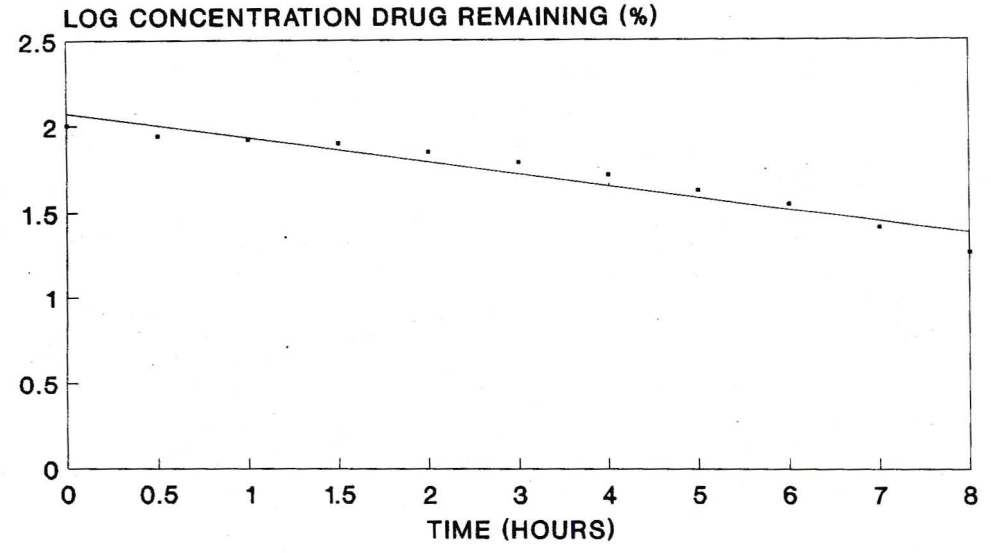
K_1, K_2 and K_3 are the dissolution rate constants.

Figure 5.64: Determination of the order of drug release from Batch NH: zero-order model



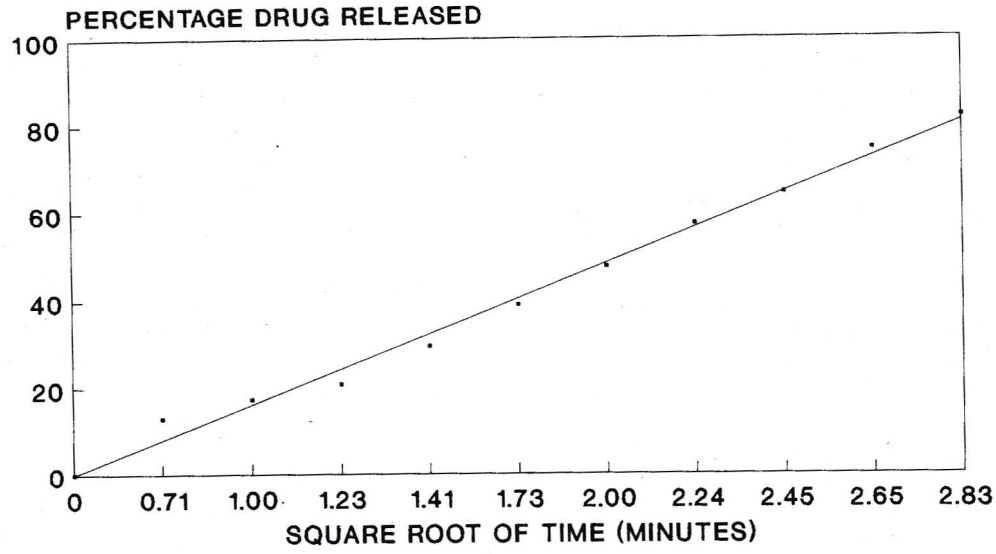
y = -9.7396x + 93.23
r squared = 0.989

Figure 5.65: Determination of the order of drug release from Batch NH: first-order model



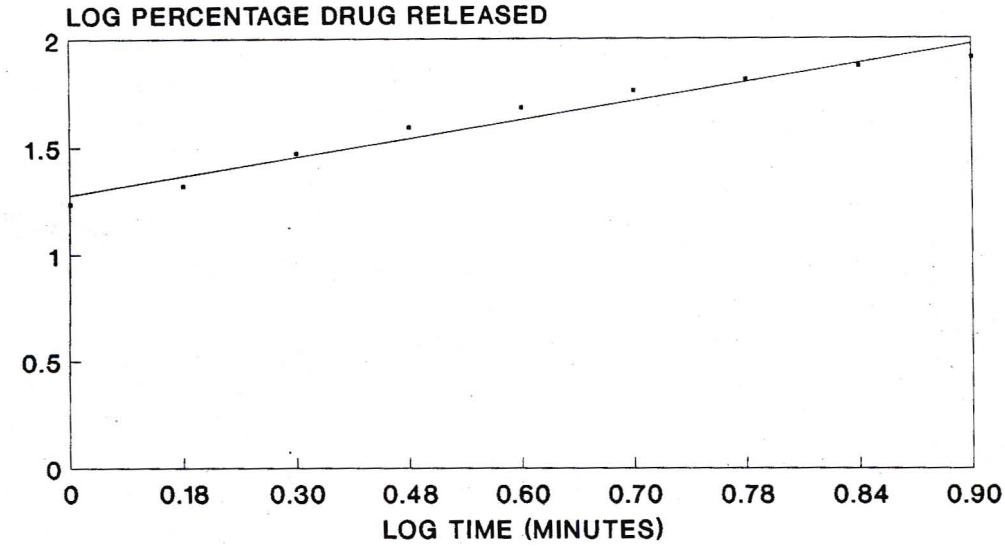
y = -0.0856x + 2.0204
r squared = 0.976

Figure 5.66: Release profile of diclofenac sodium from Batch NH as a function of the square root of time



y = 29.968x - 9.3044
r squared = 0.967

Figure 5.67: Application of the power law expression on the drug release data of Batch NH



y = 0.7647x + 1.2217
r squared = 0.995

The graphical illustrations of zero-order, first-order, Higuchi's square root of time and the power law kinetic expressions are presented in Figures 5.64, 5.65, 5.66 and 5.67 respectively. Linear regression was performed to obtain the equations and r^2 values for the respective curves. The computed dissolution rate constants are shown in Table 5.46.

The data in Figures 5.64, 5.65, 5.66 and 5.67 show that for each of the models tested, a linear relationship was derived. The computed regression coefficients were satisfactory. Based on linear regression, the close proximity of the r^2 values indicated that the diclofenac sodium Eudragit® matrices displayed mixed zero-order and first-order drug release characteristics. However, based on the r^2 value, it was ascertained that the trend towards zero-order drug release was more prominent.

The Higuchi model relates to drug transfer from a planar system as a function of the square root of time (Higuchi, 1963). A linear relationship between the amount of drug released and the square root of time is indicative of a diffusional (Gurny *et al.*, 1982) or a matrix controlled mechanism (Ritger and Peppas, 1987).

In practical situations, the linear relationship between the amount of drug released and the square root of time holds only for part of the curve, i.e. 75-80% of the time required for complete liberation of the drug. This change in the slope has been reported to be due to a modification in the release process itself, and occurs when the tablet has been completely penetrated by the dissolution liquid. When this occurs, the Higuchi Law is no longer valid, and drug dissolution occurs according to a simple diffusion model. The time period when the slope change appears, is designated the 'critical time' (Alvarez *et al.*, 1991).

The results of the present study showed that a linear relationship existed between the amount of drug released and the square root of time. When linear regression was performed on the data, a r^2 value of 0.967 was obtained. The results therefore illustrated drug release kinetics resembling the Higuchi model.

The power law expression has the ability to be applied to matrices of several geometries (slabs, cylinders, spheres and discs). The value of the kinetic exponent (n) was found to be

0.765. This indicated that the mechanism of drug release was by non-Fickian (anomalous) transport, since 0.765 falls within the range $0.5 < n < 1.0$.

The trend towards zero-order drug release was accentuated by the r^2 value generated from linear regression analysis. The power law expression generated an n value of 0.765, which is closer to 1.0 than 0.5, and further highlighted the tendency towards zero-order drug release.

Therapeutic systems are rarely dependent on dissolution only or diffusion only. Swelling-controlled release matrices that use a combination of diffusion and dissolution have been described. Swelling of the polymer allows water to enter, which causes dissolution of the drug and diffusion out of the swollen matrix, with the release rate being highly dependent on the rate of polymer swelling. With an eroding matrix, the surface area decreases as the dissolution process proceeds. However, the rate of release can only be kept constant if the surface area is constant (Grass and Robinson, 1990).

Since the trend towards zero-order drug release has been demonstrated, it can be concluded that there was an almost constant release of drug from the tablet matrices of Batch NH. However, swelling, together with matrix erosion was observed. Therefore, it can be concluded that the mechanism of drug release from the tablets of Batch NH is dependent on a combination of dissolution, diffusion and polymer erosion.

Chapter Six

Conclusions and Recommendations

6.1 CONCLUSIONS

6.1.1 *FORMULATION AND PREPARATION OF EUDRAGIT® MATRICES CONTAINING DICLOFENAC SODIUM*

6.1.1.1 Direct Compression Matrices

- Preliminary studies utilising the direct compression technique suggested that it was not a suitable method for the preparation of modified release dosage forms of diclofenac sodium. The major limitation attributed to this method was the poor flow properties of the powder blend. Attempts to improve the flow characteristics by increasing the glidant concentrations, or alternatively by substituting lactose with other suitable diluents that may possess more free flowing characteristics, also proved to be unsuitable processes.

6.1.1.2 Wet Granulated Matrices

6.1.1.2.1 Optimisation of processing conditions for the granulation

6.1.1.2.1.1 *Optimal Drying Time And Temperature*

- The first stage of the optimisation process demonstrated that a temperature of 55°C over a period of 20 minutes produced granules that were suitable for compression. Temperatures above 60°C caused a thermal change in the Eudragit® RL and

Eudragit® RS polymers. Therefore, temperatures above 55°C were not investigated.

6.1.1.2.1.2 *Optimal Granule Size Range*

- The second stage of the optimisation process showed that separation of the granules into different size ranges overcame the (intra-batch) variation in tablet mass. It was also demonstrated that granules in the rage 0-250 μm were not suitable for incorporation into the tablet, while granules in the range 251-710 μm, after compression into a tablet dosage form, provided controlled release of the drug.

6.1.1.2.1.3 *Optimal Tablet Hardness*

- The final stage in the optimisation process showed that the friability of the tablets compressed to a hardness above 4 Kp was acceptable for this study, while tablets compressed to hardnesses below 4 Kp were unacceptably friable.

6.1.2 *IN-PROCESS QUALITY CONTROL TESTS*

6.1.2.1 Drug Content Uniformity

- Content uniformity tests performed on all batches confirmed the expected theoretical drug content of diclofenac sodium.

6.1.2.2 Uniformity Of Mass

- The mass of ten tablets of each batch was measured. The mass of the tablets was found to be within an acceptable range.

6.1.2.3 Friability

- Tablet friability tests were conducted on all batches prepared, and the friability values of tablets compressed between 4-5 Kp were shown to be within an acceptable limit. The only exceptions were the tablets compressed to lower hardnesses.

6.1.2.4 Uniformity Of Tablet Thickness, Diameter And Hardness

- All tablets were measured for thickness, diameter and hardness. These dimensions, obtained by measuring ten tablets from each batch, were found to be within acceptable limits.

6.1.3 *INFLUENCE OF EUDRAGIT® POLYMERS*

6.1.3.1 Influence Of Different Types Of Eudragit® Polymers

- This study demonstrated the influence of the different Eudragit® polymers on drug release characteristics. It was clearly shown that Eudragit® L, Eudragit® S and Eudragit® NE did not have any retarding effects on drug release, while Eudragit® RL and Eudragit® RS, in comparison, significantly decreased drug release.
- The differences in the retardation effects of the different polymers were attributed to their permeability and solubility characteristics.

6.1.3.2 Influence Of Eudragit® Concentrations

- It was concluded that a significant decrease in drug release from the Eudragit® matrix tablets resulted in an increase in the concentration of the RS type of polymer, while the opposite effect was observed with the RL type. This was due to the differences in water permeability of the polymers. Based on these findings, it was concluded that

optimal drug release can be achieved by varying the concentration of the Eudragit® RL and Eudragit® RS polymers.

6.1.4 *REPRODUCIBILITY STUDY*

- Using similar formulation conditions, the drug release characteristics of lots NH(a) and NH(b) were almost identical to those of the control, Batch NH.
- It can therefore be concluded that the tabletting technique used in this study provided a reproducible approach to formulating diclofenac sodium Eudragit® matrices for modified release characteristics.

6.1.5 *SELECTION OF A DICLOFENAC SODIUM EUDRAGIT® MATRIX FORMULATION*

- The reference sample used in this study was Veltex® 100 CR. However, the relatively slow drug release characteristics, compared with other modified release formulations, showed that drug release from Veltex® 100 CR was undesirably slow.
- Furthermore, a formulation that would simulate the drug release characteristics of Veltex® 100 CR could result in incomplete release of the drug from the dosage form, due to the relatively short gastrointestinal transit time.
- It was shown that using a combination of the Eudragit® RL and Eudragit® RS polymers in equal concentrations provided the desired drug release characteristics.
- It was therefore determined that Batch NH be selected to investigate the integrity of the matrices formed by the wet granulation technique.

6.1.6 *IN VITRO DISSOLUTION TESTING*

6.1.6.1 Influence Of Dissolution Methods

- The three dissolution methods (viz. rotating basket, rotating paddle and rotating bottle methods) investigated showed dissimilar drug release patterns. All these tests were conducted at 50 rpm; therefore, any differences in drug release from the Eudragit® matrices could be solely attributed to the method employed.
- The fastest drug release occurred with the use of the rotating bottle apparatus. However, the violent agitation caused by this method resulted in disintegration of the tablets in two hours, hence suggesting a limitation of its use to evaluate modified release dosage forms.
- The rotating paddle method (50 rpm) demonstrated drug release rates that were much slower than those obtained using the rotating bottle method (50 rpm), yet faster than the rates recorded using the rotating basket method (50 rpm).
- The rotating basket method on the other hand, resulted in the formation of an unstirred conical heap of powder at the bottom of the vessel. It was concluded that the mesh of the basket was instrumental in increasing surface erosion of the tablet.
- Since the method of agitation impacted significantly on the drug release mechanism, and consequently on the drug release rates, it was concluded that comparisons using the same dissolution methods should be explored in order to establish optimal drug release characteristics of a particular formulation.

6.1.6.2 Influence Of Agitation Rates

- The release of diclofenac sodium from the Eudragit® matrices was shown to be dependent on the agitation rate. The present study demonstrated that drug release was increased as the agitation rate was increased. It was therefore concluded that drug release was dependent on matrix erosion characteristics.

6.1.6.3 Influence Of Media pH

- The Eudragit® RL and Eudragit® RS polymers display pH independent permeability characteristics. Diclofenac sodium on the other hand displays pH dependent solubility. Therefore, drug release from the matrices was almost negligible at lower pH values (i.e. at pH 1.5 and pH 4.5), and increased as the pH was further increased.
- *In vitro* dissolution testing of the diclofenac sodium Eudragit® matrices in media that simulated the gastrointestinal milieu following oral administration produced acceptable modified release profiles of diclofenac sodium. Although drug release was slow initially, increased release rates were observed when the pH of the media was increased to 7.5.
- These results confirmed the pH dependent release characteristics of diclofenac sodium, and it was also shown that the technique used in the present study was successful in modifying the release of diclofenac sodium from the Eudragit® matrices.

6.1.6.4 Influence Of Media Ionic Concentration

- The ionic strength of the dissolution medium was shown to have a significant effect on the release of diclofenac sodium from Eudragit® matrices. There was a drastic increase in drug release when the ionic concentration of the medium was decreased. This effect can have serious implications *in vivo*, as the ionic strength of the gastrointestinal fluid is vulnerable to change.

6.1.6.5 Influence Of Dissolution Media

- The demonstrated difference in the drug release characteristics of diclofenac sodium from Eudragit® matrices in the various media is of great significance, due to the absence of a dissolution monograph for diclofenac sodium. Drug release from the matrices was optimised in 0.2 M phosphate buffer pH 6.8. However, it was shown that a 'dose dumping' effect occurred in distilled water and USP phosphate buffer

pH 6.8. The Eudragit® matrices were unable to maintain their integrity in different buffer compositions.

6.1.7 *INFLUENCE OF FORMULATION EXCIPIENTS*

6.1.7.1 Influence Of Lactose

- The diclofenac sodium Eudragit® matrices containing increasing concentrations of lactose showed increased drug release patterns. Increased erosion of the tablet, due to increased concentrations of the water soluble diluent, lactose, was responsible for this increase in drug release.

6.1.7.2 Influence Of Types Of Diluents

- The selection of a diluent was shown to have a dramatic effect on the release of drug from the Eudragit® matrices. The use of microcrystalline cellulose resulted in very fast release of the drug, and hence a loss of retardant effect, while matrices containing dicalcium phosphate, due to its water insoluble nature, retarded drug release to a greater extent than the lactose containing matrices. It was therefore concluded that the differences in the physical properties of the diluents can significantly affect drug release behaviour.

6.1.7.3 Influence Of Starch

- The results indicated that the use of starch in increasing concentrations resulted in a corresponding increase in drug release from the tablet matrices. The physical appearance of the tablets also showed that the method of incorporation of starch was suitable for producing the tablets.

6.1.7.4 Influence Of Magnesium Stearate

- Although the results indicated significantly similar drug release profiles for tablets containing magnesium stearate as an external lubricant, and tablets containing magnesium stearate as an internal lubricant, the tendency of the tablets to stick to the punches, as well as the increased tablet friability of the batch containing the internal lubricant, showed that it was not a suitable method for incorporation of the magnesium stearate.

6.1.8 *INFLUENCE OF PROCESSING VARIABLES*

6.1.8.1 Influence Of Tablet Hardness

- As the hardness to which the tablets were compressed was increased, there was a decrease in tablet friability. However, an increase in tablet hardness was accompanied by a decrease in drug release characteristics, due to a decrease in matrix porosity. This latter phenomenon was elucidated with the aid of scanning electron microscopy.

6.1.9 *ELECTRON MICROSCOPY*

6.1.9.1 Scanning Electron Microscopy

- Scanning electron microscopy revealed the surface of the tablet of Batch NH to be even and smooth.
- Furthermore, it was shown that the tablets had a 'cracked' appearance, which indicated the porous nature of the matrices.

6.1.9.2 Energy Dispersive X-ray Microprobe Analysis (EDX)

- EDX adequately reflected the elemental composition of the tablets of Batch NH. The results obtained were consistent with the expected outcome of the investigation.
- Sodium and chloride ions were found in large concentrations in the tablets of Batch NH, while magnesium ions were present at very low concentrations.

6.1.10 *X-RAY DIFFRACTION (XRD)*

- XRD was used to elucidate the crystalline nature of diclofenac sodium. This technique confirmed the amorphous nature of the Eudragit® polymers used in the present study. XRD also showed that the amorphous structure of the Eudragit® polymers was retained after the process of granulation.
- The x-ray diffraction patterns of the various excipients used in the formulation revealed the characteristic crystalline nature of each component.
- XRD also showed that no change had occurred in the atomic disposition during the processes of granulation and compression.

6.1.11 *STABILITY STUDIES*

- The high performance liquid chromatographic assays of the tablets stored at the various simulated temperature and humidity conditions demonstrated almost constant drug potencies.
- The moisture content of the tablets prior to and after 4, 8 and 12 weeks of storage at the various simulated conditions remained almost unchanged.
- The tablet hardness testing conducted on the tablets at the various storage conditions showed that there was an increase in tablet hardness of the samples stored at 37°C (80 % relative humidity) and 40°C.
- However, there were virtually no changes in the hardness of tablets stored at room temperature (22 ± 1°C) and low temperature (5 ± 1°C).

- There was no significant change in the drug release profile relative to the initial drug release data when samples were stored at room temperature (22±1°C) and low temperature (5±1°C). However, samples stored at 37°C (80 % relative humidity) and 40°C displayed markedly slower drug release characteristics, compared to the initial sample.
- The surface morphology of the samples remained unchanged after storage under the various simulated conditions.
- It was therefore concluded that the diclofenac sodium Eudragit® matrix tablets were stable at room temperature (22±1°C) and low temperature (5±1°C), while storage at 37°C (80 % relative humidity) and 40°C resulted in changes in tablet hardness, as well as drug release.

6.1.12 *CHARACTERISATION OF DRUG RELEASE FROM THE DICLOFENAC SODIUM EUDRAGIT® MATRIX TABLETS*

- It was concluded that drug release from the Eudragit® matrices occurred by a mixed zero- and first-order process, with a greater tendency towards the zero-order model.
- Drug release was concluded to be dependent on a combination of diffusion, dissolution and matrix erosion.

The tabletting of the drug with the Eudragit® polymers provided a formulation containing 100 mg diclofenac sodium that was stable at room temperature (22±1°C) and low temperature (5±1°C). In conclusion, it is therefore argued that the tabletting technique as used in this study is a suitable approach to modifying the oral release of diclofenac sodium from Eudragit® matrices. The application of the various auxiliary methods proved tabletting to be both reproducible and non-destructive. The relative simplicity, economy and time saving attributes as demonstrated in the study make the technique pharmaceutically acceptable for modified drug release technology.

6.2 RECOMMENDATIONS

The following recommendations may be considered for further studies on tabletting of diclofenac sodium with Eudragit® polymers:

- The granules produced by the wet granulation method in the size range 0-250 μm may be considered for tabletting. However, the present study showed that drug release from matrices produced with granules in this size range released the drug very fast, with a subsequent loss of retardant effect. Hence, the granules may be suitable for modified release tablets if there is further addition of Eudragit® RLPO and Eudragit® RSPO polymers to the granules prior to compression.
- Food-drug interactions can create a significant impact on *in vivo* drug release and absorption. Therefore, controlled *in vivo* studies are required to fully characterise drug release characteristics.
- Thermal analytical techniques such as differential scanning calorimetry (DSC), thermogravimetric (TGA) and thermomechanical (TMA) analyses could be performed on the tablets. DSC and TGA can be used to assess the stability of the dosage form, while TMA can be used to measure visco-elastic changes in the matrices. The Eudragit® polymers have been reported to undergo a change in viscosity on storage.
- Additional EDX studies on the individual tabletting components can be obtained to fully characterise the elemental composition.
- X-ray mapping (XRM) can be used to determine the elemental distribution of the ions. Furthermore, XRM can also be obtained to establish correlations between uniform and non-uniform distributions of drug or excipients.
- A scale-up method can be investigated to assess the feasibility of producing such a dosage form by industries.

Appendices

1. The principle materials employed during the study together with their suppliers

MATERIALS	SUPPLIERS
Diclofenac sodium	Lennon Ltd
Diclofenac sodium reference standard	United States Pharmacopoeial Convention
Eudragit® polymers	
◘ Eudragit® RL30D	Röhm Pharma
◘ Eudragit® RS30D	Röhm Pharma
◘ Eudragit® NE30D	Röhm Pharma
◘ Eudragit® RLPO	Röhm Pharma
◘ Eudragit® RSPO	Röhm Pharma
◘ Eudragit® L100	Röhm Pharma
◘ Eudragit® S100	Röhm Pharma
Veltex® 100 CR capsules	Vesta Pharmaceuticals
Potassium dihydrogen orthophosphate	SAAR Chem
Disodium hydrogen orthophosphate	SAAR Chem
Hydrochloric acid	BDH Chemicals
Methanol (chromatography grade)	Romil
Acetic Acid (chromatography grade)	Romil
Karl Fischer solution	SAAR Chem
Super-tab®	Sandvet Pharmaceuticals
Aerosil® 200	Cabot Corporation
Magnesium stearate	Hopkin and Williams
Dicalcium phosphate	Medicolab
Avicel® pH 101	FMC Corp
Avicel® pH 102	FMC Corp
Lactose powder BP	Medicolab
Starch amylum BP	Medicolab
Para-nitrobenzoic acid	Janssen Chimica
Sodium hydroxide	BDH Chemicals
Hydrochloric acid	BDH Chemical

2. Preparation of buffer solutions

The required buffer solutions for dissolution testing were prepared as follows:

0.2 M phosphate buffer pH 4.5
0.2 M phosphate buffer pH 6.2
0.2 M phosphate buffer pH 6.8
0.2 M phosphate buffer pH 7.5
0.2 M phosphate buffer pH 8.0
0.1 M phosphate buffer pH 6.8

The above buffers were prepared as per the method described by Chetty *et al.* (1994). Solutions of potassium dihydrogen orthophosphate (KH_2PO_4) and disodium hydrogen orthophosphate (Na_2HPO_4) of similar ionic strengths were combined to achieve the desired pH.

phosphate buffer pH 6.8 (USP)

The pH 6.8 USP phosphate buffer was prepared as outlined in the USP XXIII (1995). A volume of 50 ml of monobasic potassium phosphate solution was placed in a 200 ml flask. To this, 16.5 ml of sodium hydroxide solution was added, and then water, to bring up to volume.

The potassium phosphate monobasic 0.2 M solution was prepared as follows: 27.22 g of monobasic potassium phosphate (KH_2PO_4) was dissolved in water, and diluted with water to 1000 ml.

hydrochloric acid buffer pH 1.5

The hydrochloric acid buffer pH 1.5 was prepared as outlined in the USP XXIII (1995). A volume of 50 ml of potassium chloride solution was placed in a 200 ml volumetric flask. To this, 41.4 ml of hydrochloric acid was added, and then water, to bring the solution up to volume.

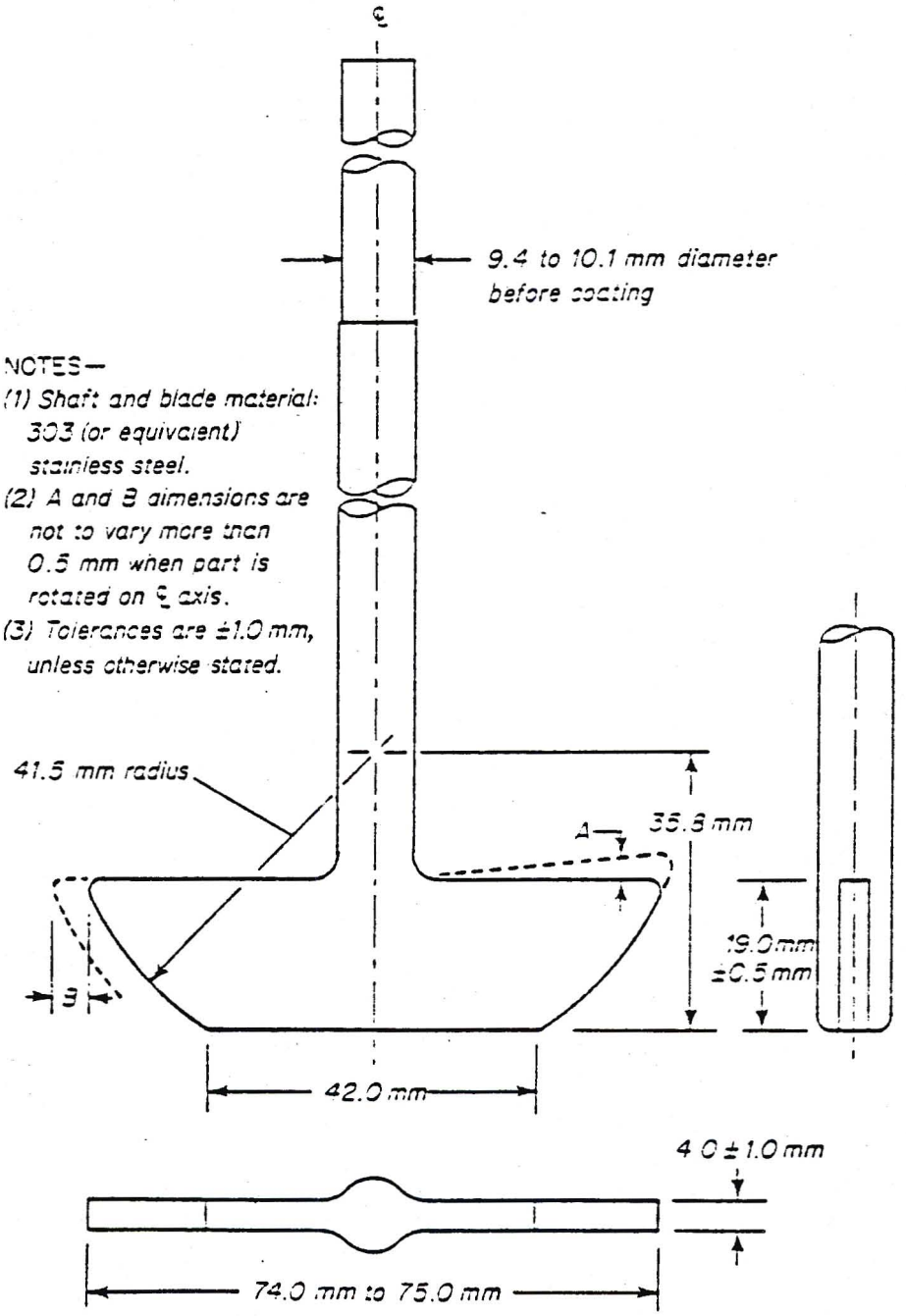
The potassium chlroide 0.2 M solution was prepared as follows: 14.91 g of potassium chloride (KCl) was dissolved in water, and then diluted with water to 1000 ml.

acetate buffer pH 3.7

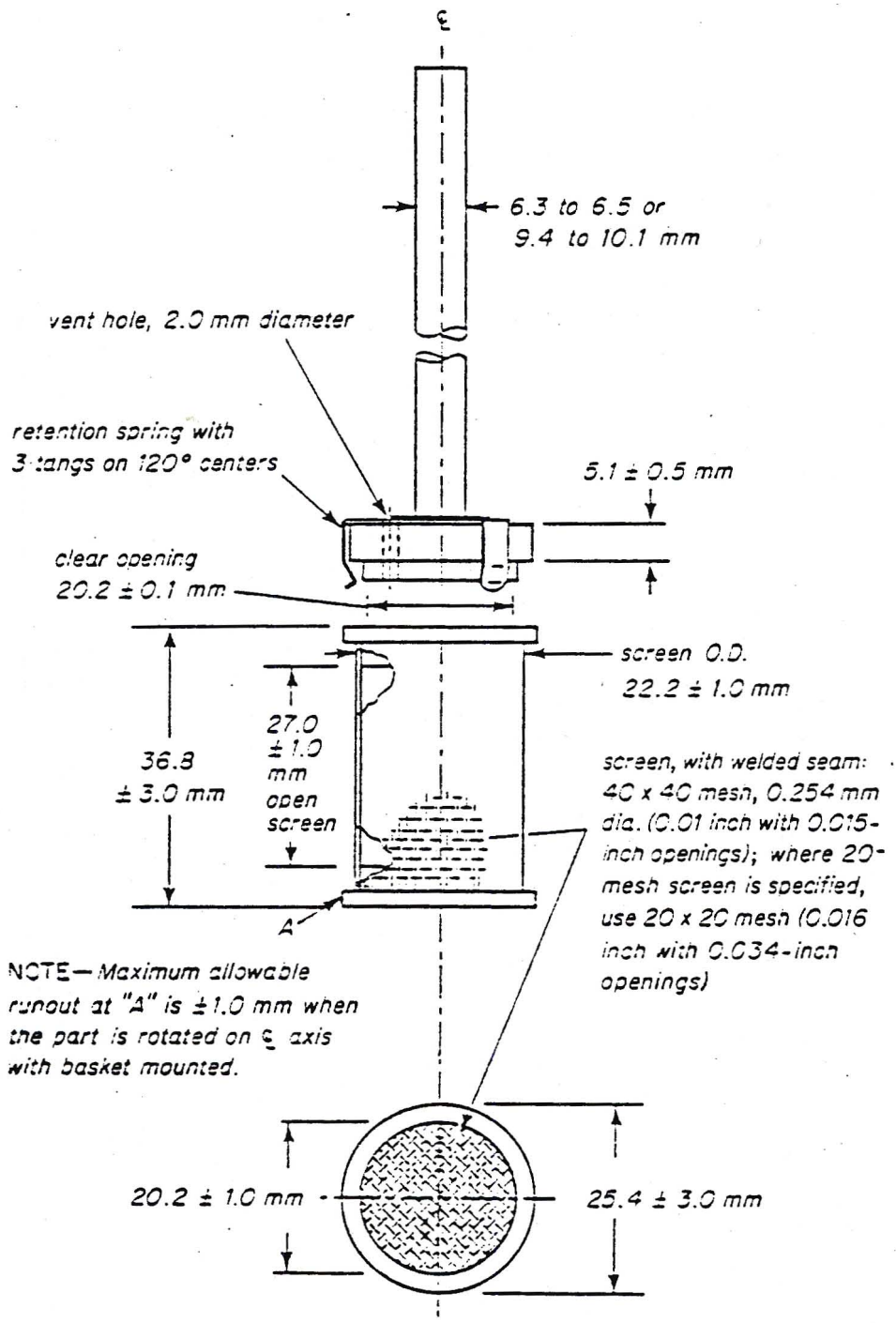
The acetate buffer pH 3.7 was prepared as outlined in the Diem (1962). An amount of 45 ml of 0.2 M acetic acid was combined with 5 ml of 0.2 M sodium acetate, and the solution was made up to 100 ml with water.

The 0.2 M sodium acetate solution was prepared as follows: 16.4 g of sodium acetate ($C_2H_3O_2Na$) was dissolved in water, and then diluted in water to 1000 ml.

3. Specifications for the rotating paddle apparatus (USP XXIII, 1995)



4. Specifications for the rotating basket apparatus (USP XXIII, 1995)



5. Example of Quattro Pro® cell formulae used to compute dissolution data

TIME	CONCENTRATION (mg/l)	CORRECTION FACTOR	CORRECTED CONCENTRATION	MEAN CONCENTRATION	STANDARD DEVIATION
0.5		0	@SUM(B10+C10)	@SUM((D10+D11+D12)/3)	@STDS(D10..D12)
		0	@SUM(B11+C11)		
		0	@SUM(B12+C12)		
1		@SUM(B10/1000*5)	@SUM(B20+C20)	@SUM((D20+D21+D22)/3)	@STDS(D20..D22)
		@SUM(B11/1000*5)	@SUM(B21+C21)		
		@SUM(B12/1000*5)	@SUM(B22+C22)		
1.5		@SUM((B20/1000*5)+C20)	@SUM(B30+C30)	@SUM((D30+D31+D32)/3)	@STDS(D30..D32)
		@SUM((B21/1000*5)+C21)	@SUM(B31+C31)		
		@SUM((B22/1000*5)+C22)	@SUM(B32+C32)		
2		@SUM((B30/1000*5)+C30)	@SUM(B40+C40)	@SUM((D40+D41+D42)/3)	@STDS(D40..D42)
		@SUM((B31/1000*5)+C31)	@SUM(B41+C41)		
		@SUM((B32/1000*5)+C32)	@SUM(B42+C42)		
3		@SUM((B40/1000*5)+C40)	@SUM(B50+C50)	@SUM((D50+D51+D52)/3)	@STDS(D50..D52)
		@SUM((B41/1000*5)+C41)	@SUM(B51+C51)		
		@SUM((B42/1000*5)+C42)	@SUM(B52+C52)		

4		@SUM((B50/1000*5)+C50)	@SUM(B60+C60)	@SUM((D60+D61+D62)/3)	@STDS(D60..D62)
		@SUM((B51/1000*5)+C51)	@SUM(B61+C61)		
		@SUM((B52/1000*5)+C52)	@SUM(B62+C62)		
5		@SUM((B60/1000*5)+C60)	@SUM(B70+C70)	@SUM((D70+D71+D72)/3)	@STDS(D70..D72)
		@SUM((B61/1000*5)+C61)	@SUM(B71+C71)		
		@SUM((B62/1000*5)+C62)	@SUM(B72+C72)		
6		@SUM((B70/1000*5)+C70)	@SUM(B80+C80)	@SUM((D80+D81+D82)/3)	@STDS(D80..D82)
		@SUM((B71/1000*5)+C71)	@SUM(B81+C81)		
		@SUM((B72/1000*5)+C72)	@SUM(B82+C82)		
7		@SUM((B80/1000*5)+C80)	@SUM(B90+C90)	@SUM((D90+D91+D92)/3)	@STDS(D90..D92)
		@SUM((B81/1000*5)+C81)	@SUM(B91+C91)		
		@SUM((B82/1000*5)+C82)	@SUM(B92+C92)		
8		@SUM((B90/1000*5)+C90)	@SUM(B100+C100)	@SUM((D100+D101+D102)/3)	@STDS(D100..D102)
		@SUM((B91/1000*5)+C91)	@SUM(B101+C101)		
		@SUM((B92/1000*5)+C92)	@SUM(B102+C102)		

NB. The concentration units are mg/l. Since each formulation contained 100 mg of diclofenac sodium, the % drug released is calculated by dividing the corrected concentration value by 100, and then multiplying by 100 (to convert to a percentage). Hence, the same value is obtained. Therefore, this column was omitted in the calculations, and the corrected concentration values also reflect the % drug released.

6. HPLC data for calculating the potency of diclofenac sodium in Veltex® 100 CR capsules and tablets of Batch NH

6.1 Veltex® 100 CR

Data for calibration curve

CONCENTRATION	PEAK HEIGHT RATIOS DICLOFENAC SODIUM: PARA-NITROBENZOIC ACID	AVERAGE PEAK HEIGHT RATIOS
0.02	0.647	0.643
	0.639	
0.04	1.308	1.306
	1.303	
0.06	1.957	1.992
	2.027	
0.08	2.606	2.594
	2.582	
0.10	3.666	3.450
	3.233	

Peak height ratios of sample

PEAK HEIGHT RATIO OF SAMPLE	CONCENTRATION	PERCENTAGE DRUG CONCENTRATION	AVERAGE PERCENTAGE DRUG CONCENTRATION
1.563	0.0470	94.0	94.0
1.562	0.0470	94.0	

6.2 Batch NH (prior to storage)

Data for calibration curve

CONCENTRATION	PEAK HEIGHT RATIOS DICLOFENAC SODIUM: PARA-NITROBENZOIC ACID	AVERAGE PEAK HEIGHT RATIOS
0.02	0.647	0.643
	0.639	
0.04	1.308	1.306
	1.303	
0.06	1.957	1.992
	2.027	
0.08	2.606	2.594
	2.582	
0.10	3.666	3.450
	3.233	

Peak height ratios of sample:

PEAK HEIGHT RATIO OF SAMPLE	CONCENTRATION	PERCENTAGE DRUG CONCENTRATION	AVERAGE PERCENTAGE DRUG CONCENTRATION
1.496	0.0451	90.2	91.6
1.545	0.0465	93.0	

6.3 Batch NH (after 4 weeks of storage)

Data for calibration curve

CONCENTRATION	PEAK HEIGHT RATIOS DICLOFENAC SODIUM: PARA-NITROBENZOIC ACID	AVERAGE PEAK HEIGHT RATIOS
0.02	0.724	0.727
	0.729	
0.04	1.284	1.285
	1.285	
0.06	1.920	1.918
	1.916	
0.08	2.545	2.522
	2.499	
0.10	3.159	3.166
	3.172	

Peak height ratios of sample

STORAGE CONDITION	PEAK HEIGHT RATIO OF SAMPLE	CONCENTRATION	PERCENTAGE DRUG CONCENTRATION	AVERAGE PERCENTAGE DRUG CONCENTRATION
room temperature	1.489	0.0463	92.6	91.3
	1.431	0.0445	90.0	
5°C	1.434	0.0466	90.0	90.0
	1.420	0.0441	90.0	
37°C (with 80% RH)	1.517	0.0473	94.6	94.6
	1.519	0.0473	94.6	
40°C	1.471	0.0458	91.6	91.1
	1.457	0.0453	90.6	

RH = relative humidity

6.4 Batch NH (after 8 weeks of storage)

Data for calibration curve

CONCENTRATION	PEAK HEIGHT RATIOS DICLOFENAC SODIUM: PARA-NITROBENZOIC ACID	AVERAGE PEAK HEIGHT RATIOS
0.02	0.705	0.686
	0.667	
0.04	1.285	1.279
	1.273	
0.06	1.886	1.887
	1.888	
0.08	2.603	2.569
	2.534	
0.10	3.221	3.212
	3.203	

Peak height ratios of sample

STORAGE CONDITION	PEAK HEIGHT RATIO OF SAMPLE	CONCENTRATION	PERCENTAGE DRUG CONCENTRATION	AVERAGE PERCENTAGE DRUG CONCENTRATION
room temperature	1.500	0.0467	93.4	94.2
	1.525	0.0475	95.0	
5°C	1.444	0.0449	90.0	90.0
	1.437	0.0447	90.0	
37°C (with 80% RH)	1.450	0.0451	90.2	91.3
	1.484	0.0462	92.4	
40°C	1.500	0.0467	93.4	93.1
	1.490	0.0464	92.8	

RH = relative humidity

6.5 Batch NH (after 12 weeks of storage)

Data for calibration curve

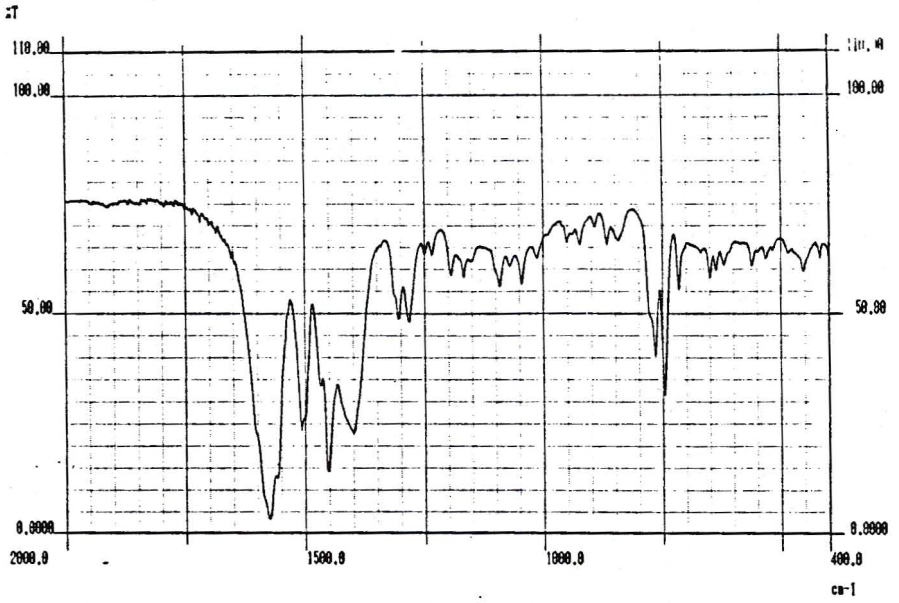
CONCENTRATION	PEAK HEIGHT RATIOS DICLOFENAC SODIUM: PARA-NITROBENZOIC ACID	AVERAGE PEAK HEIGHT RATIOS
0.02	0.592	0.591
	0.590	
0.04	1.174	1.171
	1.168	
0.06	1.747	1.749
	1.751	
0.08	2.322	2.322
	2.311	
0.10	2.942	2.931
	2.919	

Peak height ratios of sample

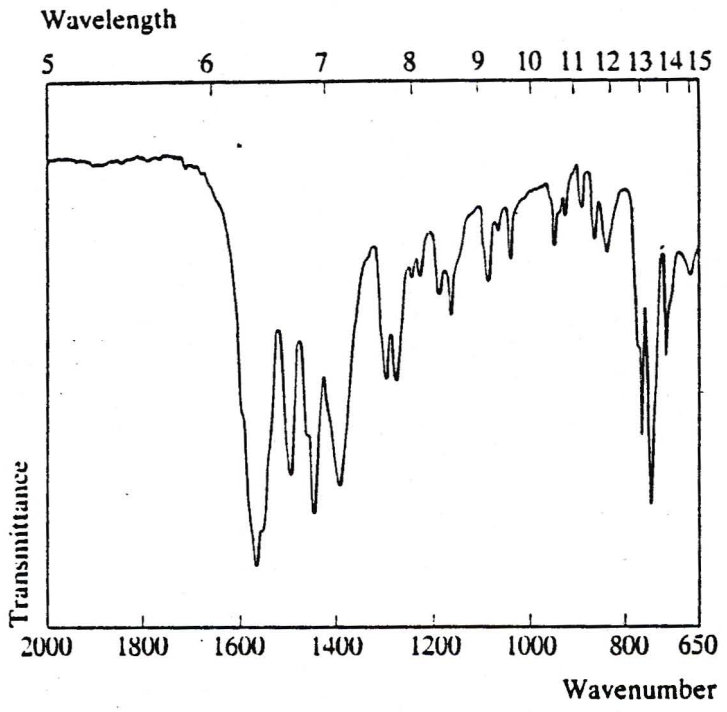
STORAGE CONDITION	PEAK HEIGHT RATIO OF SAMPLE	CONCENTRATION	PERCENTAGE DRUG CONCENTRATION	AVERAGE PERCENTAGE DRUG CONCENTRATION
room temperature	1.556	0.0533	106.6	106.8
	1.564	0.0535	107.0	
5°C	1.529	0.0523	104.6	105.5
	1.553	0.0532	106.4	
37°C (with 80% RH)	1.482	0.0507	101.4	101.4
	1.482	0.0507	101.4	
40°C	1.444	0.0494	98.8	99.5
	1.463	0.0501	100.2	

RH = relative humidity

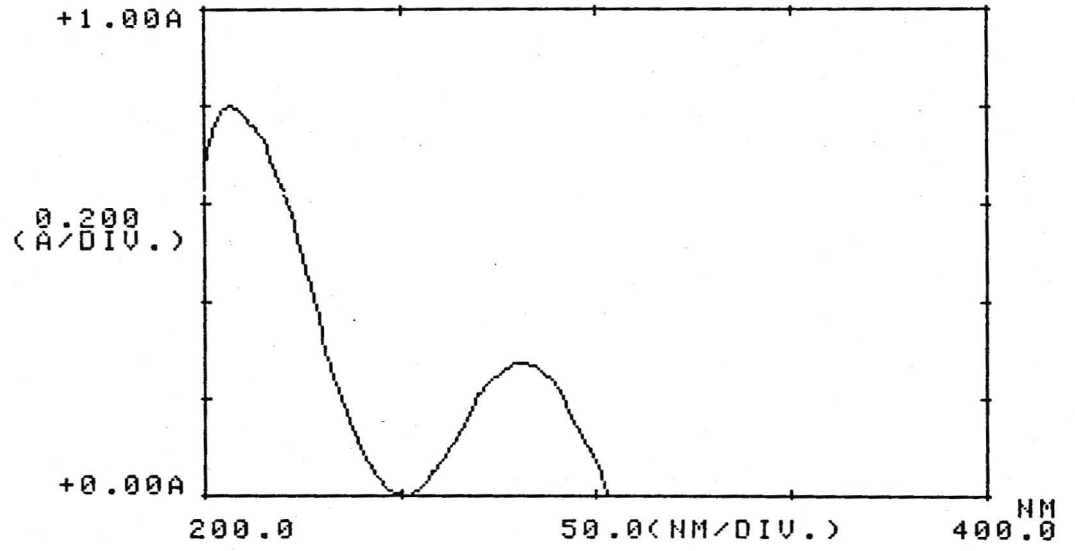
7. Infrared absorption spectrum of diclofenac sodium obtained in the present study



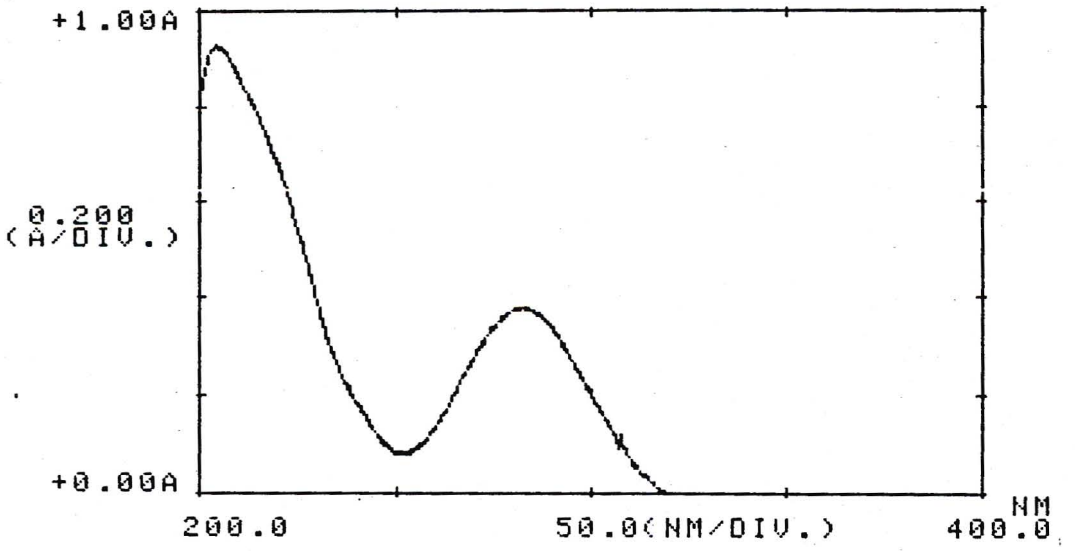
Infrared reference spectrum of diclofenac sodium (Moffat *et al.*, 1986 - page 533)



8. Ultraviolet absorption spectrum of diclofenac sodium powder in methanol



Ultraviolet absorption spectrum of diclofenac sodium USP reference standard in methanol



9. Cumulative percentages of diclofenac sodium released from Veltex® 100 CR capsules

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.25	3.16	3.79	4.42	3.79±0.63
0.5	7.60	7.28	8.24	7.71±0.49
1	13.94	14.58	14.89	14.47±0.48
1.5	20.29	19.67	20.63	20.20±0.49
2	25.09	24.16	25.11	24.79±0.54
3	33.02	33.34	33.97	33.44±0.48
4	43.43	44.05	44.07	43.85±0.36
5	48.29	48.60	48.62	48.50±0.19
6	54.68	55.00	54.71	54.80±0.17
7	59.56	59.88	60.82	60.09±0.65
8	67.51	67.21	67.55	67.42±0.19
9	71.19	70.59	70.62	70.80±0.34
10	74.29	74.29	74.32	74.30±0.02
11	77.38	76.78	78.02	77.39±0.62
12	81.10	81.09	81.13	81.11±0.02

10. Cumulative percentages of diclofenac sodium released from Batch DC1

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN±SD
	S1	S2	S3	
0.5	8.21	9.48	10.42	9.37±1.11
1	12.67	13.31	16.45	14.14±2.02
1.5	17.45	16.20	21.87	18.51±2.98
2	22.87	21.30	27.61	23.93±3.28
3	32.97	28.61	33.37	31.65±2.64
4	46.18	42.12	43.77	44.02±2.04
5	60.87	60.82	64.00	61.90±1.82
6	72.78	72.73	80.46	75.32±4.45
7	82.25	83.71	84.17	83.38±1.01
8	86.88	86.24	89.13	87.42±1.52

11. Cumulative percentages of diclofenac sodium released from Batch DC2

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN±SD
	S1	S2	S3	
0.5	8.53	6.63	6.95	7.37±1.02
1	11.41	9.19	10.45	10.35±1.11
1.5	19.64	16.80	18.38	18.27±1.42
2	28.82	23.78	23.80	25.47±2.90
3	41.71	31.40	34.22	35.78±5.33
4	54.58	46.76	44.01	48.45±5.48
5	65.89	57.16	54.10	59.05±6.12
6	74.75	67.24	63.27	68.42±5.83
7	81.19	75.80	71.21	76.07±4.99
8	85.52	81.03	76.74	81.10±4.39

12. Cumulative percentages of diclofenac sodium released from Batch DC3

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	7.58	9.16	7.58	8.11 ± 0.91
1	10.46	12.05	10.46	10.99 ± 0.92
1.5	15.24	16.51	15.55	15.77 ± 0.66
2	18.77	20.05	19.40	19.40 ± 0.64
3	26.69	27.66	27.63	27.33 ± 0.55
4	34.93	35.58	36.50	35.67 ± 0.79
5	41.00	43.21	43.19	42.47 ± 1.27
6	52.95	52.69	51.13	52.26 ± 0.98
7	55.06	59.10	58.16	57.44 ± 2.12
8	62.70	66.43	66.40	65.18 ± 2.15

13. Cumulative percentages of diclofenac sodium released from Batch DC4

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	7.58	7.58	8.53	7.90 ± 0.55
1	9.20	9.20	11.41	9.94 ± 1.28
1.5	12.71	12.08	12.41	12.40 ± 0.32
2	14.04	12.14	14.05	13.41 ± 1.10
3	16.62	16.29	18.21	17.04 ± 1.03
4	19.53	18.57	20.49	19.53 ± 0.96
5	23.07	22.75	25.29	23.70 ± 1.38
6	26.32	25.99	25.73	26.01 ± 0.30
7	30.51	28.61	29.60	29.57 ± 0.95
8	32.84	33.74	33.18	33.25 ± 0.46

14. Cumulative percentages of diclofenac sodium released from Batch DC9

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	85.18	80.26	78.92	81.45 ± 3.30
1	98.69	95.53	90.83	95.02 ± 3.95
1.5	100.70	100.04	100.42	100.38 ± 0.33
2	101.21	100.92	101.02	101.05 ± 0.14
3	102.08	101.65	101.66	101.80 ± 0.24
4	103.00	102.22	102.21	102.48 ± 0.45
5	103.58	102.77	102.77	103.04 ± 0.47
6	104.17	103.39	103.50	103.69 ± 0.42
7	104.83	103.97	104.04	104.28 ± 0.48
8	105.38	104.56	104.59	104.84 ± 0.46

15. Cumulative percentages of diclofenac sodium released from Batch DC10

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	7.90	6.95	7.58	7.48 ± 0.48
1	11.09	10.77	10.46	10.77 ± 0.32
1.5	16.18	15.55	14.61	15.45 ± 0.79
2	20.98	20.97	19.39	20.44 ± 0.91
3	26.40	26.39	24.82	25.87 ± 0.91
4	34.33	33.70	31.50	33.18 ± 1.48
5	42.57	41.32	38.50	40.79 ± 2.09
6	50.20	49.87	45.51	48.53 ± 2.62
7	56.61	57.82	53.13	55.85 ± 2.43
8	61.79	65.45	59.85	62.37 ± 2.84

16. Cumulative percentages of diclofenac sodium released from Batch NHH

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	25.81	31.12	33.45	30.12 ± 3.91
1	53.28	56.40	58.21	55.96 ± 2.49
1.5	82.34	87.92	91.68	87.32 ± 4.70
2	99.40	99.40	99.63	99.47 ± 0.13
3	100.51	100.19	100.23	100.31 ± 0.17
4	101.58	100.88	101.15	101.20 ± 0.36
5	100.89	100.99	101.03	100.97 ± 0.07
6	101.42	101.56	101.41	101.46 ± 0.08
7	101.65	101.98	101.83	101.82 ± 0.17
8	102.06	102.55	102.66	102.42 ± 0.32

17. Cumulative percentages of diclofenac sodium released from Batch NH

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	13.09	12.71	12.75	12.85 ± 0.21
1	17.81	18.23	15.83	17.29 ± 1.29
1.5	21.19	20.12	20.87	20.73 ± 0.55
2	30.61	29.50	28.00	29.37 ± 1.31
3	40.92	36.86	38.76	38.85 ± 2.03
4	49.91	46.02	47.01	47.64 ± 2.02
5	59.89	57.17	54.72	57.26 ± 2.59
6	67.79	63.26	62.02	64.35 ± 3.04
7	76.90	71.89	74.51	74.43 ± 2.51
8	83.09	81.68	80.64	81.80 ± 1.23

18. Cumulative percentages of diclofenac sodium released from Batch NRL

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	14.58	13.05	14.66	14.10±0.90
1	22.10	20.50	19.81	20.80±1.18
1.5	28.32	26.32	26.21	26.95±1.19
2	35.98	34.74	31.99	34.24±2.04
3	47.96	45.98	44.60	46.18±1.69
4	59.73	58.55	56.62	58.30±1.57
5	70.53	67.73	66.90	68.39±1.90
6	79.51	78.38	76.59	78.16±1.47
7	85.13	82.55	81.47	83.05±1.88
8	90.25	88.60	85.54	88.13±2.39

19. Cumulative percentages of diclofenac sodium released from Batch NRS

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	9.54	11.07	11.03	10.54±0.87
1	12.87	13.87	14.71	13.82±0.92
1.5	17.02	18.90	19.75	18.56±1.40
2	21.95	22.55	23.97	22.82±1.04
3	26.15	27.82	28.79	27.58±1.33
4	31.63	33.80	34.81	33.41±1.63
5	36.56	38.51	39.76	38.27±1.61
6	42.96	43.32	45.68	43.99±1.48
7	48.40	49.79	51.36	49.85±1.48
8	53.19	55.31	56.12	54.87±1.52

20. Cumulative percentages of diclofenac sodium released from Batch NL

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	48.27	53.31	45.94	49.17 ± 3.76
1	83.04	89.02	86.27	86.11 ± 2.99
1.5	98.29	98.69	98.37	98.45 ± 0.21
2	99.39	99.18	98.75	99.11 ± 0.33
3	99.16	99.18	98.59	98.97 ± 0.33
4	99.72	99.74	99.72	99.73 ± 0.01
5	100.10	100.42	99.83	100.11 ± 0.30
6	100.58	101.33	100.96	100.96 ± 0.37
7	101.45	101.66	101.45	101.52 ± 0.12
8	101.87	102.04	102.17	102.03 ± 0.15

21. Cumulative percentages of diclofenac sodium released from Batch NS

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	75.93	69.83	77.80	74.52 ± 4.17
1	99.62	99.63	98.79	99.35 ± 0.48
1.5	99.28	99.32	101.37	99.99 ± 1.20
2	100.19	100.08	102.26	100.85 ± 1.23
3	101.56	101.42	101.43	101.47 ± 0.08
4	102.10	101.84	101.74	101.89 ± 0.18
5	102.33	102.60	102.85	102.59 ± 0.26
6	103.09	102.91	103.20	103.07 ± 0.14
7	103.55	102.84	103.35	103.25 ± 0.37
8	103.82	103.86	104.04	103.91 ± 0.11

22. Cumulative percentages of diclofenac sodium released from Batch NN

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	90.77	94.70	95.27	93.58 ± 2.45
1	99.73	98.53	100.02	99.43 ± 0.79
1.5	100.65	100.74	100.67	100.69 ± 0.05
2	100.99	100.74	101.17	100.97 ± 0.22
3	101.34	101.66	101.29	101.43 ± 0.20
4	102.84	101.93	101.94	101.90 ± 0.06
5	102.45	102.73	102.32	102.50 ± 0.21
6	102.60	102.50	103.05	102.72 ± 0.29
7	102.95	102.85	103.31	103.04 ± 0.25
8	103.48	103.53	103.66	103.56 ± 0.09

23. Cumulative percentages of diclofenac sodium released from Batch RLRS21

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	12.86	14.20	13.32	13.46 ± 0.68
1	19.99	21.83	20.26	20.69 ± 0.99
1.5	27.73	30.80	29.87	29.47 ± 1.58
2	34.74	38.43	36.89	36.69 ± 1.85
3	44.80	49.21	46.85	46.95 ± 2.20
4	53.85	58.04	55.18	55.69 ± 2.14
5	60.53	64.48	62.33	62.44 ± 1.98
6	69.19	72.59	70.39	70.72 ± 1.72
7	74.72	78.75	76.00	76.49 ± 2.06
8	80.70	84.36	82.87	82.64 ± 1.84

24. Cumulative percentages of diclofenac sodium released from Batch RLRS12

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	15.15	17.41	14.85	15.80 ± 1.40
1	19.20	20.17	18.59	19.32 ± 0.80
1.5	25.14	27.83	24.48	25.82 ± 1.77
2	29.65	32.17	28.84	30.22 ± 1.73
3	39.92	41.53	38.12	39.86 ± 1.71
4	49.86	51.13	47.58	49.52 ± 1.80
5	57.93	59.21	55.65	57.60 ± 1.80
6	64.02	67.52	63.25	64.93 ± 2.27
7	71.02	74.04	68.87	71.31 ± 2.60
8	76.64	78.26	74.02	76.31 ± 2.14

25. Cumulative percentages of diclofenac sodium released from Batch NH(1)

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	12.33	13.20	12.36	12.63 ± 0.50
1	17.47	15.87	18.38	17.24 ± 1.27
1.5	20.53	19.92	21.84	20.76 ± 0.98
2	28.12	26.97	31.11	28.73 ± 2.14
3	38.49	35.88	39.44	37.94 ± 1.84
4	48.08	46.68	50.97	48.58 ± 2.19
5	57.37	55.12	59.93	57.47 ± 2.41
6	66.89	62.19	68.63	65.90 ± 3.33
7	75.70	72.81	78.06	75.52 ± 2.63
8	83.36	81.26	84.51	83.05 ± 1.65

26. Cumulative percentages of diclofenac sodium released from Batch NH(2)

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	12.59	12.96	13.36	12.97 ± 0.38
1	16.25	17.24	18.20	17.23 ± 0.98
1.5	20.03	21.64	21.88	21.18 ± 1.00
2	27.04	28.09	31.27	28.80 ± 2.20
3	36.65	38.96	40.21	38.60 ± 1.80
4	46.03	48.36	49.65	48.01 ± 1.83
5	55.43	57.19	59.67	57.43 ± 2.13
6	62.65	66.98	67.98	65.87 ± 2.83
7	72.66	75.25	77.71	75.21 ± 2.53
8	80.69	82.88	84.01	82.53 ± 1.69

27. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating paddle method at 50 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.20	14.46	15.34	14.34 ± 1.08
1	16.75	18.51	18.97	18.07 ± 1.17
1.5	21.87	22.69	24.11	22.89 ± 1.13
2	25.30	26.35	27.32	26.32 ± 1.01
3	29.55	30.15	32.50	30.73 ± 1.56
4	34.05	35.53	37.43	35.67 ± 1.69
5	37.96	39.52	41.09	39.52 ± 1.56
6	41.70	42.69	44.00	42.80 ± 1.16
7	46.79	48.10	48.69	47.86 ± 0.97
8	49.96	52.19	53.05	51.73 ± 1.59

28. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating basket method at 50 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	8.74	8.47	9.04	8.75 ± 0.29
1	10.69	10.73	12.64	11.35 ± 1.12
1.5	13.99	14.52	15.03	14.51 ± 0.52
2	17.95	18.64	18.77	18.64 ± 0.44
3	22.28	22.36	23.52	22.72 ± 0.70
4	25.26	27.67	27.34	26.76 ± 1.31
5	28.74	29.79	31.76	30.10 ± 1.53
6	33.12	32.49	34.62	33.41 ± 1.09
7	35.08	35.17	36.97	35.74 ± 1.07
8	38.42	40.50	41.62	40.18 ± 1.62

29. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating bottle method at 50 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	79.02	81.10	76.71	78.94 ± 2.20
1	81.74	81.35	86.18	83.09 ± 2.68
1.5	85.74	83.53	88.16	85.81 ± 2.32
2	90.59	89.77	88.55	89.64 ± 1.03
3	96.02	96.99	94.98	96.00 ± 1.01
4	99.30	100.43	100.22	99.98 ± 0.60
5	100.28	100.60	101.28	100.72 ± 0.51
6	101.69	101.45	101.34	101.49 ± 0.18
7	101.76	101.70	101.36	101.61 ± 0.22
8	101.76	101.76	101.62	101.72 ± 0.08

30. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating paddle method at 100 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	13.09	12.71	12.75	12.85 ± 0.21
1	17.81	18.23	15.83	17.29 ± 1.29
1.5	21.19	20.12	20.87	20.73 ± 0.55
2	30.61	29.50	28.00	29.37 ± 1.31
3	40.92	36.86	38.76	38.85 ± 2.03
4	49.91	46.02	47.01	47.64 ± 2.02
5	59.89	57.17	54.72	57.26 ± 2.59
6	67.79	63.26	62.02	64.35 ± 3.04
7	76.90	71.89	74.51	74.43 ± 2.51
8	83.09	81.68	80.64	81.80 ± 1.23

31. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating paddle method at 150 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	10.65	14.54	12.78	12.66 ± 1.95
1	18.15	22.75	21.03	20.64 ± 2.33
1.5	26.45	30.16	28.76	28.45 ± 1.87
2	37.39	42.26	40.36	40.00 ± 2.46
3	56.36	60.00	58.44	58.27 ± 1.82
4	69.05	72.90	71.02	70.99 ± 1.92
5	75.92	81.35	80.08	79.12 ± 2.84
6	84.51	86.68	85.75	85.65 ± 1.09
7	90.08	93.52	91.55	91.72 ± 1.73
8	98.85	99.75	96.58	98.39 ± 1.63

32. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating basket method at 100 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	8.39	9.35	9.69	9.14 ± 0.67
1	12.71	14.32	15.09	14.04 ± 1.21
1.5	16.33	17.33	19.21	17.62 ± 1.46
2	20.61	21.08	23.62	21.77 ± 1.62
3	27.36	29.63	30.65	29.21 ± 1.69
4	35.24	37.03	38.82	37.03 ± 1.79
5	41.18	43.78	45.31	43.43 ± 2.09
6	47.69	50.57	52.26	50.17 ± 2.31
7	53.80	55.67	57.29	55.59 ± 1.74
8	58.27	60.03	62.50	60.26 ± 2.12

33. Cumulative percentages of diclofenac sodium released from Batch NH using the rotating basket method at 150 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	20.08	20.77	22.94	21.26 ± 1.50
1	29.46	31.07	33.02	31.18 ± 1.79
1.5	35.26	37.22	38.96	37.14 ± 1.85
2	42.27	43.44	45.15	43.62 ± 1.45
3	48.32	49.65	51.98	49.98 ± 1.85
4	54.21	55.58	57.88	55.89 ± 1.86
5	60.13	63.15	64.39	62.56 ± 2.19
6	67.53	68.19	71.01	68.91 ± 1.85
7	72.21	74.75	76.32	74.43 ± 2.07
8	78.48	80.92	81.51	80.30 ± 1.60

34. Cumulative percentages of diclofenac sodium released from Batch NH in hydrochloric acid buffer pH 1.5

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	0.45	0.43	0.35	0.41 ± 0.05
1	0.15	0.35	0.25	0.25 ± 0.10
1.5	0.50	0.38	0.33	0.40 ± 0.08
2	0.44	0.42	0.46	0.44 ± 0.02
3	0.48	0.97	0.83	0.76 ± 0.25
4	0.69	1.06	0.93	0.89 ± 0.19
5	0.89	1.08	0.88	0.95 ± 0.11
6	1.04	0.92	0.88	0.95 ± 0.08
7	0.88	0.89	1.01	0.93 ± 0.07
8	1.01	0.95	0.95	0.97 ± 0.03

35. Cumulative percentages of diclofenac sodium released from Batch NH in 0.2 M phosphate buffer buffer pH 4.5

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	0.56	0.47	0.49	0.51 ± 0.05
1	0.58	0.47	0.51	0.52 ± 0.06
1.5	0.65	0.59	0.62	0.62 ± 0.03
2	0.82	0.77	0.74	0.78 ± 0.04
3	0.89	0.84	0.91	0.88 ± 0.03
4	1.19	1.21	1.14	1.18 ± 0.04
5	1.16	1.13	1.16	1.15 ± 0.02
6	1.16	1.18	1.17	1.17 ± 0.01
7	1.18	1.39	1.41	1.32 ± 0.13
8	1.38	1.33	1.41	1.37 ± 0.04

36. Cumulative percentages of diclofenac sodium released from Batch NH in 0.2 M phosphate buffer pH 6.2

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	5.76	6.18	5.26	5.73 ± 0.46
1	6.36	6.55	6.13	6.34 ± 0.21
1.5	7.30	7.30	7.22	7.27 ± 0.05
2	8.47	8.67	8.17	8.44 ± 0.25
3	11.36	12.13	11.06	11.52 ± 0.55
4	14.38	15.30	14.95	14.88 ± 0.46
5	17.57	17.85	17.91	17.77 ± 0.18
6	20.24	20.29	20.88	20.47 ± 0.36
7	23.22	23.84	23.15	23.40 ± 0.38
8	25.39	26.05	25.27	25.57 ± 0.42

37. Cumulative percentages of diclofenac sodium released from Batch NH in 0.2 M phosphate buffer pH 6.8

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	13.09	12.71	12.75	12.85 ± 0.21
1	17.81	18.23	15.83	17.29 ± 1.29
1.5	21.19	20.12	20.87	20.73 ± 0.55
2	30.61	29.50	28.00	29.37 ± 1.31
3	40.92	36.86	38.76	38.85 ± 2.03
4	49.91	46.02	47.01	47.64 ± 2.02
5	59.89	57.17	54.72	57.26 ± 2.59
6	67.79	63.26	62.02	64.35 ± 3.04
7	76.90	71.89	74.51	74.43 ± 2.51
8	83.09	81.68	80.64	81.80 ± 1.23

38. Cumulative percentages of diclofenac sodium released from Batch NH in 0.2 M phosphate buffer buffer pH 7.5

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	17.22	19.30	22.23	19.58 ± 2.52
1	28.64	32.21	33.65	31.50 ± 2.58
1.5	39.40	41.84	43.80	41.68 ± 2.21
2	49.65	51.69	54.52	51.95 ± 2.45
3	62.61	68.43	69.10	66.71 ± 3.57
4	78.23	81.80	84.13	81.38 ± 2.97
5	86.32	87.80	90.11	88.08 ± 1.91
6	94.07	95.73	97.63	95.81 ± 1.78
7	100.86	101.04	101.46	101.12 ± 0.31
8	102.01	101.60	102.03	101.88 ± 0.24

39. Cumulative percentages of diclofenac sodium released from Batch NH in 0.2 M phosphate buffer pH 8

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	25.57	27.90	29.03	27.50 ± 1.77
1	38.12	40.25	41.90	40.09 ± 1.90
1.5	50.95	53.74	56.18	53.62 ± 2.62
2	62.54	65.65	67.71	65.30 ± 2.60
3	82.93	85.58	88.48	85.66 ± 2.77
4	95.38	97.82	99.48	97.56 ± 2.06
5	101.22	101.51	101.27	101.33 ± 0.16
6	101.89	102.14	101.81	101.94 ± 0.17
7	102.39	102.72	102.22	102.44 ± 0.26
8	102.84	103.01	102.93	102.93 ± 0.08

40. Cumulative percentages of diclofenac sodium released from Batch NH in media of various pH gradients

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	0.33	0.64	0.41	0.46±0.16
1	0.82	0.62	0.64	0.69±0.11
1.5	1.23	1.11	1.11	1.15±0.07
2	1.32	1.22	1.17	1.24±0.08
3	8.07	10.33	9.56	9.32±1.15
4	18.73	20.13	16.38	18.41±1.89
5	28.11	30.84	26.32	28.42±2.28
6	60.88	66.24	58.30	61.80±4.05
7	77.32	83.21	73.87	78.13±4.72
8	88.83	93.15	81.26	87.75±6.02

41. Cumulative percentages of diclofenac sodium released from Batch NH in 0.1 M phosphate buffer pH 6.8

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	43.83	46.05	42.10	43.99±1.98
1	49.27	53.23	47.92	50.14±2.76
1.5	72.38	74.52	69.93	72.28±2.30
2	85.93	88.44	84.00	86.13±2.23
3	95.50	98.06	93.13	95.56±2.46
4	100.17	100.23	99.87	100.09±0.19
5	100.77	101.26	101.46	101.16±0.36
6	100.80	100.97	101.11	100.96±0.15
7	102.00	101.96	102.55	102.17±0.33
8	101.82	101.99	102.24	102.02±0.21

42. Cumulative percentages of diclofenac sodium released from Batch NH in distilled water

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	95.72	98.68	97.08	97.16 ± 1.48
1	100.17	100.03	100.10	100.10 ± 0.07
1.5	100.36	100.52	100.71	100.53 ± 0.18
2	101.01	101.37	101.21	101.20 ± 0.18
3	100.88	101.09	101.09	101.02 ± 0.12
4	101.57	101.32	101.39	101.43 ± 0.13
5	101.99	102.00	102.23	102.08 ± 0.14
6	102.41	102.62	102.34	102.45 ± 0.15
7	103.10	103.42	102.91	103.14 ± 0.26
8	103.79	103.53	103.48	103.60 ± 0.16

43. Cumulative percentages of diclofenac sodium released from Batch NH in USP phosphate buffer pH 6.8

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	34.48	31.23	38.79	34.83 ± 3.79
1	71.37	68.49	73.19	71.02 ± 2.37
1.5	90.43	87.19	94.26	90.63 ± 3.54
2	93.27	95.30	97.82	95.46 ± 2.28
3	102.14	101.63	102.29	102.02 ± 0.34
4	102.72	101.94	100.49	101.72 ± 1.13
5	101.08	101.03	100.98	101.03 ± 0.05
6	102.78	105.05	102.92	103.58 ± 1.27
7	101.64	101.18	100.92	101.24 ± 0.37
8	101.54	100.61	101.68	101.28 ± 0.58

44. Cumulative percentages of diclofenac sodium released from Batch NHL30

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	14.69	14.50	13.47	14.22 ± 0.66
1	21.03	18.93	17.82	19.26 ± 1.63
1.5	24.72	23.76	21.91	23.47 ± 1.43
2	28.25	27.24	25.88	27.12 ± 1.19
3	36.56	35.32	33.30	35.06 ± 1.64
4	43.16	41.98	40.69	41.94 ± 1.24
5	49.78	48.41	45.62	47.94 ± 2.12
6	58.20	56.94	55.01	56.72 ± 1.61
7	63.03	59.74	59.48	60.75 ± 1.98
8	68.42	66.45	63.52	66.13 ± 2.47

45. Cumulative percentages of diclofenac sodium released from Batch NHL50

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	14.92	13.28	12.78	13.66 ± 1.12
1	19.47	17.81	16.51	17.93 ± 1.48
1.5	24.60	24.51	23.36	24.16 ± 0.70
2	29.73	28.41	26.60	28.25 ± 1.57
3	40.99	39.74	36.47	39.07 ± 2.33
4	54.90	53.35	52.12	53.46 ± 1.39
5	73.20	69.99	66.40	69.86 ± 3.40
6	82.73	81.34	78.90	80.99 ± 1.93
7	89.01	86.66	85.40	87.03 ± 1.83
8	94.91	93.08	90.83	92.94 ± 2.05

46. Cumulative percentages of diclofenac sodium released from Batch DCP

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	12.33	11.60	10.72	11.55 ± 0.80
1	15.90	13.34	13.41	14.22 ± 1.46
1.5	18.27	17.22	15.62	17.04 ± 1.34
2	21.30	20.40	18.14	19.95 ± 1.63
3	26.56	24.78	22.73	24.69 ± 1.92
4	34.26	32.16	30.67	32.36 ± 1.80
5	38.93	36.79	36.10	37.27 ± 1.48
6	46.19	44.22	42.46	44.29 ± 1.86
7	56.92	55.48	51.72	54.70 ± 2.68
8	68.58	66.06	63.93	66.19 ± 2.33

47. Cumulative percentages of diclofenac sodium released from Batch MCC

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	83.13	81.34	80.04	81.50 ± 1.55
1	95.61	91.71	89.41	92.24 ± 3.14
1.5	98.15	96.33	96.62	97.03 ± 0.98
2	100.01	99.78	100.07	99.96 ± 0.15
3	100.93	101.08	100.38	100.79 ± 0.37
4	101.35	101.12	101.02	101.16 ± 0.17
5	101.84	101.69	101.25	101.59 ± 0.31
6	101.07	101.76	101.32	101.38 ± 0.35
7	101.72	101.91	102.54	102.05 ± 0.43
8	102.44	102.40	101.85	102.23 ± 0.33

48. Cumulative percentages of diclofenac sodium released from Batch NHS2

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	12.02	13.32	12.86	12.73 ± 0.66
1	13.80	15.52	17.05	15.46 ± 1.63
1.5	18.76	19.34	19.43	19.17 ± 0.37
2	21.98	23.33	24.68	23.33 ± 1.35
3	27.24	29.18	30.03	28.82 ± 1.43
4	35.40	36.88	37.86	36.71 ± 1.24
5	41.15	42.41	44.46	42.67 ± 1.67
6	48.38	49.27	51.78	49.81 ± 1.76
7	54.19	55.08	58.03	55.77 ± 2.01
8	62.06	65.93	67.18	65.06 ± 2.67

49. Cumulative percentages of diclofenac sodium released from Batch NHS4

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	14.35	16.76	15.72	15.61 ± 1.21
1	20.15	22.34	23.82	22.10 ± 1.85
1.5	28.27	30.36	31.05	29.89 ± 1.44
2	37.42	39.52	41.09	39.34 ± 1.84
3	46.58	49.72	51.53	49.28 ± 2.50
4	55.18	58.25	59.96	57.80 ± 2.42
5	67.52	69.23	71.10	69.28 ± 1.79
6	74.38	78.09	80.96	77.81 ± 3.30
7	83.95	85.81	87.58	85.78 ± 1.81
8	91.27	93.33	95.65	93.24 ± 2.19

50. Cumulative percentages of diclofenac sodium released from Batch NHM

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.28	14.46	15.61	14.45 ± 1.16
1	25.11	24.31	22.30	23.91 ± 1.45
1.5	29.02	26.84	25.73	27.19 ± 1.67
2	33.40	30.79	30.02	31.40 ± 1.77
3	42.81	44.77	45.79	44.45 ± 1.52
4	49.24	50.99	53.42	51.22 ± 2.10
5	57.28	60.25	61.67	59.73 ± 2.24
6	67.91	68.34	71.14	69.13 ± 1.75
7	75.65	76.46	79.51	77.21 ± 2.03
8	83.92	85.42	87.84	85.73 ± 1.98

51. Cumulative percentages of diclofenac sodium released from Batch HARD 34

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.09	14.16	14.01	13.75 ± 0.58
1	16.86	18.16	19.04	18.02 ± 1.10
1.5	23.24	25.55	26.28	25.02 ± 1.58
2	28.71	30.87	33.85	31.14 ± 2.58
3	38.13	39.58	41.81	39.84 ± 1.86
4	50.16	51.34	53.59	51.70 ± 1.74
5	62.01	65.23	66.54	64.59 ± 2.33
6	74.69	77.01	78.55	76.75 ± 1.94
7	82.01	83.73	87.22	84.32 ± 2.66
8	92.76	96.82	98.38	95.99 ± 2.90

52. Cumulative percentages of diclofenac sodium released from Batch HARD 67

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	8.05	7.09	7.82	7.65 ± 0.50
1	10.76	11.41	12.44	11.54 ± 0.85
1.5	13.95	14.98	16.63	15.18 ± 1.35
2	17.61	19.06	20.26	18.98 ± 1.33
3	23.57	25.00	25.37	24.65 ± 0.95
4	31.29	32.76	33.85	32.64 ± 1.29
5	38.05	38.73	37.65	38.14 ± 0.54
6	40.04	43.54	44.21	42.60 ± 2.24
7	45.58	48.49	49.59	47.88 ± 2.07
8	51.38	54.19	55.10	53.55 ± 1.94

53. Cumulative percentages of diclofenac sodium released from Batch NH prior to storage under the various simulated conditions (week 0)

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN ± SD
0.5	11.49	12.30	12.37	12.05 ± 0.49
1	15.94	17.32	18.01	17.09 ± 1.05
1.5	22.98	23.52	24.71	23.74 ± 0.89
2	28.59	29.33	32.02	29.98 ± 1.80
3	38.33	40.29	41.96	40.19 ± 1.82
4	48.72	51.04	53.24	51.00 ± 2.26
5	54.27	56.06	57.41	55.91 ± 1.57
6	62.10	63.98	66.48	64.19 ± 2.19
7	71.08	73.50	74.63	73.07 ± 1.82
8	78.53	79.56	81.69	79.93 ± 1.61

54. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 4 weeks at 21±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN±SD
	S1	S2	S3	
0.5	12.18	12.60	12.79	12.53±0.31
1	15.49	16.56	18.47	16.84±1.51
1.5	19.85	21.53	22.46	21.28±1.33
2	25.68	28.10	29.37	27.72±1.88
3	40.78	42.07	45.07	42.64±2.20
4	50.42	53.20	54.01	52.54±1.88
5	57.97	59.43	61.61	59.67±1.83
6	65.43	69.35	69.74	68.18±2.38
7	73.13	75.15	77.19	75.16±2.03
8	82.47	84.54	85.48	84.16±1.54

55. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 8 weeks at 21±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN±SD
	S1	S2	S3	
0.5	10.00	10.65	11.91	10.86±0.97
1	13.26	14.60	15.72	14.53±1.23
1.5	19.63	19.64	21.68	20.32±1.18
2	26.03	26.58	29.43	27.35±1.82
3	35.98	37.26	41.00	38.08±2.61
4	45.29	46.50	49.00	46.93±1.89
5	53.88	56.20	58.87	56.32±2.49
6	66.30	68.67	71.19	68.72±2.45
7	74.00	75.42	76.97	75.46±1.48
8	80.29	81.07	82.62	81.32±1.19

56. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 12 weeks at 21±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN±SD
0.5	10.54	10.88	11.11	10.84±0.29
1	14.14	14.41	16.21	14.92±1.12
1.5	18.61	19.61	20.84	19.68±1.12
2	23.40	23.83	26.33	24.52±1.58
3	38.76	40.76	42.20	40.57±1.73
4	47.13	49.44	51.08	49.22±1.99
5	57.03	58.67	62.07	59.25±2.57
6	65.33	66.44	68.91	66.90±1.83
7	74.02	73.91	78.11	75.35±2.39
8	80.23	81.00	81.97	81.07±0.87

57. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 4 weeks at 5±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN±SD
0.5	10.96	11.95	12.79	11.90±0.92
1	14.72	15.26	15.68	15.22±0.48
1.5	20.14	21.30	22.91	21.45±1.39
2	25.74	27.74	29.29	27.59±1.78
3	42.87	43.32	45.82	44.00±1.59
4	49.96	52.17	54.46	52.20±2.25
5	58.88	60.07	60.57	59.84±0.87
6	64.52	67.24	67.63	66.46±1.69
7	71.87	75.29	77.36	74.84±2.77
8	81.31	81.46	83.32	82.03±1.12

58. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 8 weeks at 5±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN±SD
0.5	10.65	12.07	12.60	11.77±1.01
1	17.13	18.74	19.54	18.47±1.23
1.5	22.56	23.15	24.45	23.39±0.97
2	29.43	31.17	33.90	31.50±2.25
3	37.91	39.73	42.62	40.09±2.38
4	45.82	48.26	50.97	48.35±2.58
5	54.71	55.72	57.68	56.04±1.51
6	61.52	64.13	65.53	63.73±2.04
7	70.30	72.54	75.40	72.75±2.56
8	80.16	82.11	82.46	81.58±1.24

59. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 12 weeks at 5±1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			
	S1	S2	S3	MEAN±SD
0.5	13.90	15.54	15.69	15.04±0.99
1	18.89	21.41	22.10	20.80±1.69
1.5	24.86	28.20	27.17	26.74±1.71
2	30.70	33.41	31.96	32.02±1.35
3	41.58	44.07	44.52	43.39±1.59
4	52.35	53.79	54.08	53.41±0.93
5	61.00	66.76	64.27	64.01±2.89
6	70.61	73.23	74.58	72.81±2.02
7	79.04	81.29	83.00	81.11±1.98
8	85.12	86.61	86.04	85.92±0.75

60. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 4 weeks at 37°C with 80% relative humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.63	13.44	13.32	13.46±0.15
1	19.57	18.66	17.24	18.49±1.17
1.5	24.48	24.89	21.91	23.76±1.62
2	27.42	25.51	27.74	26.89±1.21
3	34.92	33.99	35.85	34.92±0.93
4	41.81	41.71	44.23	42.58±1.43
5	47.62	48.29	48.95	48.29±0.66
6	53.77	55.21	53.69	54.22±0.85
7	58.76	60.85	59.14	59.59±1.11
8	65.96	65.54	64.16	65.22±0.94

61. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 8 weeks at 37°C with 80% relative humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.10	13.37	13.94	13.47±0.43
1	15.72	15.99	17.10	16.27±0.73
1.5	18.09	18.90	20.24	19.08±1.09
2	22.31	22.89	24.66	23.29±1.23
3	27.96	30.19	31.70	29.95±1.88
4	33.56	34.84	36.90	35.10±1.68
5	41.87	42.96	44.23	43.02±1.18
6	47.96	50.01	52.32	50.10±2.18
7	56.48	58.09	59.83	58.14±1.67
8	61.46	63.00	64.71	63.06±1.63

62. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 12 weeks at 37°C with 80% relative humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	12.68	12.56	11.99	12.41 ± 0.37
1	16.55	16.25	16.09	16.30 ± 0.23
1.5	19.65	19.46	19.68	19.60 ± 0.12
2	24.44	23.41	22.68	23.51 ± 0.88
3	30.86	30.58	29.32	30.25 ± 0.82
4	37.38	37.33	36.25	36.99 ± 0.64
5	43.52	44.08	43.87	43.82 ± 0.28
6	48.69	49.83	50.27	49.59 ± 0.81
7	53.13	55.79	55.89	54.94 ± 1.57
8	57.89	60.34	59.79	59.34 ± 1.29

63. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 4 weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	13.02	13.82	13.60	13.48 ± 0.41
1	15.46	15.88	18.13	16.49 ± 1.44
1.5	19.05	19.93	21.24	20.07 ± 1.10
2	21.17	22.55	24.63	22.78 ± 1.74
3	28.61	30.12	32.63	30.45 ± 2.03
4	34.90	37.45	37.98	36.78 ± 1.65
5	42.45	44.39	46.12	44.32 ± 1.84
6	51.79	53.17	54.67	53.21 ± 1.44
7	59.34	60.68	62.62	60.88 ± 1.65
8	66.66	67.52	68.70	67.63 ± 1.02

64. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 8 weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	14.58	14.51	12.98	14.02 ± 0.90
1	18.97	17.44	19.00	18.47 ± 0.89
1.5	23.11	21.04	22.33	22.16 ± 1.05
2	26.54	25.03	25.31	25.63 ± 0.80
3	33.39	30.31	30.66	31.45 ± 1.69
4	40.57	41.18	40.39	40.71 ± 0.41
5	46.23	43.29	43.07	44.19 ± 1.76
6	52.06	48.42	48.73	49.74 ± 2.02
7	57.58	54.23	57.02	56.28 ± 1.80
8	64.88	63.73	61.80	63.47 ± 1.56

65. Cumulative percentages of diclofenac sodium released from Batch NH after storage for 12 weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE DRUG RELEASED			MEAN ± SD
	S1	S2	S3	
0.5	14.39	13.90	13.29	13.86 ± 0.55
1	16.18	15.95	15.87	16.00 ± 0.16
1.5	21.07	21.10	21.40	21.19 ± 0.18
2	23.84	25.18	23.30	24.11 ± 0.96
3	28.62	29.42	27.96	28.67 ± 0.73
4	32.61	30.98	31.34	31.64 ± 0.86
5	38.61	36.24	37.45	37.43 ± 1.18
6	43.83	41.26	42.02	42.37 ± 1.32
7	48.13	46.16	46.57	46.95 ± 1.04
8	50.77	48.56	49.28	49.54 ± 1.13

66. Drug release rates from Veltex® 100 CR capsules in 0.2 M phosphate buffer pH 6.8

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN±SD
1	13.94	14.58	14.89	14.47±0.48
2	11.15	9.58	10.22	10.32±0.79
3	7.93	9.18	8.86	8.66±0.65
4	10.41	10.71	10.10	10.41±0.31
5	4.86	4.55	4.55	4.65±0.18
6	6.39	6.40	6.09	6.29±0.18
7	4.88	4.88	6.11	5.29±0.71
8	7.95	7.33	6.73	7.34±0.61
9	3.68	3.38	3.07	3.38±0.31
10	3.10	3.70	3.68	3.49±0.34
11	3.09	2.49	3.70	3.09±0.61
12	3.72	4.31	3.11	3.71±0.60

67. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN±SD
1	17.81	18.23	15.83	17.29±1.29
2	12.80	11.27	12.17	12.08±0.77
3	10.31	7.36	10.76	9.48±1.85
4	8.99	9.16	8.25	8.80±0.48
5	9.98	11.15	7.71	9.61±1.75
6	7.90	6.09	7.30	7.10±0.92
7	9.11	8.63	12.49	10.08±2.10
8	6.19	9.79	6.13	7.37±2.10

68. Drug release rates from Batch NRL

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	22.10	20.50	19.81	20.80 ± 1.18
2	13.88	14.24	12.18	13.43 ± 1.10
3	11.98	11.24	12.61	11.94 ± 0.69
4	11.77	12.57	12.02	12.12 ± 0.41
5	10.80	9.18	10.28	10.09 ± 0.83
6	8.98	10.65	9.69	9.77 ± 0.84
7	5.62	4.17	4.88	4.89 ± 0.73
8	5.12	6.05	4.07	5.08 ± 0.99

69. Drug release rates from Batch NRS

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	12.87	13.87	14.71	13.82 ± 0.92
2	9.08	8.68	9.26	9.01 ± 0.30
3	4.20	5.27	4.82	4.76 ± 0.54
4	5.48	5.98	6.02	5.83 ± 0.30
5	4.93	4.71	4.95	4.86 ± 0.13
6	6.40	4.81	5.92	5.71 ± 0.82
7	5.44	6.47	5.68	5.86 ± 0.54
8	4.79	5.52	4.76	5.02 ± 0.43

70. Drug release rates from Batch NL

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	83.04	89.02	86.27	86.11 ± 2.99
2	16.35	10.16	12.48	13.00 ± 3.13
3	-0.23	0.00	-0.16	-0.13 ± 0.12
4	0.56	0.56	1.13	0.75 ± 0.33
5	0.38	0.68	0.11	0.39 ± 0.29
6	0.48	0.91	1.13	0.84 ± 0.33
7	0.87	0.33	0.49	0.56 ± 0.28
8	0.42	0.38	0.72	0.51 ± 0.19

71. Drug release rates from Batch NS

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	99.62	99.63	98.79	99.35 ± 0.48
2	0.57	0.45	3.47	1.50 ± 1.71
3	1.37	1.34	-0.83	0.63 ± 1.26
4	0.54	0.42	0.31	0.42 ± 0.12
5	0.23	0.76	1.11	0.70 ± 0.44
6	0.76	0.31	0.35	0.47 ± 0.25
7	0.46	-0.07	0.15	0.18 ± 0.27
8	0.27	1.02	0.69	0.66 ± 0.38

72. Drug release rates from Batch NN

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	99.73	98.53	100.02	99.43 ± 0.79
2	1.26	2.21	1.15	1.54 ± 0.58
3	0.35	0.92	0.12	0.46 ± 0.41
4	0.50	0.27	0.65	0.47 ± 0.19
5	0.61	0.80	0.38	0.60 ± 0.21
6	0.15	-0.23	0.73	0.22 ± 0.48
7	0.35	0.35	0.26	0.32 ± 0.05
8	0.53	0.68	0.35	0.52 ± 0.17

73. Drug release rates from Batch RLRS21

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	19.99	21.83	20.26	20.69 ± 0.99
2	14.75	16.60	16.63	15.99 ± 1.08
3	10.06	10.78	9.96	10.27 ± 0.45
4	9.05	8.83	8.33	8.74 ± 0.37
5	6.68	6.44	7.15	6.76 ± 0.36
6	8.66	8.11	8.06	8.28 ± 0.33
7	5.53	6.16	5.61	5.77 ± 0.34
8	5.89	5.61	6.87	6.15 ± 0.65

74. Drug release rates from Batch RLRS12

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	19.20	20.17	18.59	19.32 ± 0.80
2	10.45	12.00	10.25	10.90 ± 0.96
3	10.27	9.36	9.28	9.64 ± 0.55
4	9.94	9.60	9.46	9.67 ± 0.25
5	8.07	8.08	8.07	8.07 ± 0.01
6	6.09	8.31	7.60	7.33 ± 1.13
7	7.00	6.52	5.62	6.38 ± 0.70
8	5.62	4.22	5.51	5.00 ± 0.71

75. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating paddle method at 50 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	16.75	18.51	18.97	18.07 ± 1.17
2	8.55	7.84	8.35	8.25 ± 0.37
3	4.25	3.80	5.18	4.41 ± 0.70
4	4.50	5.38	4.93	4.94 ± 0.44
5	3.91	3.99	3.66	3.85 ± 0.17
6	3.74	3.17	2.91	3.27 ± 0.42
7	5.09	5.41	4.69	5.06 ± 0.36
8	3.17	4.09	4.36	3.87 ± 0.62

76. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating basket method at 50 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	10.69	10.73	12.64	11.35±1.12
2	7.26	7.91	6.13	7.10±0.90
3	4.33	3.72	4.75	4.27±0.52
4	2.98	5.31	3.82	4.04±1.18
5	3.48	2.12	4.42	3.34±1.16
6	4.38	2.70	2.86	3.31±0.93
7	1.96	2.68	2.35	2.33±0.36
8	3.34	5.33	4.65	4.44±1.01

77. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating bottle method at 50 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	81.74	81.35	86.18	83.09±2.68
2	8.85	8.42	2.37	6.55±3.62
3	5.43	7.22	6.43	6.36±0.90
4	3.28	3.44	5.24	3.99±1.09
5	0.98	0.17	1.06	0.74±0.49
6	1.41	0.85	0.06	0.77±0.68
7	0.07	0.25	0.02	0.11±0.12
8	0.00	0.06	0.26	0.11±0.14

78. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating paddle method at 100 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	17.81	18.23	15.83	17.29 ± 1.29
2	12.80	11.27	12.17	12.08 ± 0.77
3	10.31	7.36	10.76	9.48 ± 1.85
4	8.99	9.16	8.25	8.80 ± 0.48
5	9.98	11.15	7.71	9.61 ± 1.75
6	7.90	6.09	7.30	7.10 ± 0.92
7	9.11	8.63	12.49	10.08 ± 2.10
8	6.19	9.79	6.13	7.37 ± 2.10

79. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating paddle method at 150 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	18.15	22.75	21.03	20.64 ± 2.33
2	19.24	19.51	19.33	19.36 ± 0.14
3	18.97	17.74	18.08	18.26 ± 0.64
4	12.69	12.90	12.58	12.72 ± 0.16
5	6.87	8.45	9.06	8.13 ± 1.13
6	8.59	5.33	5.67	6.53 ± 1.79
7	5.57	6.84	5.80	6.07 ± 0.68
8	8.77	6.23	5.03	6.68 ± 1.91

80. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating basket method at 100 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	12.71	14.32	15.09	14.04 ± 1.21
2	7.90	6.76	8.53	7.73 ± 0.90
3	6.75	8.55	7.03	7.44 ± 0.97
4	7.88	7.40	8.17	7.82 ± 0.39
5	5.94	6.75	6.49	6.39 ± 0.41
6	6.51	6.79	6.95	6.75 ± 0.22
7	6.11	5.10	5.03	5.41 ± 0.60
8	4.47	4.36	5.21	4.68 ± 0.46

81. Drug release rates from Batch NH in 0.2 M phosphate buffer pH 6.8 using the rotating basket method at 150 rpm

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	29.46	31.07	33.02	31.18 ± 1.79
2	12.81	12.37	12.13	12.44 ± 0.34
3	6.05	6.21	6.83	6.36 ± 0.41
4	5.89	5.93	5.90	5.91 ± 0.02
5	5.92	7.57	6.51	6.67 ± 0.84
6	7.40	5.04	6.62	6.35 ± 1.20
7	4.68	6.56	5.31	5.52 ± 0.96
8	6.27	6.17	5.19	5.88 ± 0.60

82. Drug release rates from Batch NH in various pH gradients

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	0.82	0.62	0.64	0.69 ± 0.11
2	0.50	0.60	0.53	0.54 ± 0.05
3	6.75	9.11	8.39	8.08 ± 1.21
4	10.66	9.80	6.82	9.09 ± 2.02
5	9.38	10.71	9.94	10.01 ± 0.67
6	32.77	35.40	31.98	33.38 ± 1.79
7	16.44	16.97	15.57	16.33 ± 0.71
8	11.51	9.94	7.39	9.61 ± 2.08

83. Drug release rates from Batch NHL30

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	21.03	18.93	17.82	19.26 ± 1.63
2	7.22	8.31	8.06	7.86 ± 0.57
3	8.31	8.08	7.42	7.94 ± 0.46
4	6.60	6.66	7.39	6.88 ± 0.44
5	6.62	6.43	4.93	5.99 ± 0.93
6	8.42	8.53	9.39	8.78 ± 0.53
7	4.83	2.80	4.47	4.03 ± 1.08
8	5.39	6.71	4.04	5.38 ± 1.34

84. Drug release rates from Batch NHL50

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	19.47	17.81	16.51	17.93 ± 1.48
2	10.26	10.60	10.09	10.32 ± 0.26
3	11.26	11.33	9.87	10.82 ± 0.82
4	13.91	13.61	15.65	14.39 ± 1.10
5	18.30	16.64	14.28	16.41 ± 2.02
6	9.53	11.35	12.50	11.13 ± 1.50
7	6.28	5.32	6.50	6.03 ± 0.63
8	5.90	6.42	5.43	5.92 ± 0.50

85. Drug release rates from Batch DCP

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	15.90	13.34	13.41	14.22 ± 1.46
2	5.40	7.06	4.73	5.73 ± 1.20
3	5.26	4.38	4.59	4.74 ± 0.46
4	7.70	7.38	7.94	7.67 ± 0.28
5	4.67	4.63	5.43	4.91 ± 0.45
6	7.26	7.43	6.36	7.02 ± 0.58
7	10.73	11.26	9.26	10.42 ± 1.04
8	11.66	10.58	12.21	11.48 ± 0.83

86. Drug release rates from Batch MCC

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	95.61	91.71	89.41	92.24 ± 3.14
2	4.4	8.07	10.66	7.71 ± 3.15
3	0.92	1.30	0.31	0.84 ± 0.50
4	0.42	0.04	0.64	0.37 ± 0.30
5	0.49	0.57	0.23	0.43 ± 0.18
6	-0.77	0.07	0.07	-0.21 ± 0.48
7	0.65	0.15	1.22	0.67 ± 0.54
8	0.72	0.49	-0.69	0.17 ± 0.76

87. Drug release rates from Batch NHS2

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN ± SD
	S1	S2	S3	
1	13.80	15.52	17.05	15.46 ± 1.63
2	8.18	7.81	7.63	7.87 ± 0.28
3	5.26	5.85	5.35	5.49 ± 0.32
4	8.16	7.70	7.83	7.90 ± 0.24
5	5.75	5.53	6.60	5.96 ± 0.57
6	7.23	6.86	7.32	7.14 ± 0.24
7	5.81	5.81	6.25	5.96 ± 0.25
8	7.87	10.85	9.15	9.29 ± 1.49

88. Drug release rates from Batch NHS4

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN±SD
	S1	S2	S3	
1	20.15	22.34	23.82	22.10±1.85
2	17.27	17.18	17.27	17.24±0.05
3	9.16	10.20	10.44	9.93±0.68
4	8.60	8.53	8.43	8.52±0.09
5	12.34	10.98	11.14	11.49±0.74
6	6.86	8.86	9.86	8.53±1.53
7	9.57	7.72	6.62	7.97±1.49
8	7.32	7.52	8.07	7.64±0.39

89. Drug release rates from Batch NHM

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			MEAN±SD
	S1	S2	S3	
1	25.11	24.31	22.30	23.91±1.45
2	8.29	6.48	7.72	7.50±0.93
3	9.41	13.98	15.77	13.05±3.28
4	6.43	6.22	7.63	6.76±0.76
5	8.04	9.26	8.25	8.52±0.65
6	10.63	8.09	9.47	9.40±1.27
7	7.74	8.12	8.37	8.08±0.32
8	8.27	8.96	8.33	8.52±0.38

90. Drug release rates from Batch HARD 34

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	16.86	18.16	19.04	18.02 ± 1.10
2	11.85	12.71	14.81	13.12 ± 1.52
3	9.42	8.71	7.96	8.70 ± 0.73
4	12.03	11.76	11.78	11.86 ± 0.15
5	11.85	13.89	12.95	12.90 ± 1.02
6	12.68	11.78	12.01	12.16 ± 0.47
7	7.32	6.72	8.67	7.57 ± 1.00
8	10.75	13.09	11.16	11.67 ± 1.25

91. Drug release rates from Batch HARD 67

TIME (HOURS)	DRUG RELEASE RATE (%/HOUR)			
	S1	S2	S3	MEAN ± SD
1	10.76	11.41	12.44	11.54 ± 0.85
2	6.85	7.65	7.82	7.44 ± 0.52
3	5.96	5.94	5.11	5.67 ± 0.49
4	7.72	7.76	8.48	7.99 ± 0.43
5	6.76	5.97	3.80	5.51 ± 1.53
6	1.99	4.81	6.56	4.45 ± 2.31
7	5.54	4.95	5.38	5.29 ± 0.31
8	5.80	5.70	5.51	5.67 ± 0.15

92. Repose angles of powder blends prepared for the direct compression batches

BATCH	REPOSE ANGLE (°)			MEAN REPOSE ANGLE ± SD
	A1	A2	A3	
DC1	62.93	59.97	60.73	61.21±1.54
DC2	58.51	57.63	58.11	58.08±0.44
DC3	57.86	57.06	57.95	57.62±0.49
DC4	56.14	56.02	56.25	56.14±0.12
DC5	55.04	54.85	54.28	54.72±0.40
DC6	54.77	53.98	53.19	53.98±0.79
DC7	53.61	52.49	53.52	53.21±0.62
DC8	51.24	52.79	51.10	51.71±0.94
DC9	34.12	32.52	32.51	33.05±0.92
DC10	66.37	67.74	68.43	67.51±1.05

93. Drug content determinations

BATCH	PERCENTAGE DRUG CONTENT			MEAN DRUG CONCENTRATION ± SD
	C1	C2	C3	
DC1	103.46	103.40	103.52	103.46±0.06
DC2	99.67	99.04	99.70	99.67±0.03
DC3	101.40	101.35	101.32	101.36±0.04
DC4	100.46	100.50	100.44	100.47±0.03
DC9	104.72	104.80	104.75	104.76±0.04
DC10	100.04	99.96	99.88	99.96±0.08
NHH	102.50	102.44	102.51	102.48±0.04
NH	103.16	103.50	103.18	103.18±0.02
NHRL	104.26	104.22	104.19	104.22±0.04
NHRS	102.11	102.08	102.10	102.10±0.02
NHL	102.08	102.10	102.09	102.09±0.01
NHS	103.99	103.95	103.96	103.97±0.02
NNE	103.50	103.45	103.48	103.48±0.03
RLRS21	98.46	98.50	98.47	98.48±0.02
RLRS12	97.11	97.08	97.06	97.08±0.03
NH(1)	99.12	99.15	99.08	99.12±0.04
NH(2)	98.16	98.20	98.21	98.19±0.03
NHL30	97.88	97.90	97.89	97.89±0.01
NHL50	99.06	99.07	99.04	99.06±0.02
DCP	102.26	102.30	102.29	102.28±0.02
MCC	102.31	102.27	102.26	102.28±0.03
NHS2	97.12	97.11	97.08	97.10±0.02
NHS4	99.12	99.15	99.16	99.14±0.02
NHM	98.78	98.77	98.80	98.78±0.02
HARD 34	98.66	98.65	98.60	98.64±0.03
HARD 67	101.54	101.53	101.56	101.54±0.02

94. Uniformity of mass determinations

BATCH	MASS OF TABLETS (mg)										MEAN MASS OF TABLETS ± SD
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	
DC1	195	208	215	210	190	189	199	207	216	209	203.80±9.87
DC2	209	218	230	234	239	227	219	221	232	216	224.50±9.37
DC3	248	256	235	230	229	240	253	259	239	243	243.20±10.56
DC4	255	270	274	259	263	269	258	376	266	260	265.00±7.13
DC9	220	218	229	226	221	227	230	216	219	224	223.00±4.88
DC10	207	232	209	217	219	212	229	234	236	239	223.40±11.96
NHH	355	354	356	352	350	349	355	352	350	354	352.70±2.45
NH	352	355	350	356	354	351	352	353	354	355	353.20±1.93
NHRL	353	359	356	355	352	354	353	351	350	349	353.20±2.97
NHRS	350	353	351	356	355	350	349	353	350	353	352.00±2.36
NHL	359	355	350	354	352	356	353	350	355	349	353.30±3.13
NHS	349	353	352	352	353	351	350	349	357	356	352.20±2.70
NNE	350	349	359	356	357	349	350	352	354	355	353.10±3.60
RLRS21	349	356	353	351	349	355	354	355	352	350	352.40±2.59
RLRS12	351	352	351	350	351	359	352	350	351	349	351.60±2.76
NH(1)	358	356	358	353	352	350	357	352	349	357	354.20±3.39
NH(2)	357	351	356	350	351	352	351	350	353	355	352.60±2.55

NHL30	245	344	348	346	345	345	347	346	343	344	346.20±3.12
NHL50	360	**350**	358	359	357	360	360	357	358	354	358.20±1.87
DCP	352	**351**	355	355	354	353	356	355	355	354	354.00±1.56
MCC	359	**360**	358	359	357	356	355	358	359	361	358.20±1.81
NHS2	346	**348**	349	346	347	345	349	350	349	344	347.30±2.00
NHS4	358	**357**	356	355	354	359	357	358	356	357	356.70±1.49
NHM	351	350	354	354	353	352	355	356	354	355	353.40±1.90
HARD 34	350	349	353	353	352	351	356	357	355	354	353.00±2.58
HARD 67	352	355	355	354	353	356	358	354	353	355	354.50±1.72

95. Friability determinations

BATCH	FRIABILITY (%)
DC1	0.72
DC2	0.75
DC3	0.68
DC4	0.65
DC9	0.80
DC10	0.81
NHH	1.06
NH	0.93
NHRL	0.88
NHRS	0.99
NHL	1.01
NHS	1.04
NNE	1.11
RLRS21	0.81
RLRS12	0.83
NH(1)	0.98
NH(2)	0.91
NHL30	1.21
NHL50	1.04
DCP	1.07
MCC	0.98
NHS2	0.80
NHS4	0.82
NHM	0.98
HARD 34	1.73
HARD 67	0.77

96. Uniformity of tablet thickness, diameter and hardness

96.1 Tablet thickness determinations

BATCH	THICKNESS OF TABLETS (mm)										MEAN THICKNESS OF TABLETS ± SD
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	
DC1	2.04	2.10	2.15	2.18	2.20	2.16	1.90	1.85	1.99	2.25	2.08±0.13
DC2	2.44	2.38	2.55	2.45	2.36	2.55	2.40	2.49	2.39	2.40	2.44±0.07
DC3	2.79	2.84	2.72	2.69	2.90	2.88	2.75	2.85	2.76	2.90	2.81±0.08
DC4	3.63	3.66	3.67	3.74	3.60	3.58	3.75	3.68	3.72	3.70	3.67±0.06
DC9	2.50	2.36	2.55	2.48	2.36	2.40	2.42	2.49	2.52	2.38	2.45±0.07
DC10	3.76	3.83	3.86	3.85	3.85	3.83	3.82	3.84	3.84	3.96	3.84±0.05
NHH	3.44	3.44	3.43	3.43	3.44	3.43	3.45	3.44	3.44	3.44	3.44±0.01
NH	3.70	3.70	3.71	3.71	3.71	3.70	3.69	3.71	3.70	3.69	3.70±0.01
NHRL	3.79	3.80	3.81	3.81	3.81	3.79	3.80	3.82	3.81	3.80	3.80±0.01
NHRS	3.75	3.73	3.72	3.73	3.75	3.74	3.80	3.73	3.80	3.79	3.75±0.03
NHL	3.87	3.85	3.85	3.86	3.86	3.86	3.85	3.85	3.85	3.85	3.86±0.01
NHS	3.83	3.86	3.85	3.86	3.87	3.86	3.85	3.85	3.86	3.85	3.85±0.01
NNE	3.72	3.72	3.75	3.74	3.74	3.74	3.73	3.74	3.75	3.73	3.73±0.01
RLRS21	3.75	3.76	3.75	3.75	3.77	3.75	3.75	3.74	3.75	3.75	3.75±0.01
RLRS12	3.81	3.81	3.81	3.80	3.82	3.82	3.80	3.81	3.80	3.81	3.81±0.01

NH(1)	3.71	3.70	3.70	3.70	3.71	3.71	3.70	3.72	3.71	3.70	3.71±0.01
NH(2)	3.70	3.70	3.69	3.69	3.70	3.70	3.71	3.70	3.70	3.71	3.70±0.01
NHL30	3.64	3.62	3.64	3.65	3.64	3.65	3.64	3.63	3.63	3.62	3.64±0.01
NHL50	3.87	3.86	3.88	3.88	3.87	3.87	3.86	3.88	3.87	3.86	3.87±0.01
DCP	3.40	3.71	3.39	3.42	3.41	3.42	3.43	3.40	3.41	3.43	3.41±0.01
MCC	3.79	3.80	3.82	3.81	3.80	3.80	3.81	3.82	3.80	3.50	3.81±0.01
NHS2	3.73	3.73	3.72	3.71	3.72	3.71	3.71	3.73	3.73	3.72	3.72±0.01
NHS4	3.80	3.80	3.79	3.80	3.78	3.80	3.80	3.80	3.79	3.80	3.80±0.01
NHM	3.75	3.74	3.74	3.73	3.74	3.75	3.75	3.74	3.73	3.74	3.74±0.01
HARD 34	4.04	4.07	4.05	4.04	4.06	4.05	4.07	4.05	4.04	4.04	4.05±0.01
HARD 67	3.58	3.57	3.59	3.60	3.57	3.58	3.58	3.60	3.59	3.57	3.58±0.01

96.2 Tablet diameter determinations

BATCH	DIAMETER OF TABLETS										MEAN DIAMETER OF TABLETS ± SD
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	
DC1	10.03	10.04	10.04	10.02	10.02	10.03	10.04	10.04	10.04	10.02	10.03±0.01
DC2	10.04	10.04	10.05	10.04	10.04	10.04	10.03	10.05	10.05	10.04	10.04±0.01
DC3	10.02	10.03	10.04	10.04	10.04	10.03	10.02	10.02	10.03	10.04	10.03±0.01
DC4	10.02	10.01	10.01	10.01	10.02	10.03	10.02	10.01	10.01	10.02	10.02±0.01
DC9	10.03	10.03	10.02	10.02	10.02	10.03	10.03	10.02	10.01	10.02	10.02±0.01
DC10	10.02	10.02	10.03	10.02	10.02	10.02	10.03	10.02	10.02	10.03	10.02±0.00
NHH	10.05	10.04	10.04	10.05	10.05	10.03	10.04	10.04	10.05	10.04	10.04±0.01
NH	10.03	10.03	10.02	10.03	10.02	10.03	10.03	10.03	10.03	10.03	10.03±0.00
NHRL	10.05	10.05	10.05	10.05	10.05	10.04	10.05	10.04	10.05	10.05	10.05±0.00
NHRS	10.02	10.03	10.02	10.02	10.03	10.02	10.03	10.03	10.02	10.03	10.03±0.01
NHL	10.03	10.03	10.03	10.02	10.03	10.03	10.02	10.03	10.02	10.02	10.03±0.01
NHS	10.04	10.03	10.03	10.04	10.04	10.04	10.01	10.02	10.04	10.04	10.03±0.01
NNE	10.02	10.02	10.01	10.02	10.01	10.01	10.02	10.01	10.01	10.01	10.01±0.01
RLRS21	10.02	10.02	10.03	10.02	10.02	10.02	10.03	10.03	10.02	10.03	10.02±0.01
RLRS12	10.05	10.05	10.05	10.03	10.04	10.05	10.05	10.04	10.04	10.05	10.05±0.01
NH(1)	10.02	10.02	10.02	10.03	10.02	10.03	10.02	10.02	10.02	10.03	10.02±0.00

NH(2)	10.03	10.03	10.03	10.02	10.02	10.03	10.02	10.02	10.03	10.02	10.03±0.01
NHL30	10.03	10.02	10.02	10.02	10.02	10.02	10.02	10.02	10.03	10.02	10.02±0.00
NHL50	10.04	10.04	10.03	10.03	10.03	10.03	10.04	10.04	10.03	10.04	10.04±0.01
DCP	10.02	10.02	10.03	10.01	10.02	10.01	10.02	10.02	10.02	10.01	10.02±0.01
MCC	10.04	10.05	10.04	10.04	10.04	10.05	10.05	10.04	10.04	10.04	10.04±0.00
NHS2	10.00	10.01	10.03	10.03	10.01	10.03	10.03	10.02	10.02	10.02	10.02±0.01
NHS4	10.04	10.03	10.04	10.03	10.03	10.04	10.03	10.04	10.04	10.04	10.04±0.01
NHM	10.02	10.03	10.03	10.03	10.02	10.02	10.03	10.02	10.03	10.03	10.03±0.01
HARD 34	10.02	10.03	10.03	10.02	10.03	10.03	10.02	10.02	10.04	10.02	10.03±0.01
HARD 67	10.03	10.04	10.03	10.03	10.02	10.03	10.04	10.03	10.03	10.02	10.03±0.01

96.3 Tablet hardness determinations

BATCH	HARDNESS OF TABLETS										MEAN HARDNESS OF TABLETS ± SD
	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	
DC1	4.7	4.8	4.9	5.0	4.4	4.4	4.6	4.7	4.9	5.0	4.74±0.22
DC2	4.8	4.6	4.5	4.4	4.3	4.3	5.0	4.8	4.9	4.4	4.55±0.22
DC3	4.9	4.6	4.4	4.2	4.7	5.0	4.9	4.6	4.4	4.1	4.58±0.30
DC4	4.3	4.8	4.4	4.7	4.8	4.6	4.7	4.4	4.3	4.3	4.53±0.21
DC9	4.2	4.3	4.3	4.9	4.7	4.4	4.8	4.3	4.8	4.2	4.49±0.28
DC10	4.1	4.4	4.6	4.6	4.5	4.7	4.4	4.4	4.6	4.7	4.50±0.18
NHH	4.8	4.4	4.6	4.7	4.8	4.9	4.6	4.5	4.6	4.7	4.66±0.15
NH	4.5	4.6	4.7	4.6	4.8	4.9	4.6	4.5	4.8	5.0	4.70±0.17
NHRL	4.2	4.4	4.5	4.3	4.2	4.4	4.6	4.9	4.8	4.5	4.48±0.23
NHRS	4.8	4.7	4.8	4.6	4.3	4.4	4.6	4.7	4.5	4.3	4.57±0.19
NHL	4.6	4.8	4.4	4.6	4.3	4.8	4.7	4.8	4.9	4.5	4.64±0.20
NHS	4.8	4.9	4.4	4.6	4.8	4.3	4.7	4.9	4.8	4.6	4.68±0.20
NNE	4.8	4.6	4.4	4.5	4.9	4.8	4.7	4.2	4.6	4.8	4.63±0.22
RLRS21	4.9	4.4	4.6	4.3	4.5	4.8	4.8	4.7	4.6	4.7	4.63±0.19
RLRS12	4.8	4.9	4.5	4.6	4.9	4.5	4.5	4.8	4.6	4.7	4.63±0.16
NH(1)	4.4	4.9	4.5	4.6	4.5	4.5	4.8	4.7	4.6	4.8	4.63±0.16

NH(2)	4.6	4.8	4.9	4.8	4.9	4.5	4.4	4.3	4.2	4.2	4.56±0.28
NHL30	4.9	4.8	4.4	4.6	4.5	4.2	4.3	4.6	4.8	4.5	4.56±0.23
NHL50	4.8	4.5	4.6	4.9	5.0	4.5	4.6	4.8	4.7	4.7	4.71±0.17
DCP	4.8	4.3	4.2	4.2	4.5	4.3	4.5	4.5	4.6	4.9	4.48±0.24
MCC	4.6	4.6	4.5	4.8	4.5	4.8	4.7	4.6	4.8	4.4	4.63±0.14
NHS2	4.8	4.8	5.0	4.5	4.6	4.7	4.4	4.6	4.3	4.3	4.60±0.23
NHS4	4.4	4.4	4.3	4.7	4.6	4.8	5.0	4.3	4.2	4.3	4.50±0.26
NHM	4.7	4.2	4.3	4.2	4.3	4.8	4.5	4.9	4.6	4.5	4.50±0.25
HARD 34	3.1	3.3	3.7	3.5	3.8	3.9	3.6	3.2	3.3	3.4	3.48±0.27
HARD 67	6.2	6.4	6.2	6.5	6.6	6.3	6.7	6.3	6.2	6.1	6.35±0.28

97. Anova tables

TIME (HOURS)	p VALUE
0.5	0.5769
1	0.9976
1.5	0.7815
2	0.9070
3	0.8357
4	0.8535
5	0.9935
6	0.7875
7	0.8691
8	0.6311

98. Moisture content of tablets of Batch NH after storage under various conditions of temperature and humidity

STORAGE PERIOD (WEEKS)	MOISTURE CONTENT			MEAN MOISTURE CONTENT ± SD
	MC1	MC2	MC3	
ROOM TEMPERATURE (21 ± 1°C)				
0	6.88	6.90	6.96	6.91 ± 0.04
4	7.55	8.20	8.10	7.95 ± 0.35
8	6.15	7.15	7.38	6.89 ± 0.65
12	7.43	7.43	7.45	7.41 ± 0.06
5 ± 1°C				
0	6.88	6.90	6.96	6.91 ± 0.04
4	8.58	9.25	8.86	8.90 ± 0.34
8	7.94	7.97	7.90	7.94 ± 0.04
12	8.02	7.99	7.95	7.99 ± 0.04
37°C WITH 80% RELATIVE HUMIDITY				
0	6.88	6.90	6.96	6.91 ± 0.04
4	9.58	9.67	9.17	9.47 ± 0.27
8	8.99	9.22	9.55	9.25 ± 0.28
12	8.51	8.34	9.20	8.68 ± 0.46
40°C				
0	6.88	6.90	6.96	6.91 ± 0.04
4	9.26	9.79	9.64	9.56 ± 0.27
8	8.71	9.58	7.81	8.70 ± 0.8
12	8.09	8.75	8.31	8.38 ± 0.34

99. Hardness of tablets of Batch NH after storage under various conditions of temperature and humidity

STORAGE PERIOD (WEEKS)	TABLET HARDNESS					MEAN TABLET HARDNESS ± SD
	T1	T2	T3	T4	T5	
ROOM TEMPERATURE (21±1°C)						
0	4.6	4.8	4.8	4.7	4.5	4.68±0.13
4	4.4	4.6	4.3	4.6	4.7	4.52±0.16
8	4.3	4.8	4.6	4.9	4.8	4.68±0.24
12	4.4	4.4	4.6	4.3	4.9	4.52±0.24
5±1°C						
0	4.6	4.8	4.8	4.7	4.5	4.68±0.13
4	4.5	4.6	4.5	4.6	4.4	4.52±0.08
8	4.5	4.4	4.3	4.2	4.1	4.30±0.16
12	4.0	4.1	4.2	4.1	4.0	4.08±0.08
37°C WITH 80% RELATIVE HUMIDITY						
0	4.6	4.8	4.8	4.7	4.5	4.68±0.13
4	5.2	5.3	5.2	5.4	5.3	5.28±0.08
8	5.8	5.9	5.7	5.8	6.2	5.88±0.19
12	6.4	6.8	6.7	6.5	6.4	6.56±0.18
40°C						
0	4.6	4.8	4.8	4.7	4.5	4.68±0.13
4	4.9	5.1	5.2	5.3	5.5	5.20±0.22
8	5.9	6.0	6.1	6.0	5.8	5.96±0.11
12	6.1	6.3	6.4	6.5	6.3	6.32±0.15

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