Formulation, Evaluation and Characterization of an Oral Modified Release Naproxen Sodium Preparation

by

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Summary

The motivation for the present study is systematically presented and the aims and objectives of the study are clearly defined. A comprehensive review on modified release drug delivery has been presented to provide the basis for the meltable aqueous dispersion technique as an approach to the formulation of a multiple-unit oral modified release drug delivery system. In addition, a brief discussion on the theory of dissolution testing and the mechanisms and interpretation of the dissolution process has been presented. Naproxen sodium, a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic activity employed in the study, has been briefly discussed.

In the present study, the coacervation phase separation technique utilizing ethylcellulose was initially investigated but proved unsuccessful in producing a formulation displaying suitable drug release characteristics. Subsequently, the meltable aqueous dispersion technique utilizing cetostearyl alcohol was successfully employed to formulate a multiple-unit modified release naproxen sodium preparation containing 550 mg of naproxen sodium. The use of cetostearyl alcohol, as a retarding material, generated modified drug release characteristics as a function of its content. Magnesium stearate (anti-tackiness agent) and Span 20 and Tween 60 (surfactants) were incorporated in the formulation to optimize particle size and sphericity. The influence of various formulation variables on drug release characteristics were investigated.

An optimized formulation displaying a desirable modified release profile of naproxen sodium was achieved employing a 1:1 ratio of naproxen sodium:cetostearyl alcohol, 2% $^m/_m$ magnesium stearate, and 1% $^m/_m$ Span 20 dispersed in a liquid manufacturing vehicle of pH 0.6 containing 2% $^m/_m$ Tween 60. In vitro dissolution studies on the selected formulation showed drug release to be predictable and reproducible, dependent on the dissolution method, agitation rate, and the pH of the dissolution media (i.e. pH-dependent drug release). The density of the microspheres was shown to decrease as the concentration of cetostearyl alcohol increased whilst the mean specific surface area increased with increasing concentrations of cetostearyl alcohol.

Differential scanning calorimetric studies reveals a change in the thermograms which is suggestive of eutectic formation. Scanning electron microscopy proved useful in evaluating the integrity and surface morphology of the microspheres as well as in elucidating the drug release characteristics of the formulation. Energy dispersive x-ray microprobe analysis revealed the elemental composition of the microspheres to be a composite of the pure ingredients. X-ray mapping and the line scan depicted the homogenous distribution of drug within the microspheres and confirmed that the formulation is a matrix-type modified release preparation.

Stability studies were performed on the selected formulation at room temperature (21 ± 1 °C), 40 °C, 37 °C with 80% relative humidity, and at low temperature (5 ± 1 °C). The shelf-life of the selected formulation was determined to be 1.29 years. Applying the data to

five different kinetic models to investigate the drug release mechanisms showed that first-order and cube-root release characteristics were exhibited by the microspheres.

Key terms: *Naproxen sodium, cetostearyl alcohol, modified drug release, meltable aqueous dispersion, kinetic modeling, stability data*

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Chapter One

Motivation for and Aim of Study

1.1 MOTIVATION FOR AN ORAL MODIFIED RELEASE MULTIPLE-UNIT PREPARATION OF NAPROXEN SODIUM

The attainment of 'steady state' blood levels and the minimization of 'peak and troughs' in the plasma concentration time profile is an important therapeutic goal (Wilson and Washington, 1985). In the clinical situation, the simplest approach to 'steady state' blood levels is by intravenous infusion. However, the disadvantage of this route of administration is that it is invasive and requires direct medical intervention. Consequently, the oral route remains the principal route of drug administration and is a major area of modified release product development (Livingstone and Livingstone, 1988).

In addition to providing constant 'steady state' drug blood levels, modified release delivery systems offer numerous advantages. These include:-

i) The extension of the duration of action, and consequently, a more convenient dosage regimen which may lead to improvements in patient compliance.

ii) The elimination of extremely high peak plasma concentrations which may lead to a reduction in side-effects.

iii) The capacity of cost effective therapy by reducing the non-compliance potential seen with frequent dosing of conventional drug products. The consequence of improved patient compliance is better disease management and shorter hospitalization periods which contribute to the overall reduction in health-care costs.

The oral route is therefore preferable and a constant therapeutic level is best approximated by modified release technology. Thus the present study is directed to the development of an oral modified release delivery system.

1.1.1 Modified Release of Naproxen sodium

Naproxen sodium, a propionic acid derivative, is a potent non-steroidal compound that possesses anti-inflammatory, analgesic and antipyretic activities. Naproxen sodium is a phenylpropionic acid derivative and is used in the treatment of degenerative joint diseases such as rheumatoid arthritis and other rheumatic or muscloskeletal disorders. The drug is a useful analgesic in a variety of acute pain states, such as migraine, tension headache, acute gout, primary and secondary dysmenorrhoea, post-operative pain, post partum pain and pain associated with a variety of gynaecological procedures. It has also been used successfully in the prophylaxis of migraine, reducing the severity and frequency of migraine attacks (Todd and Clissold, 1990).

The usefulness of naproxen sodium and other non-steroidal anti-inflammatory drugs (NSAIDS) is however, marred by the relatively high incidence of gastrointestinal side-effects. These range from mild to severe side-effects such as indigestion, hemorrhage, mucosal erosion and ulceration. The mechanism of such side-effects is complex, and has been partly attributed to both systemic (due to prostaglandin deficiency with resultant loss of mucosal integrity) and local irritation due to physicochemical action on the gastric mucosa (Oddsson *et al.*, 1989).

Naproxen sodium has a half-life of 12-15 hours and a pKa of 4.2 at room temperature (Al-Shammary *et al.*, 1991). It is excreted mostly in the urine (95%), 10% unchanged and the rest as the glucuronide and other conjugated metabolites. In spite of the long half-life of naproxen sodium, a modified release preparation would be of great advantage considering the fact that gastrointestinal side-effects are dose related and conventional dosage forms provide a high concentration of drug at the time of administration which may result in

gastrointestinal distress (Adams, 1992). In contrast to immediate release preparations, modified release formulations would release smaller amounts of drug over an extended period of time and it is therefore postulated that the incidence of gastrointestinal distress would be drastically reduced.

The naproxen anion is extensively protein bound to plasma albumin, which results in the nonlinear kinetics of naproxen sodium. The nonlinear pharmacokinetics result in an increased urinary excretion of naproxen sodium and its metabolites as the dose and plasma concentration increases. Due to these pharmacokinetics, it may be more efficient to deliver the drug at controlled, but reduced input rate compared with an oral bolus dose occurring from an immediate release dosage form. This theory was proven by Dahl *et al.* (1990) who showed that controlled and efficient drug delivery from three modified release matrix preparations undoubtedly accounts for higher AUC values compared with that obtained from an equivalent dose of an immediate release formulation of naproxen sodium.

1.1.2 Multiple Unit Drug Delivery

A perusal of relevant pharmaceutical literature reveals that the multiple unit approach to dosage form design is gaining wide acceptance in pharmaceutical technology in the area of modified release drug delivery systems. Charles and Mogg (1994) reported the absorption of naproxen to be rate limited by stomach emptying prior to subsequent dissolution in the small intestine. A significant advantage of multiple unit preparations is the property of random gastric emptying thereby eliminating the dependency of the depot on gastric emptying, since individual subunits are sufficiently small (less than 2 mm in diameter) to pass through the pyloric sphincter even when it is closed. Accordingly, individual variations in gastric emptying of these subunits are minimal and the subunits exhibit highly reproducible transport throughout the gastrointestinal tract (Bechgaard and Christensen, 1982).

Multiple unit preparations are considered to be potentially safer than intact or single unit dosage forms since these preparations are uniformly distributed over a large surface area. Due to the distribution of subunits over the entire length of the gastrointestinal tract, the risk of local damage as a result of 'dose dumping' of a single unit preparation will be minimized (Ghebre-Sellassie, 1989). This advantage is especially pertinent to a naproxen sodium formulation since gastrointestinal side-effects are dose related (Adams, 1992). The above advantages clearly justify the incorporation of naproxen sodium into a multiple unit drug delivery system.

1.1.3 The Meltable Aqueous Dispersion Technique

Modification of the drug release rate from a delivery system may be achieved through the use of different mechanisms and formulation techniques. Also, for any one technique, the modulation of release rate may be achieved using different grades of polymer or rate-controlling substances (Nakano *et al.*, 1983), different types of polymers or rate-controlling substances (Baveja *et al.*,1987), insoluble fillers (Rao *et al.*, 1990), or soluble fillers (Ford *et al.*, 1991) and the alteration of physical variables (eg. mixing rate, temperature) during the formulation process.

Wax matrices have been commonly employed in the formulation of modified release drug delivery systems. As early as 1960, Yamamoto and Baba patented a method involving cooling induced solidification of the oily phase of a two-phase system (Draper and Becker, 1966). Despite the flexibility of this technique, there is a paucity of literature with respect to the application of this technique in the formulation of modified release drug delivery systems. However, since the mid eighties numerous researchers have investigated the applicability of this method to various drugs. Modification of the two phases have led to the production of microspheres of both water-soluble and water-insoluble drugs (Benita and Donbrow, 1986; Kawata *et al.*, 1986; Das and Gupta, 1988; Wong *et al.*, 1992; Giannola *et al.*, 1995).

The simplicity of innovative pharmaceutical technology is imperative in the attainment of optimized, cost-effective drug therapy. The meltable aqueous dispersion technique is a relatively simple and straightforward approach to the formulation of multiple-unit delivery systems and requires no investment in high cost equipment (Al-Kassas *et al.*, 1993). Furthermore, the formulation process is fairly rapid which contributes to the cost-effectiveness of the technique. Consequently, the present study employed the meltable aqueous dispersion technique to formulate wax-based microspheres by the dispersion of the drug-wax melt in an aqueous acidified medium.

1.1.4 Cetostearyl Alcohol

In the present study, cetostearyl alcohol was employed to formulate a multiple unit wax matrix delivery system. The following points justify the use of cetostearyl alcohol:

i) Cetostearyl alcohol is generally regarded as non-toxic, essentially non-irritant material and has been utilized in oral pharmaceutical dosage forms such as emulsions. Furthermore, cetostearyl alcohol is not readily absorbed from the gastrointestinal tract.

ii) Naproxen sodium-cetostearyl alcohol microspheres will afford the patient the numerous distinct advantages of multiple unit preparations.

iii) The use of cetostearyl alcohol sanctions the employment of simple pharmaceutical technology to develop novel drug delivery systems. The meltable aqueous dispersion technique is a relatively simple technique that employs wax material (such as cetostearyl alcohol) to formulate a multiple unit preparation.

1.2 AIM AND OBJECTIVES OF THE STUDY

The fundamental aim of the study was to ascertain the *in vitro* drug release characteristics of a novel oral modified release multiple unit preparation of naproxen sodium. To realize this aim, the coacervation phase separation utilizing ethylcellulose was investigated. However, drug release data revealed the inadequacy of this technique and the polymer to retard drug release efficiently. Therefore, the meltable aqueous dispersion technique using cetostearyl alcohol was employed to formulate a multiple unit preparation containing 550 mg of naproxen sodium in order to facilitate a once daily dosage regimen.

The influence of various formulation factors on the drug release profiles was examined in an attempt to achieve microspheres possessing desirable modified release characteristics. The drug release behaviour of the naproxen sodium cetostearyl alcohol microspheres was evaluated using the compendial methods (USP XXIII, 1995),with modification, in view of its proven reliability and stringent regulatory requirements.

On the basis of the *in vitro* drug release data an optimized formulation was selected for further evaluation which included the following considerations:

i) the reproducibility of the manufacturing process;

ii) the influence of different dissolution method/ media and agitation rates on the drug release characteristics;

iii) the stability of the formulation under various storage conditions over a period of three months;

iv) the moisture content of the microspheres prior to and during the three month storage period under various predetermined conditions;

v) surface topography, integrity and elemental composition of the newly formulated microspheres.

In addition to the above evaluations, Differential Scanning Calorimetric studies were performed on various formulations.

At present, naproxen sodium is commercially available as an immediate release preparation. In view of the numerous advantages of a modified release multiple unit preparations, the present study could result in the introduction of a modified release formulation of naproxen sodium to the market. Furthermore, the formulation of a novel oral modified release naproxen sodium preparation would be of significance as the initiation and development of modified release technologies in South Africa could ultimately reduce the dependency of the local pharmaceutical industry on expensive imported modified release preparations.

Chapter Two

Oral Modified Release Drug Delivery Systems

2.1 MODIFIED DRUG RELEASE

2.1.1 Introduction

Modified release drug delivery systems have been developed for the purpose of maintaining safe and therapeutically effective concentrations of drug in the systemic circulation for extended periods of time thereby eliminating the large fluctuations in drug-plasma concentrations often associated with the frequent dosing of conventional dosage forms.

The oral route, being the principal and most convenient route of drug administration, is a major area of modified release product development. However, this route has been plagued with the problems of unpredictable, haphazard bioavailability and variability in the gastrointestinal transit time of a particular drug delivery unit. Hence, the oral route presents a challenge to the pharmaceutical development scientist with respect to the assessment and development of oral modified release drug delivery systems (Banaker, 1994a).

Prior to the advent of modified release technology, the primary foci of dosage form design included product aesthetics, stability, purity, identification and a drug quantity specification. Subsequently, substantial advances in modern pharmaceutical technology has made possible the design of dosage forms that modify the timing, the rate and the location of drug release from a dosage form (USP XXIII, 1995). Consequently, an array of dosage forms have emerged with simple to sophisticated mechanisms of drug release.

These range from simple, slowly dissolving pellets or tablets (Juliano, 1980) to the more complex delivery systems such as the hydrodynamic pressure-controlled drug delivery system and the two-chamber push-pull osmotic system outlined by Chien (1983) and Lippold (1991).

Irrespective of the type or complexity of the system used, the ultimate goal of modified release drug delivery is to release drug at a constant, zero-order rate where a quantity of drug which is equivalent to that eliminated from the body is continuously released over a period of time thereby maintaining constant plasma drug levels for the duration of therapy. Unfortunately, most systems that release drug by zero-order kinetics *in vitro* do not demonstrate zero-order drug absorption *in vivo* (Shargel and Yu, 1985). Hence, the optimisation of drug therapy via the oral route continues to challenge pharmaceutical scientists. It is obvious, that current developments in pharmaceutical research are being emphasised to a great extent on rate-controlled drug administration. Given the current impetus in oral modified release drug delivery, the increase in the knowledge base in the gastrointestinal area and extensive experimental explorations in the employment of polymer technology, one can anticipate that a substantial number of new products will emerge in the coming five to ten years.

2.1.2 Terminology and Concepts of Modified Release Systems

The differentiation between a conventional dosage form and a drug delivery system is fundamental to the understanding of the concept of modified release drug delivery. A conventional or immediate release product is defined as a system in which the rate of appearance of drug in the body is controlled by the biological absorption process (Longer *et al.*, 1988). In comparison, a drug delivery system has been broadly defined as a chemical, mechanical or electrochemical device designed to input drugs into the systemic circulation or to specific target sites in the body at predetermined, controlled rates (Smolen, 1984). However, most of the currently available drug products can best be described as "drug dump systems", in that the time course of their release is generally fortuitous rather that being predetermined or designed on the basis of rational pharmacological criteria (Smolen, 1984).

A perusal of literature reveals a myriad of terms that have been utilised to describe the different types and modes of action of modified release drug delivery systems. Some of the more commonly employed terms used to describe existing drug delivery systems are presented in Table 2.1.

Table 2.1 : Terminology Used to Describe Solid Oral Drug Delivery Systems

TYPE	CHARACTERISTICS	REFERENCE\S
Modified release	drug release characteristics of time course and/or location have been chosen to accomplish therapeutic and convenience objectives not offered by conventional dosage forms.	USP XXIII, 1995 (Supplement 4, May 1996)
Extended release	allows at least a two-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance as compared to that presented as a conventional dosage form.	USP XXIII, 1995 (Supplement 4, May 1996)
Delayed release	releases a drug at a time other than promptly after administration.	USP XXIII, 1995 (Supplement 4, May 1996)
Sustained release	delivers an initial dose of the drug (loading dose) followed by slower and constant release of drug (maintenance dose); rate of release of maintenance dose is designed so that the amount of drug loss from the body by elimination is constantly replaced; constant plasma drug levels may be achieved.	Shargel and Yu (1985)
Repeat action	Releases a single dose of drug initially and then a second dose at a later time, or even a third dose some	De Haan and Lerk, 1984;

	time later; continued action therapy provided but peak and trough blood levels are exhibited.	Abdou, 1989
Prolonged action	provides slow release of drug at a rate sufficient to cause a therapeutic response over an extended period of time; constant drug levels not maintained formulation does not contain a loading dose.	De Haan and Lerk (1984)
Controlled release	collective term for preparations of which onset and/or drug release is altered by galenical manipulations provides extended duration of action; implies predictability and reproducibility of drug release kinetics.	De Haan and Lerk (1984); Chien (1983)

For compendial purposes, the USP XXIII 1995 (Supplement 4, May 1996) has defined the term modified release as outlined in Table 2.1. This term infers that the rate of release of drug from the delivery system has either been increased, slowed or designed to deliver drug to a specific site in the body (Pillay, 1996). Presently, only two types of modified release dosage forms are recognised and defined, viz.: extended release and delayed release.

The terms sustained release and controlled release are frequently used interchangeably without distinction of the precise release mechanism for all systems that release drug over an extended period of time (Chetty, 1990). In comparison, the USP XXIII (1995) considers the terms controlled release, prolonged action and sustained release to be synonymous with the term extended release. For the purpose of this presentation the term modified release will be employed to obviate any confusion that may arise due to the absence of standard nomenclature to describe systems in which the release of drug occurs over an extended period of time.

The fundamental objective in the development of an ideal modified release system is the concept of zero-order release kinetics from the delivery system. Until recently, constant rate

intravenous infusion, by means of a carefully controlled drip or mechanical pump, was the sole means of attaining constant blood or tissue levels of drug. Presently, there are delivery systems intended for oral, ocular, intravaginal and intramuscular administration that release drug in a zero-order or near zero-order fashion. One such system, termed the elementary osmotic pump, has been available for some time to achieve this goal (Gibaldi, 1991).

Figure 2.1 illustrates typical drug-blood profiles achieved by some of the delivery systems described by the above terminology.

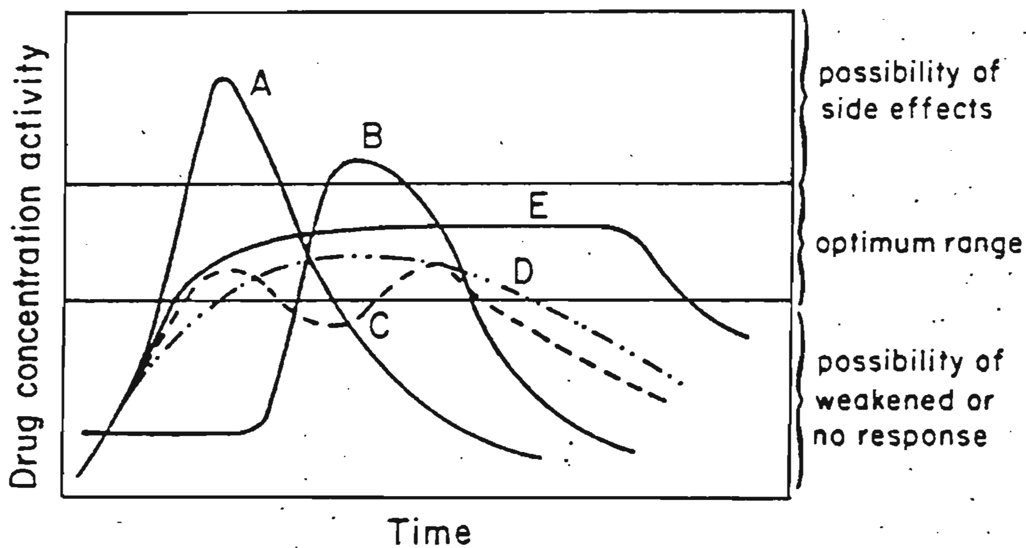


Figure 2.1 : Drug-Blood Profiles for Delivery Systems Possessing Various Release Profiles (Abdou, 1989, page 215)

Key: A-Immediate Release, B-Delayed Release, C-Repeat action, D-Prolonged Release, E-Controlled/Sustained release

2.1.3 Rationale for the Formulation of Modified Release drug Delivery Systems.

The numerous potential advantages and demerits of modified release drug delivery are well-known and have been adequately documented in the literature (Dangor, 1984; Livingstone and Livingstone, 1988; Skelly *et al.*, 1990; Perumal, 1996). Some of the more salient points have been highlighted in Table 2.2.

Table 2.2 : Advantages of Modified Release Drug Delivery Systems Over Conventional Dosage Forms

ADVANTAGE	DISCUSSION
Improved drug blood level profiles	With modified release systems, the "see-saw" fluctuations that are observed with the multiple dosing of conventional drug products are not evident. More reliable absorption results in the maintenance of a constant level of drug in the plasma (Chien, 1982).
Reduction in dosing frequency	Modified release systems deliver more than a single dose of medication and extends the dosing interval thereby reducing the frequency of dosing (Ansel and Popovich, 1990).
Enhanced patient compliance	The extension of the duration of action, and consequently, a more convenient dosage regimen may contribute to an improvement in patient compliance (Lordi, 1986).
Improved side-effect profile	Modified release products yield "flattened" blood concentration time curves that do not exceed the therapeutic range. Since drug blood levels do not enter the toxic range, adverse effects that are associated with the fluctuating blood levels of conventional dosage forms are reduced or totally eliminated (Gibaldi, 1991).
Cost effectiveness	Modified release drug delivery systems offer the advantage of the capacity of cost effective therapy by reducing the non-compliance potential seen with the frequent dosing of conventional drug products, which may lead to better drug utilization and decrease costs of nursing time in hospitals (De Haan and Lerk, 1984).

2.1.4 Limitations of Modified Release Drug Delivery Systems

There are several disadvantages that are associated with modified release drug delivery systems, some of which have been outlined in Table 2.3.

Table 2.3 : Disadvantages Of Modified Release Drug Delivery

DISADVANTAGE	DISCUSSION
Dose dumping	Failure of the dosage form can result in premature, immediate release of the drug which may result in peak plasma levels that exceed the maximum toxic concentration (therapeutic range). Hence, the patient may be subjected to serious side effects and potential drug toxicity (De Haan and Lerk, 1984).
Variable gastrointestinal physiology	For drugs that are not absorbed uniformly throughout the gastrointestinal tract, administration as a monolithic modified release system may lead to variability in the onset and duration of therapeutic effect due to erratic absorption (Merkus, 1986).
Loss of flexibility in dosage regimens	Most modified release delivery systems do not afford the physician the option of tailoring drug therapy to the unique needs of the individual patient. Furthermore, immediate termination of effect may not be possible and idiosyncratic reactions may be difficult to control (Lordi, 1986).
Administration problems	Improper administration of a modified release drug delivery system, such as chewing and masticating, may be extremely hazardous as most of these systems contain relatively larger amounts of drug than their immediate release counterparts.

Problematic treatment of adverse drug reactions	Removal of drug from the body is more difficult than with immediate release dosage forms. Thus, patients may be exposed to untoward drug effects for prolonged periods of time. Accidental and / or suicidal intoxications may pose special treatment problems not encountered with conventional dosage forms (Shargel and Yu, 1985).

Notwithstanding the several disadvantages of modified release systems, it is clearly evident that modified release technology offers a superior form of drug intervention that is beneficial to the patient. Many of the disadvantages can be overcome or totally eradicated if the formulation scientist takes cognescence of the physicochemical and biopharmaceutical factors affecting the release and absorption of the specific drug from the delivery system. Ensuring proper counselling of patients when dispensing modified release drug delivery systems will further reduce potential disadvantages of such systems. Thus, the challenge to formulators for the development of and optimization in the design of a modified release system for a specific drug is to aim for the development of an ideal drug delivery system.

2.1.5 Criteria for the Selection of Drug Candidates for Modified Release Drug Delivery Systems

In the Utopian context, the application of the principle of modified release drug delivery to all drugs would be desirable. However, for the formulation of a drug candidate into a modified release system, it is imperative that the drug satisfies certain requirements that allow for its incorporation into such a system. Krowczynski (1987) expressly stated that a drug must possess specific attributes to allow for its incorporation into a modified release system. Table 2.4 outlines some of the important criteria that need to be considered in assessing the suitability of a drug candidate with regards to its incorporation into a modified release system.

Table 2.4 : Important Criteria that Determine the Suitability of a Drug Candidate for Modified Release

CRITERION	DISCUSSION
Aqueous solubility	Dictates the feasibility of incorporation of a drug into a modified release preparation. A solubility of less than 0.1 mg/mL may pose formulation difficulties (Lee and Robinson, 1982) and it may be difficult to control the release of a drug with an extremely high solubility. pH-dependent solubility creates further difficulties in the design and formulation process.
Absorption	Drugs that display incomplete and erratic absorption may be unsuitable or even impossible to formulate as a modified release system. Drugs that are uniformly absorbed throughout the gastrointestinal tract are suitable candidates. Drugs that are preferentially absorbed from certain sites in the gastrointestinal tract will be difficult to formulate as modified release systems since any drug released after passing the preferred site will be poorly absorbed (Abdou, 1989).
Biological half-life	Drugs with very long biological half-lives inherently exhibit an extended duration of action (Lordi, 1986). Drugs with short half-lives require large doses to be incorporated into the system. Thus, the dosage form may be difficult to swallow and can be potentially hazardous in the event of "dose dumping" (Abdou, 1989).
Therapeutic index	Drugs with a narrow therapeutic index exhibit a small margin of safety and system failure may present serious and hazardous consequences (Chang and Robinson, 1990).

The following criteria may be used as a guideline for the selection of drug candidates for the incorporation into modified release drug delivery systems. However, exclusion of a drug candidate has to be based on a number of factors. Thus, only after careful consideration of all factors can one deduce the suitability of a drug candidate for modified release drug delivery.

2.1.6 Classification of Oral Modified release Drug Delivery Systems

Numerous researchers have attempted to present a comprehensive classification system for the vast number of modified release drug delivery systems that are available (Chien, 1982; Langer and Peppas, 1983; Merkus, 1986). In most cases the classification has been one-sided and do not always give the desired mechanism of drug release, or on the contrary are very complicated and cumbersome.

For the development of a truly comprehensive classification system, it is imperative to include the mechanism of drug release and formulation principles in the system. Rachev *et al.* (1989) developed a system of classification that incorporates the mechanism of release as well as the kind of technological methods for its preparation. Pillay (1996) tabulated a classification system for modified release delivery systems, based on the classification proposed by Rachev *et al.* (1989), as follows :-

Physical Systems

* Diffusion controlled systems
  - Reservoir systems
  - Matrix systems
* Osmotically controlled systems
* Swellable controlled systems
* Ion-exchange systems
* Hydrodynamically controlled systems
* Systems with prolonged gastric residence time
* Bioadhesive systems

Chemical Systems

- * Immobilisation systems
- * Prodrugs

Bioengineering Systems

- * Autoregulation systems

For the present study, an in-depth discussion of diffusion controlled systems is considered pertinent. A diffusion controlled system is one in which the mechanism of drug release is diffusion. Diffusion controlled systems are the most widely used for the delivery of bioactive agents and are comprised of reservoir and matrix systems (Langer and Peppas, 1983).
Table 2.5 presents a synopsis of currently available diffusion controlled modified release systems.

Table 2.5 : Classification of Diffusion Controlled Modified Release Drug Delivery Systems

SYSTEM TYPE	DISCUSSION
1. Reservoir Systems	Consists of a rigid semi-permeable membrane that separates a core of bioactive agent from the biological environment. Diffusion of drug through the polymer is the rate-limiting step in drug delivery (Langer and Peppas, 1983).
1.1 Non-porous membrane systems	Consists of a homogenous polymeric film. Diffusion is accomplished through an amorphous phase to a polymeric structure (Rachev *et al.*, 1989).
1.2 Microporous membrane systems	Release of drug occurs through fluid filled pores (Bruck, 1983).
2. Matrix Systems	Consists of an inert solid vehicle in which a drug is homogeneously dispersed as discrete crystals or solid particles (Chien, 1982; Shargel and Yu, 1985).
2.1 Systems with dissolved drug	Drug is dissolved in the polymer below its solubility limit, either by preparing a drug-polymer solution, casting it in a desirable geometrical form and partially or totally evaporating the solvent; or by soaking the polymer in a drug solution (Peppas, 1984).
2.2 Systems with dispersed drug	Contain solute originally dispersed in the polymer at a concentration which is higher than the solubility limit of the solute in the polymer (Langer and Peppas, 1983).

2.3 Porous matrix systems	Solute diffusion occurs almost exclusively through large interconnecting channels at almost zero-order release rates. Release of drug is believed to occur as a result of dissolution- and diffusion-controlled phenomenon, or by percolation effects (Peppas, 1984).
2.4 Hydrogel systems	Drug is incorporated in a nonsoluble substance that swells in contact with biological systems. The delivery is a function of both the rate of entry of fluid into the system and the diffusion of drug through the gel-forming layer (Rachev *et al.*, 1989; Singh *et al.*, 1993).
2.5 Bioerodible matrix systems	Release occurs through the degradation of the polymer or the polymer-drug conjugate. Drug release is proportional to square root of time (Merkus, 1986).
3 Sandwich-type Systems	Developed with the objective of hybridizing the constant release kinetics of the reservoir system and the mechanical superiority of the matrix system (Chien, 1982).

2.2. DESIGN AND FABRICATION OF ORAL MODIFIED RELEASE DRUG DELIVERY SYSTEMS

A plurality of different types of oral modified release systems have been developed. These range from simple to complex technological systems that release drug by a variety of mechanisms that result in a zero-order or first order drug release rate profile. From a technological viewpoint, the major types of oral modified release systems are :-

* Multiple unit preparations
* Matrix tablets
* Ion-exchange resins
* Osmotically controlled devices

The present study undertook to investigate the formulation of a multiple unit preparation of the non-steroidal anti-inflammatory drug naproxen sodium, using a wax material. Thus an extensive discussion of multiple unit preparations will be presented.

2.2.1 Multiple Unit Preparations for Oral Modified Release Drug Delivery

Modified release systems may be divided into two basic categories :-

* Single unit (monolithic) systems
* Multiple unit (multiparticulate) systems

However, both groups rely on some physical or chemical "barrier" which retards drug release (Livingstone and Livingstone, 1988). Multiple unit systems have also been termed polydisperse systems (Blume, 1991). As the name implies, multiple unit dosage forms consist of a combination of subunits of the dosage form which may either be unique (homogeneous) or different (heterogeneous). Multiple unit dosage forms are usually based on such subunits as granules or spheroids, beads or beadlets, pellets, microcapsules. Other terms that have been used to describe multiple unit preparations include microspheres (Pavanetto *et al.*, 1994), spherules (Ganderton, 1985), nanospheres and nanocapsules (Fessi *et al.*, 1989; Niwa *et al.*, 1994). These subunits are usually delivered in hard gelatin capsules (Khan, 1995).

Alternatively, the individual subunits may be compressed into a tablet that disintegrates rapidly to release the individual subunits in the gastrointestinal tract (Livingstone and Livingstone, 1988).

The discovery of the multiple unit system principle can be credited to Israel Lipowski, who patented the pellets approach in 1938 (De Haan and Lerk, 1984). However, the first truly effective oral drug delivery system, the "Spansule", was commercially introduced by Smith Kline and French Laboratories and was used to sustain the release of dextroamphetamine (Ranade, 1991).

Numerous researchers have adopted the multiple unit approach in the formulation of drug delivery systems (Chetty, 1990; Govender, 1992; Tirkkonen and Paronen, 1992; Pillay, 1996). Although the technology employed and the polymeric systems utilized may differ vastly, the ultimate goal is realized in the formulation of a multiple unit system.

A common method utilized in the manufacture of multiple unit preparations entails coating of a drug solution onto non-pareils (sugar seeds) which are subsequently coated with a retardant layer, which is usually some kind of polymeric material (Abdou, 1989). A multitude of chemical or polymeric substances have been utilized as coating/matrix forming materials. These include wax or wax-like substances (such as cetostearyl alcohol), ethylcellulose, acrylic polymers (Eudragits®), fatty alcohols, acids and esters (De Haan and Lerk, 1984; Khan, 1995). To achieve the desired release profile, a multiple unit system may be comprised of subunits of varying thicknesses of a slowly dispersible substance such that a relatively constant rate of drug release is produced. Alternatively, the coating may be nondispersible so drug release is controlled by diffusion of the drug through the coating (Livingstone and Livingstone, 1988).

2.2.2 Rationale for the Formulation of Multiple Unit Preparations

The distinct advantages of multiple unit systems over their single unit counterparts have been extensively documented in the literature (Ganderton, 1985; Eskilson, 1985a; Ghebre-Sallassie, 1989; Khan, 1995; Perumal, 1995; Pillay, 1996).

A multiple unit system may be made aesthetically appealing by the incorporation of different shades of colour or different colours which may lead to an enhancement of patient acceptance (Ghebre-Sellassie, 1989). This may have the added advantage in the ability to distinguish between subunits of different coating thicknesses since thicker coatings will be darker in colour (Ansel and Popovich, 1990), as well as allowing for differentiation between subunits that are comprised of different bioactive substances.

It has been argued that a significant advantage of multiple unit formulations is the property of random gastric emptying which leads to a wider distribution of individual subunits throughout the gastrointestinal tract. This would prolong the transit of the formulation through the small intestine resulting in increased bioavailability of poorly absorbed preparations (Wilson and Washington, 1985). The application of the multiple unit principle eliminates the dependency of the depot on gastric emptying, since individual subunits are sufficiently small (less than 2mm in diameter) to pass through the pyloric sphincter even when it is closed. Accordingly, individual variations in the gastric emptying of these subunits are minimal and the subunits exhibit highly reproducible transport throughout the gastrointestinal tract (Bechgaard and Christensen, 1982). The role of food has been reported to have major implications on gastric emptying (Davis, 1987). In the fasted mode both single units and pellets are emptied rapidly. On a lightly fed stomach single units will be delayed, but pellets can be emptied, the rate of emptying of the latter and their spreading in the small intestine depends on the quantity of food. A heavy meal will result in a steady emptying of multiple units from the stomach with a large amount of spreading as compared to single units which will remain in the stomach so long as it is in the digestive mode (Davis, 1987).

Some pharmaceutical scientists judge multiple unit preparations to be potentially safer than intact or single unit dosage forms since a mechanical failure of the coating or matrix would result in the immediate release of only a small fraction of the entire dose. However, a mechanical failure of a single unit may result in immediate dumping of the entire dose which may contain a quantity of drug that is 2 or 3 times more than is contained in a conventional dosage form (Gibaldi, 1991). Similarly, failure of a single unit to release its contents will result in a loss of therapeutic effect as compared to the minimal effect of a few pellets failing to release their contents (Lordi, 1986). Furthermore, due to the distribution of subunits over the entire length of the gastrointestinal tract, the risk of local damage as a result of "dose dumping" of a single unit preparation will be minimized (Ghebre-Sellassie, 1989).

An important advantage of multiple unit systems is the attainment of the desired drug release profile by the combination of subunits with varying coating thicknesses, polymer concentrations or particle sizes within a single delivery system (Livingstone and Livingstone, 1988). Furthermore, some chronic disease states (such as hypertension) may require combination drug therapy. In these circumstances, for improved patient compliance it is desirable to deliver two or more drugs via a single delivery system. Thus, multiple unit systems, as well as multilayered tablets may be employed to realize this goal. However, while multilayered tablets or tablets with multiple coatings require complex manufacturing techniques, multiple unit dosage forms are easy to design to meet this criteria since such a preparation would simply entail the combination of different types of subunits of the dosage form prepared separately (Khan, 1995).

Multiple unit preparations are also useful when drug-excipient or drug-drug physico-chemical interactions is inevitable in a single unit dosage form (Khan, 1995).

2.2.3 Recent Studies Utilizing the Multiple Unit Principle

The application of the multiple unit principle is rapidly becoming the favoured approach in the design of modified release drug delivery systems. Perusal of scientific pharmaceutical

journals reveal the vast amount of research being devoted to the development of multiple unit preparations. In the quest for the discovery of the ideal oral delivery system, pharmaceutical scientists have discovered and developed a multitude of technologies and polymeric systems that have been extensively reported in the literature (Li *et al.*, 1993; Pavenetto *et al.*, 1994; Bachtsi and Kiparissides, 1995; Bhatnagar *et al.*, 1995).

Fessi *et al.* (1989) reported a process of interfacial polymer deposition following solvent displacement. In their method, indomethacin-loaded spherical vesicular nanocapsules were prepared by deposition of poly-(D,L-lactide) polymer at the oil-water interface following acetone displacement from the oily nanodroplets. The mechanism of formation of the nanocapsules was attributed to the Marangoni effect, which occurs as a result of interfacial turbulence or spontaneous agitation of the interface between two unequilibrated liquid phases, involving flow, diffusion and surface processes.

Torres *et al.* (1990) formulated microcapsules containing sodium fluoresceinate using ion-exchange resins by a process of interfacial nylon polycondensation. Optical microscopy was employed to verify the encapsulation of the drug resin complexes by the nylon polymer. Release of drug was delayed due to reticulation of the resin and the presence of the polymeric nylon coating. This study showed that the degree of crosslinking of the resin complexes markedly affected drug release characteristics.

Recently, numerous studies utilizing poly-(D,L-lactic acid)-co-gylcolic acid (PLGA) have been undertaken. Niwa *et al.* (1994) reported the use of PLGA in the preparation of nafarelin microspheres by a novel spontaneous emulsification solvent diffusion technique. Drug release from the nanospheres in acidic medium was shown to follow a biphasic pattern of initial burst and sustained release. Diazepam loaded polylactide microspheres were also prepared by Pavenetto *et al.* (1994). The microspheres were prepared by two techniques :-

- solvent evaporation
- spray drying

The solvent evaporation technique proved to be more viable in terms of the desired release characteristics. The encapsulation efficiency and the yield was higher, and drug release,

although similar, was more gradual. In addition, microspheres were smaller and depicted a smoother, continuous surface. In both cases a bimodal release pattern was observed. The advantage of polylactide and PLGA is that they are non-toxic, biodegradable, biocompatible polymers that can be used in the delivery of a wide variety of bioactive substances, including peptide drugs (Niwa *et al.*, 1994; O'Hagan *et al.*, 1994).

In recent years, much attention has been devoted towards the formulation of swelling controlled release matrix based formulations (Singh *et al.*, 1993). These systems have been termed hydrogels. Hydrogels have been extensively used as modified release delivery devices of various biomolecules including drugs, enzymes and antibodies (Bachtsi and Kiparissides, 1995). Carelli *et al.* (1993) formulated a modified release multiple unit system for progesterone based on crosslinked poly (ethylene oxides) by an impregnation technique and subsequent solvent evaporation. Release of progesterone was retarded over a period of 180 hours. A reproducible drug loading of 8.3% to 10.5% was achieved with crosslinked poly (ethylene oxides) of crosslinking degrees adequate to confer the required mechanical stability on the swollen matrix. The researchers were able to achieve a drug loading of 39.1% with a grade of poly (ethylene oxide) of low crosslinking degree, however this formulation showed poor mechanical properties in its fully swollen state.

Crosslinked poly (vinyl alcohol) microspheres were prepared by the addition of gluteraldehyde into a PVA methanol/water solution in the presence of 0.2 N sulphuric acid by Bachtsi and Kiparissides (1995). Spherical crosslinked particles in the size range 30 - 80 μm were obtained by varying the intensity of agitation and/or the quantity of the suspending agent used. The crosslinked particles, after washing and drying, were placed into a protease enzyme solution for loading. The release behaviour of the enzymes from crosslinked PVA particles exhibited a biphasic kinetic model.

Pillay (1996) investigated the applicability of alginate gel discs as an oral modified release system for the delivery of the non-steroidal anti-inflammatory drug, indomethacin. An optimized formulation was attained using a 2.5% sodium alginate solution with a 1:1 ratio of

sodium alginate to indomethacin. Drug release was retarded over an eight hour period which exhibited a bimodal release profile.

Bhatnagar *et al.* (1995) developed a poloxamer-coated three-ply-walled microcapsule system for controlled delivery of diclofenac sodium. The three-ply-walled microcapsules were formulated by a technique of multiple-emulsion formation polymer at the interface followed by rigidization of the wall on evaporation of the solvent. These microcapsules were subsequently coated with poloxamer 188. Coated microcapsules depicted a marked decrease in release as compared to uncoated microcapsules. Poloxamer coated microcapsules produced sustained plasma levels of diclofenac sodium for up to 24 hours. The results also indicated that surfactant coating of microcapsules results in slower blood clearance and a different organ distribution pattern as compared to uncoated microcapsules.

Perumal (1996) prepared ibuprofen microcapsules by an emulsion solvent diffusion technique using methacrylic copolymers. The stability of the microspheres at room temperature, low temperature (5 ± 1°C) and at 37°C (with 80% relative humidity) was confirmed by short term stability studies. *In vitro* dissolution tests showed drug release to be predictable, reproducible and independent of dissolution techniques. Dissolution studies showed that first order and square root of time release characteristics were exhibited by the microspheres.

2.2.4 Recent Innovations in the Field of Modified Release Drug Delivery

The focus of research and development in the pharmaceutical sciences, technology in particular, has shifted from dose (content) to the rate determining components of the dosage form. One of the challenging areas concerning the drug delivery system itself is the ability of the system to deliver the medicament at not only a programmed rate but also for an extended duration for optimal therapeutic objectives. Numerous approaches have been explored to achieve the objective of pre-programmed controlled entry of the therapeutically active substance for an extended period of time (Banaker, 1994a). A few of the more promising approaches are discussed below.

2.2.4.1 Silicone reservoir devices

Sutinen *et al.* (1990) prepared novel pH-controlled reservoir devices incorporating the model drug, propranolol (lipophilic) and sotalol (hydrophilic). The membranes for the silicone reservoir devices were made of Q7-4840 A/B medical grade silicone elastomer. The membranes were prepared by mixing A and B components in equal proportions and compressing them using a hydraulic press. Circular discs with a thickness of about 150 µm and diameter of 22 mm were cut from the membranes. Samples of the model drugs, with or without additives were placed on the silicone discs. The upper silicone membrane was glued to the lower membrane with Silastic® adhesive type B leaving the model drug and possible additives encapsulated between the membranes (Figure 2.2). Drug release from the device is activated by flux of water into the core of the device. Without additives in the device core the release of the model drugs were negligible. When pH-adjusting additives (Tris, disodium phosphate and/or sodium phosphate) were incorporated into the core of the silicone device, the resulting pH after water flux in the device increased, resulting in an increase in the rate of release of propranolol. Sotalol was too hydrophilic even in its unionized state to be released through the silicone membranes. Thus, the rate of release of bioactive substances can be controlled over a wide range with pH-adjusting agents in the device core if the unionized form of the drug is sufficiently lipid soluble to partition in silicones.

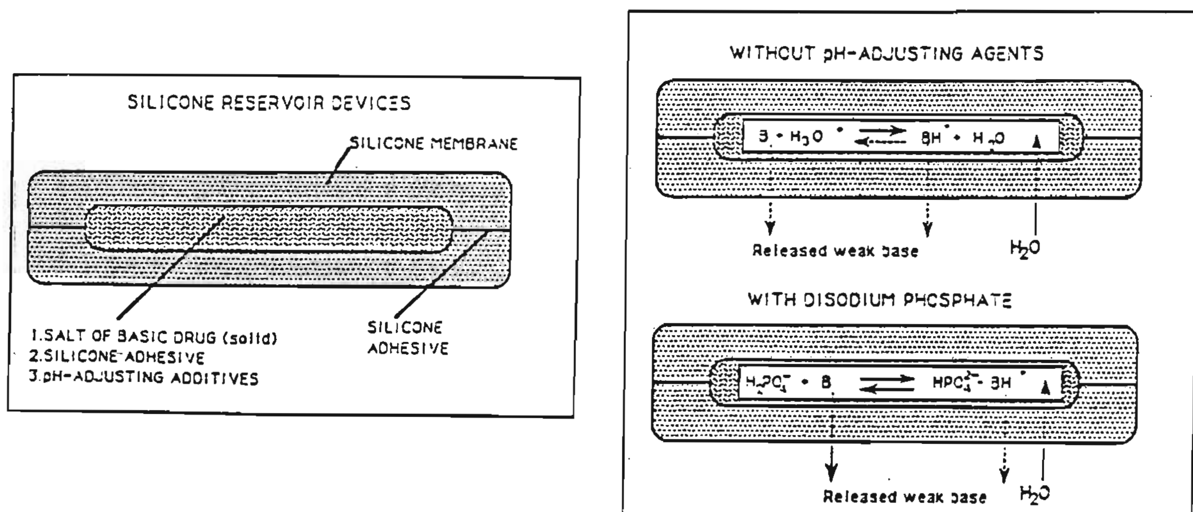


Figure 2.2 : pH Controlled Silicone Reservoir Device (Sutinen *et al.*, 1990, page 114)

2.2.4.2 Pulsatile delivery systems

There is good evidence from many systems (neurotransmitters, peptide hormones) that continuous receptor stimulation can lead to a reduced response (tachyphylaxis), while continuous receptor blockade can lead to supersensitivity. This revelation has many profound implications for the use of modified release systems. Thus, we have to consider the possibility of using systems that will permit delivery of drug in a pulsatile fashion, either predetermined or controlled by the patient (Gardiner, 1987). Pulsatile release may be in the form of one pulse coinciding with circadian rythym or in repeated pulses. The peroral route offers the most reliable and predictable possibilities to achieve pulsatile drug levels by simply adapting the dosing frequency of a suitable drug (Banaker, 1994b).

A novel delivery system capable of releasing its drug contents at either a predetermined time or at a specific site in the gastrointestinal tract known as the Pulsin® has been developed by Scherer, which consists of a water-insoluble body and a water soluble cap. The formulation contained within the body of the capsule is sealed and plugged with a hydrogel (Figure 2.3). On oral ingestion of the system, the cap dissolves in the gastric medium and the hydrogel plug swells. The ejection of the swollen plug results in the release of the drug at a predetermined and controlled time point. A modification in system design allows delivery of the drug at an exact time after leaving the stomach thereby providing a precise means for targeting drug delivery to the colon (Banaker, 1994b).

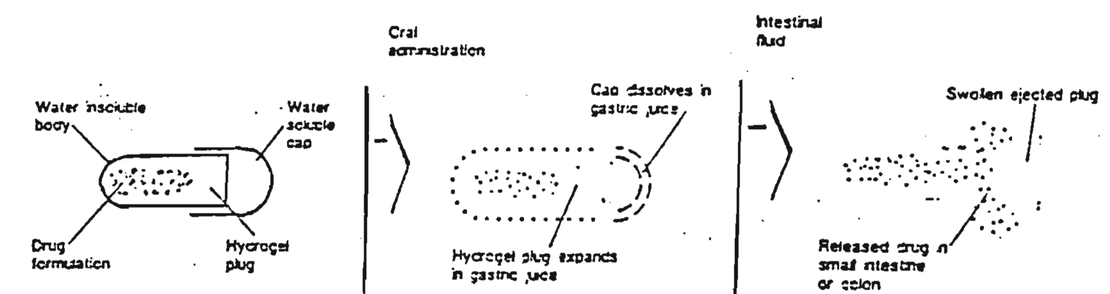


Figure 2.3 : The Pulsincap System (Banaker, 1994b, page 32)

2.2.4.3 Core-in-cup compressed tablets

Dankwerts (1994) reported a method that describes the production of an active sustained release disc-shaped matrix core which is compression coated on one side as well as around the circumference to form a cup around the core (Figure 2.4). This core-in-cup tablet releases drug from a single stable eroding surface of constant surface area. These tablets have the ability to release soluble and insoluble drugs at a zero-order rate from the inert cup. It was also reported that it is possible, through the variation of the grade of polymer used, the quantity of polymer used and the exposed surface area of the core, to produce a core-in-cup tablet that can release a constant amount of drug over a range of predetermined time periods (Dankwerts and van der Watt, 1995).

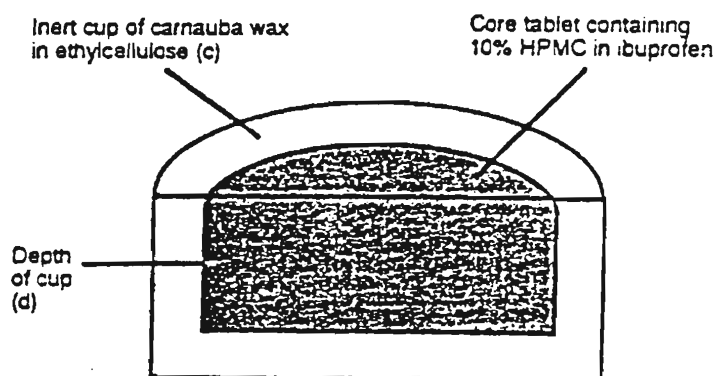


Figure 2.4 : Schematic Diagram of the Core-in-cup Tablet (Danckwerts and van der Watt, 1995, page 86)

Other innovative systems of interest include the gastroinflatable drug delivery device and the intragastric osmotic-controlled device as outlined by Banaker (1987). Both devices contain an inflatable chamber that permits prolonged residence time of the delivery system in the stomach. The latter device incorporates the concept of osmotic drug delivery which allows for zero-order release of the drug over a specified time period during which the residence of the device in the gastrointestinal tract is ensured due to the presence of the inflatable chamber.

Another concept that is receiving widespread attention is that of bioadhesive systems. Prolonging the gastrointestinal transit time of a drug delivery system can be attained by

localizing the device within a specific region by binding the product to the epithelial/mucin surface of the gastrointestinal tract. One of the great potential advantages of an oral bioadhesive would be its use in peptide drug delivery (Banaker, 1994b).

Current developments in pharmaceutical technology are being emphasised to a great extent on rate-controlled drug administration. Consequently, a vast number of novel, innovative systems to obtain modified release are being proposed. Thus, future success and the prevention of unwarranted modified release drug delivery systems necessitates stringent regulation with regard to the commercialization of such innovations.

2.2.5 Mechanisms of Drug Release

During the design stage in the development of modified release drug delivery systems or during experimental verification of their release behaviour, it is desirable to develop and use simple yet sophisticated mathematical models to describe the release kinetics of such systems (Peppas, 1984). Present technology, broadly speaking, utilizes one of three basic mechanisms in the classification of these systems. The first is dependent on diffusion or solution-diffusion controlled processes, where a reservoir or a matrix medium is used as the depot (Abdou, 1989). The second, chemically controlled systems, includes all polymeric formulations where solute diffusion is by a chemical reaction such as dissolution of the polymer matrix of cleavage of drug from a polymer backbone. Solute release is controlled, to a large degree by the geometric shape of the device (Peppas, 1984). The third mechanism is based on solvent-activated processes, such as osmosis (Abdou, 1989).

Within the broad framework of the above classification, numerous sub-classes exist. It is imperative that we fully appreciate the fact that release from a specific formulation may depend on a single mechanism or a combination of two or more processes. For the present study a detail appraisal of diffusional mechanisms is warranted.

2.2.5.1 Diffusion

In diffusion controlled release systems the transport of the solute through the polymer is achieved by molecular diffusion due to concentration gradients (Peppas, 1984a). The principles of diffusion-controlled release of drug have been adequately documented in literature (Langer and Peppas, 1983; Peppas, 1984; Lui *et al.*, 1988; Forni *et al.*, 1990; Vergnaud, 1993). Diffusion controlled systems can be subdivided into reservoir and matrix systems.

2.2.5.1.1 *Reservoir Systems*

In reservoir or membrane systems, the bioactive agent is enclosed at relatively high concentrations by a semi-permeable membrane, which is usually a water-insoluble or a partially water soluble polymeric material (Figures 2.5 and 2.6).

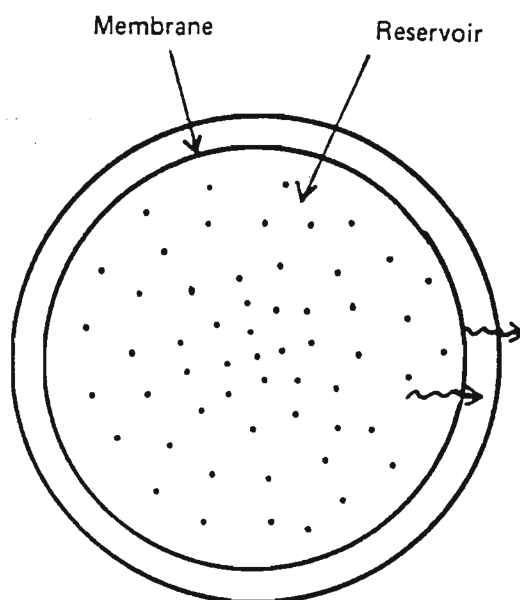


Figure 2.5 : Diffusion Control of Drug Release by a Water-insoluble Polymer
(Chang and Robinson, 1990, page 211)

Release from reservoir systems may be described in terms of Fick's first law of diffusion where the flux of drug, J (in amount/area-time), across a membrane in the direction of the decreasing concentration is given by the equation :-

$$J = -D\frac{dc}{dx} \qquad \textit{(Equation 2.1)}$$

where D = diffusion coefficient of drug in the membrane (area/time)

$\frac{dc}{dx}$ = change in concentration (C) with distance (x)

Assuming steady state, equation 2.1 can be integrated to give :-

$$J = -\frac{D\Delta C}{l} \qquad \textit{(Equation 2.2)}$$

Equation 2.2 can be expressed in terms of the drug release rate (dM/dt) for a drug core encapsulated by a water-insoluble membrane to give the following equation :-

$$\frac{dM}{dt} = \frac{ADK\Delta C}{l} \qquad \textit{(Equation 2.3)}$$

where A = effective surface area of the membrane that is available for diffusion

K = partition coefficient of the drug

l = diffusional path length

ΔC = concentration gradient across the membrane

For the above case scenario, an important parameter is the solubility of the drug in the membrane which generates the driving force for diffusion (Figure 2.5). To achieve zero-order drug release, a constant effective area of diffusion, diffusional path length, concentration gradient, and diffusion coefficient must be maintained.

For a system that utilizes a partially water soluble polymeric material in the wall (Figure 2.6), the rate of drug release may be defined by the following equation :-

$$\frac{dM}{dt} = \frac{AD}{l}\left(C_1 - C_2\right) \qquad \textit{(Equation 2.4)}$$

where C_1 = drug concentration in the core

C_2 = drug concentration in the surrounding medium

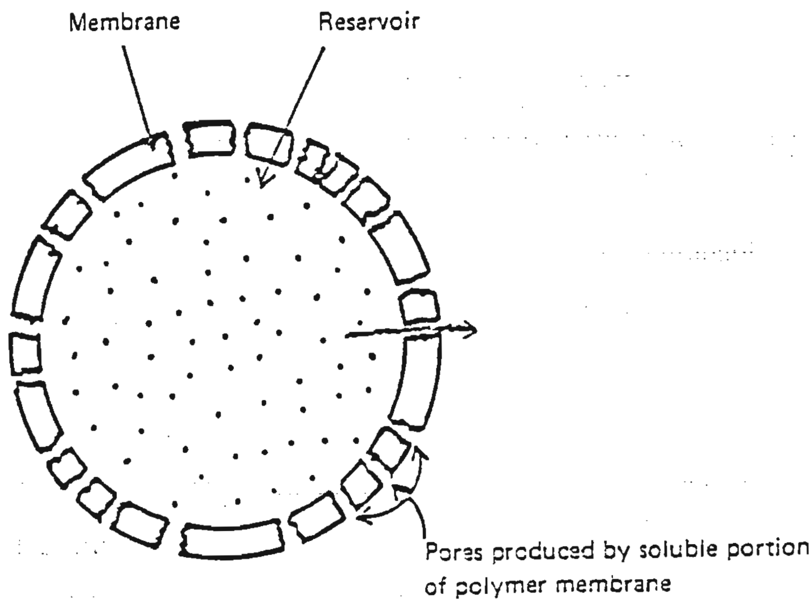
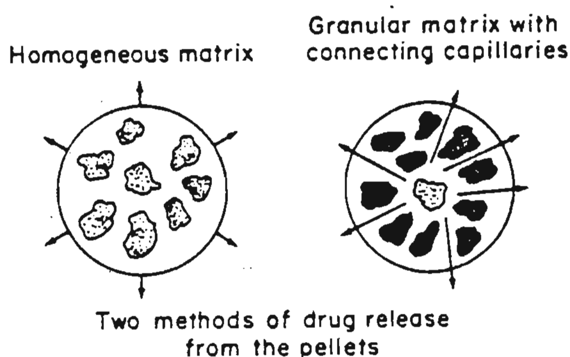


Figure 2.6 : Diffusion Control of Drug Release by a Partially Water-soluble Polymer (Chang and Robinson, 1990, page 211)

2.2.5.1.2 *Matrix Systems*

A matrix system is one in which the bioactive agent is incorporated in the polymer phase either in a dissolved or in a dispersed form. Thus, the solubility of the solute in the polymer becomes a controlling factor in the mathematical modelling of these systems (Peppas, 1984). As discussed previously, matrix systems can be split up into dissolved systems, dispersed systems and porous systems.

Higuchi (1963) outlined two systems for consideration when developing mathematical relationships for the release of drug from matrix systems. Firstly, when drug particles are dispersed in a homogeneous uniform matrix the drug is released by simple diffusion. Secondly, when drug particles are incorporated in an essentially granular matrix the release of drug occurs as a result of a leaching action of the penetrating solvent (Figure 2.7).



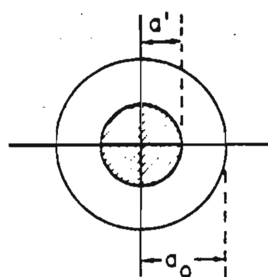


Figure 2.7 : Mechanisms of Drug Release from Matrix Pellets

(Higuchi, 1963, page 1146)

2.3 TECHNOLOGIES EMPLOYED IN THE DESIGN AND FABRICATION OF ORAL MODIFIED RELEASE DELIVERY SYSTEMS

Pharmaceutical research has led to the development of numerous technologies that can be utilized in the formation of oral modified release products. In the development of single and multiple-unit systems there has been an explosion in the novel, innovative technologies for oral modified release. These technologies include microencapsulation, direct compression or

wet granulation tabletting technology for the preparation of single-unit matrices, and various coating technologies. Since the present study involved the investigation of the process of microencapsulation as an approach to design an oral modified release drug delivery system, it was imperative to understand the underlying principles of the technique fully in order to conduct a meaningful investigation.

2.3.1 Microencapsulation

2.3.1.1 Definition

Micoencapsulation, as a process, can be considered as a means of applying relatively thin coatings to small discrete particles of solids or droplets of liquids and dispersions (Bakan, 1986). Microencapsulation of small particles in envelopes of polymeric, waxy, or other protective shell materials has become a well-established, rapidly expanding technology for coating and isolating substances until such time that their activity is required (Donbrow, 1992).

2.3.1.2 Historical perspective

The origin of the concept of modified release technology can be traced to Greco-Roman antiquity dating over 1000 years ago. The first coating of pills is recorded in the drug literature of early Islam. These were metallic-coated products that were used to mask bitter tastes (Banker, 1984).

Since then, the process of microencapsulation has made considerable advances. In the 1930's Kruyt and Bungenberg de Jong developed a technique which involved macro-molecular aggregation or phase separation processes called "coacervation". However, the earliest work in this area was not motivated by a desire to obtain sustained release coatings, but rather the National Cash Register Company wanted to find a substitute for carbon paper and carbon

ribbons. Thus tiny gelatin capsules containing a colourless dye was prepared and coated onto a sheet of paper. Pressure exerted by a pen or a typewriter would crush the capsule and release the dye which would react with the constituents of the paper and become coloured (Arshady, 1990). This technique was subsequently applied to bioactive molecules for the formulation of multiple-unit systems for modified release drug delivery. Microencapsulation has evolved substantially and at present there are a multitude of techniques that are available for the formulation of modified release systems.

2.3.1.3 Applications of microencapsulation technology

Microencapsulation techniques offer numerous advantages and have wide applicability in the medical and pharmaceutical arena. Consequently, this has led to the increased use of microcapsules in routine manufacture (Donbrow, 1992). Table 2.6 presents a synopsis of the applications of microencapsulation.

Table 2.6 : Applications of Microcapsules in the Pharmaceutical and Medical Arena

APPLICATION	DISCUSSION
Taste masking	Organoleptically, bitter tastes and unpleasant odours may be masked in alkaloids, salts, fish oils and other bioactive molecules that pose similar problems (Bakan *et al.*, 1992).
Enhanced drug stability	Degradation of the active due to atmospheric effects, excipient interactions and the effect of the contents of the gastric environment can be reduced or totally eradicated (Donbrow, 1992; Seitz *et al.*, 1986).
Modified release	Numerous modified release systems have been formulated using microencapsulation technology (Bakan, 1986).
Targeted drug delivery	targeting the site of release of pharmaceutically active material (Finch, 1993).
Reduced side effects	The encapsulation of drugs that are irritant to the gastric mucosa isolates them from direct contact with tissue cells, thereby preventing gastric bleeding and ulceration (Tirkkonen and Paronen, 1993).
Biotechnology	Diagnostic aids include temperature-sensitive microencapsulated liquid crystals for thermographic detection of tumours. Microcapsules are also used in radioimmunoassays (Donbrow, 1992).
Process improvements	Microcapsules allow for improved handling of chemicals as a result of better flow, mixing and tabletting of liquids and soft solids that are encapsulated with solid materials (Finch, 1993).

2.3.1.4 Fundamental considerations in microencapsulation

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as :-

* the active substance/core material.
* the polymeric material and formulation (Banaker and Speake, 1990b).
* the solvent (Finch, 1993).
* the surface active agent (Martin *et al.*, 1993).
* the microencapsulation methods and equipment (Eskilson, 1985b).

2.3.1.4.1 *The Active Substance/Core Material*

The core material may be liquid or solid in nature, the composition of which may be varied as the liquid core can include dispersed and/or dissolved materials (Bakan, 1986). Depending on the method of microencapsulation employed, the core may be composed solely of the active substance (Tirkkonen and Paronen, 1993) or alternatively, the active may constitute a component of the core which may include stabilizers, diluents, excipients, release retardants or accelerators (Bakan, 1986).

The physico-chemical properties of the active substance impact on the choice of membrane material and/or composition, as well as the type of core material to be used. The magnitude of water solubility, as well as the possible pH-dependence thereof is critical in the formulation of an optimized modified release product (Eskilson, 1985a). Drugs that display extremes in water solubility pose special problems in the formulation of a modified release product. The release of drugs that are highly water soluble are difficult or sometimes impossible to retard. In comparison, drugs that are extremely water-insoluble may be retarded to such an extent that release of drug and subsequent absorption are negligible (Tirkkonen and Paronen, 1993).

2.3.1.4.2 *The Polymeric Material and Formulation*

A wide and diverse selection of polymeric materials is available and the pharmaceutical scientist is expected to make a judicious and calculated decision concerning the type of material to be selected, taking into consideration the physico-chemical properties of the core substance and the desired release mechanism of the formulation (Banaker and Speake, 1990b). The choice of polymeric material is critical in the development of an optimized delivery system and is specific to the bioactive substance used.

Considerations of toxicity, allergenicity and irritancy are of primary importance and since data on newer polymers are not readily available, tested polymeric materials that have been well accepted are relied upon (Donbrow, 1992). The choice of polymer is also dictated by the manufacturing process employed, the need for a soluble or biodegradable shell, the route of administration and elimination, and the region of drug absorption.

When choosing a polymer, careful consideration of the properties of the polymer to be with the drug is of utmost importance. The general properties of polymers, from a pharmaceutical drug delivery perspective, are as follows:-

* glass transition temperature (Tg)
* tensile strength
* diffusion constants
* stiffness (elasticity)
* hardness (crystallinity)
* solubility (Banaker, 1994c).

The chemical nature and the molecular weight of the polymer employed determine the release characteristics of the formulation.

The incorporation of formulation additives can alter the properties of the polymer. Bodmeier and Paeratakul (1991) demonstrated the effect of surfactant levels on drug release from ethylcellulose pseudolatexes. The presence of a surfactant resulted in pH-dependent drug release while drug release from surfactant free psuedolatexes were insensitive to the pH of the

dissolution medium. The addition of a plasticizer to the polymer alters its glass transition temperature and flexibility. Therefore, the release rate can be controlled by the selection of the appropriate polymer, as well as the appropriate concentration of plasticizer (Chetty,1990; Govender, 1992).

2.3.1.4.3 *The Solvent*

Process solvent selection is determined not only by considerations of polymer and drug solubilities and stabilities but also process safety, economic aspects, and toxicity regulations (Donbrow, 1992). While organic polymer solutions are still widely used, aqueous colloidal polymer dispersions have been developed to eliminate the hazards associated with organic solvents (Bodmeier and Paeratakul, 1991). However, aqueous solvents have limited capacity in most processes due to solubility considerations and problems with evaporation, adhesivity and stability. Solution of the drug in the polymer system during the formulation process usually leads to the formation of a matrix type of structure. In certain instances, the use of an aqueous solvent system may necessitate pH-adjustment in order to maintain the drug in the solid state which may be required for successful encapsulation (Wong *et al.*, 1992).

Some microencapsulation techniques make use of two liquid phases, one containing the drug and the polymer in combination with other formulation excipients (the so-called disperse phase) and the other containing the surfactant (the continuous phase). A modification of this principle excludes a solvent from the dispersed phase. The disperse phase will then contain a meltable polymer which will constitute the liquid disperse phase.

2.3.1.4.4 *The Surface Active Agent*

Microencapsulation techniques based on solidified emulsions require the incorporation of appropriate emulsifiers of suitable hydrophile-lipophile balance for the specific emulsion type (Donbrow, 1992). Surfactants are utilized in many microencapsulation techniques and are

mainly included into the process to ensure emulsification and sphericity of the product. However, they may also be added to the polymer to improve release of the drug through the polymer wall (Bodmeier and Paeratakul, 1991).

Microencapsulation techniques that require the inclusion of a surfactant include :-

* solvent evaporation and solvent diffusion (Perumal, 1996).
* hot-melt microencapsulation and meltable aqueous dispersion techniques (Wong *et al.*, 1992).
* Interfacial polymerisation or polycondensation.

Depending on the process, surfactants may be incorporated either alone or in combination.

2.3.1.4.5 *The Microencapsulation Process and Equipment*

Numerous different techniques have been proposed for the production of microcapsules. Finch (1993) reported the prevalence of more than 200 microencapsulation methods that can be identified in the patent literature. The selection of an appropriate method is dependent on the nature of the active substance/core materials, the particle size range required, the simplicity of the process, and the economic viability of the process.

The equipment required to conduct microencapsulation varies from complex machines designed specifically for microencapsulation to rather simple processing equipment common to many laboratories (Bakan, 1986). Processes that require specialized equipment may require the allocation of substantial capital investment. Thus, it is mandatory to consider all factors influencing the process before selecting a suitable method for the microencapsulation of a drug product (Ghebre-Sallasie, 1989).

Some of the common methods of microencapsulation and the equipment utilized will be presented in the discussion that follows.

2.3.2 Microencapsulation Methodologies

Most of the microencapsulation technologies that are used pharmaceutically have been adapted from other industries (Bakan, 1986). Some of the more prominent microencapsulation methods that have found widespread application in the pharmaceutical industry include :-

* Coacervation phase separation
* Air suspension
* Extrusion spheronization
* Solvent evaporation/diffusion
* Pan coating
* Spray drying/spray congealing

Other methods that have been employed include interfacial polymerisation/polycodensation, multi-orifice centrifugal process, hot-melt microencapsulation, vacuum deposition and ionotropic gelation.

In the present study, the coacervation phase-separation and hot-melt microencapsulation techniques were investigated in an attempt to formulate an optimized modified release drug delivery system for naproxen sodium. Thus, a detail appraisal of the two techniques will be presented.

2.3.2.1 Coacervation phase separation

The potential of encapsulation of substances by coacervated droplets was first noted by Kruyt and Bungenberg de Jong in the 1930's, who found that organic liquids and solid particles suspended in the equilibrium fluid of a coacervate system were taken up by the coacervate droplets (Burgess and Carless, 1985). The term coacervation is derived from the latin acervus, meaning aggregation or heap, and the prefix co- to signify the preceding union of the colloidal particles (Bakan and Doshi, 1990). Coacervation is a common method of

microcapsule preparation and it is therefore important to understand the mechanisms controlling this process.

Coacervation is the separation from a lyophilic sol, on addition of another substance, of a colloidal-rich layer present in the form of an amorphous liquid. This constitutes the coacervate. If the coacervate is formed in a stirred suspension of an insoluble substance, the macromolecular material will surround the solid particles. The coated particles can then be separated and dried.

In general, the coacervation phase separation process consists of three steps carried out under continuous agitation (Figure 2.8):-

1. Formation of three immiscible phases. These three phases are formed by :-
    i. a liquid manufacturing vehicle
    ii. a core material phase
    iii. a coating material phase
2. deposition of the coating
3. rigidization of the coating (Bakan, 1986).

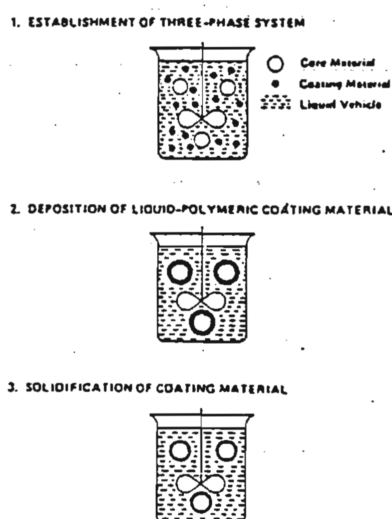


Figure 2.8 : Stepwise Schematic of the Coacervation Phase Separation Process
(Bakan and Powell, 1983, page 182)

To form the three phases, the core material is dispersed in a solution of the coating polymer, the solvent for the coating polymer being the liquid manufacturing vehicle phase. The coating material, an immiscible polymer in liquid state, is formed by utilizing one of the methods of phase separation-coacervation. The next step is accomplished by controlled physical mixing of the coating material (while liquid) and the core material in the liquid manufacturing vehicle. Deposition of the liquid polymer around the core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid manufacturing vehicle phase. Finally, a process of rigidizing the coating, usually by thermal, cross-linking or desolvation techniques, result in the formation of individual microcapsules (Bakan, 1986).

The process of coacervation can be divided into aqueous and nonaqueous phase separation (Chang and Robinson, 1990). Aqueous phase separation can be further divided into simple, complex or salt coacervation. In simple coacervation, the addition of a water-miscible solvent to an aqueous polymer solution results in the formation of a separate polymer rich phase (Finch, 1993). Complex coacervation involves the mutual neutralization of two oppositely charged colloids in aqueous solution. For complex coacervation to exist, sufficient water has to be present in the system to allow for adequate charge interaction between two polymers or polymer and microion (Bakan and Doshi, 1990). Salt coacevation involves the separation of a polymer due to "salting out", by adding an electrolyte to an aqueous polymer solution (Finch, 1993).

The process of nonaqueous coacervation phase separation may be accomplished by one of the following methods :-

1. Temperature change
2. Incompatible polymer addition
3. Nonsolvent addition
4. Salt addition
5. Polymer-polymer interaction

(Chang and Robinson, 1990; Bakan and Doshi, 1990).

A detail discussion of the temperature change method is warranted since it was employed in the initial stages of this study.

2.3.2.1.1 *Temperature Change as a Method to Promote Phase Separation*

This method of phase separation is based on the principle of differential temperature-solubility of a polymer in a solvent. For a binary system comprised of a polymer and a solvent, it is possible to construct a temperature-composition phase diagram (Figure 2.9). A system having a composition, X, exists as a single phase, homogeneous solution above the binodal FEG. Decreasing the temperature of the system along the line AEB results in the formation of two phases once the phase boundary is crossed at point E. Phase separation of the dissolved polymer occurs in the form of immiscible liquid droplets, and if the core material is present in the system, under proper conditions of polymer concentration, temperature and agitation, the liquid polymer droplets coalesce around the dispersed core material particles to form embryonic microcapsules. The binodal also indicates that with decreasing temperature, one phase becomes polymer-poor (the liquid manufacturing vehicle phase) and the other becomes polymer rich (the coating material phase). At point B, the segmented tie line suggests that the vehicle phase is essentially pure solvent (point C) and the coating material phase is a concentrated polymer solvent mixture (point D).

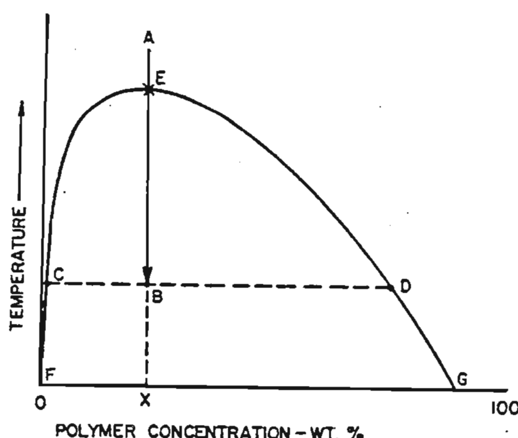


Figure 2.9 : General Phase Diagram - Coacervation Induced Thermally

(Bakan, 1986, page 422)

2.3.2.2 Hot melt microencapsulation

The technique of hot-melt microencapsulation is a relatively simple yet highly flexible technique. The process may be carried out in an organic or aqueous liquid manufacturing vehicle. In the present study, a meltable aqueous dispersion technique was employed. The technique was first patented by Yamamoto and Baba in 1960 and involved cooling-induced solidification of the oily phase of a two-phase system (Wong *et al.*, 1992). A review of the literature clearly reflects the successful use of hot-melt microencapsulation in achieving oral modified release drug delivery (Benita *et al.*, 1986; Das and Gupta, 1988; Wong *et al.*, 1992; Giannola *et al.*, 1995).

In the process of hot-melt microencapsulation, melted polymer is mixed with the drug substance to be encapsulated, which is present as solid particles. The mixture is suspended in a non-miscible solvent that is heated above the melting point of the polymer and the process is carried out under continuous agitation. After cooling, the microspheres are separated by decantation, to a give free-flowing product after drying (Mathiowitz and Langer, 1992). This method can be used for the encapsulation of both drugs and dyes.

Various waxy materials and synthetic polymers have been employed in hot-melt microencapsulation. These include carnuba wax (Benita *et al.*, 1986), Eudragit® RS (Kawata *et al.*, 1986), polyanhydrides (Mathiowitz and Langer, 1992), cetostearyl alcohol (Wong *et al.*, 1992), white beeswax and hexadecanol (Giannola *et al.*, 1995). The process may be carried out in an organic system. Previous studies have employed silicone oil (Benita *et al.*, 1986), liquid paraffin (Das.and.Gupta, 1988), olive oil (Mathiowitz and Langer, 1992), and acidified water (Wong *et al.*, 1992).

2.3.3 Polymers and Waxes

Various polymeric excipients have been incorporated into formulations in order to provide the final dosage form with certain desired physical characteristics or to modify the way the drug is released from the dosage form (Banaker and Speake, 1990a). These excipients substantially influence, if not control, the release mechanism of the active ingredient. It is therefore essential for the formulation scientist to understand the fundamental properties of the more widely used biopolymers and fats and waxes in the pharmaceutical industry (Banaker, 1994c).

Drug release from a polymer or wax matrix is governed by the rate at which the dissolution fluid penetrates the matrix i.e. release is a function of the permeability of the polymer or wax. Other factors that can influence drug release characteristics include the porosity and tortuosity of the matrix, drug diffusivity, drug solubility in the polymer or wax, wettability of the dosage unit, the presence of other additives (such as surfactants), the geometry of design, and the method used to prepare the delivery system. Most important are the properties of the polymer to be combined with the drug (Banaker, 1994c). The selection of the appropriate polymeric material dictates, to a major degree, the resultant physical and chemical properties of the delivery system. The polymeric material employed should be capable of forming a film or matrix that is cohesive with the core material, be chemically compatible and non-reactive with the core, and provide the desired properties of strength, flexibility, optical properties and stability (Bakan, 1986).

The solvent or solvent mixture and other excipients (such as plasticizers) used in the preparation of polymer film and matrices can markedly influence the properties of the polymer and the release characteristics of the delivery system. Therefore, the selection of a suitable solvent system is of crucial importance for the design of oral modified release drug delivery systems (Arwidsson and Nicklasson, 1989). Two rate-controlling excipients were employed in this study, viz. ethylcellulose and cetostearyl alcohol. Therefore, these excipients will be discussed in greater detail.

2.3.3.1 Ethylcellulose

Ethylcellulose, a cellulose ether polymer, is derived from, and hence possesses, the polymeric backbone of cellulose which contains a basic repeating structure of ß-anhydroglucose units, each having three replaceable hydroxyl groups. The number of substituent groups of these hydroxyls can be designated either by a weight percentage or by the number of points where the groups are attached. This concept is known as the degree of substitution (Rekhi and Jambhekar, 1995). Ethylcellulose products are available in a variety of viscosity grades which are proportional to the length of the polymer molecules. The grade of ethylcellulose used in the formulations of coatings invariably has an ethoxy content of 47.5 to 49% w/w corresponding to a degree of substitution of 2.42 to 2.53 (Rowe, 1986).

Ethlycellulose, alone or in combination with water-soluble polymers and various excipients is widely used in the preparation of modified release systems. Ethylcellulose has been used as a polymer in a variety of processes to formulate modified release products. These include fluid bed drying (Rowe, 1986; Bodmeier and Paeratakul, 1991), coacervation phase separation (Jalsenjak *et al.*, 1976; Tirkkonen and Paronen, 1993), direct compression (Upadrashta *et al.*, 1993), solvent evaporation (Dubernet *et al.*, 1990) and spray drying (Forni *et al.*, 1990).

Ethylcellulose has been extensively employed in the coacervation phase separation technique. The use of ethylcellulose in temperature induced coacervation phase separation was first reported by Jalsenjak *et al.* (1976). Since then numerous researchers have investigated the applicability of the technique to a variety of water soluble and water insoluble drugs (Oya Alpar and Walters, 1981; Chemtob *et al.*, 1986; Nixon and Wong, 1990; Sviensson and Kristmundsdottir, 1992; Tirkkonen and Paronen, 1993).

2.3.3.2 Cetostearyl alcohol

Cetostearyl alcohol is a wax substance which is a mixture of solid aliphatic alcohol consisting mainly of stearyl ($C_{18}H_{38}O$) and cetyl ($C_{16}H_{34}O$) alcohols with small quantities of other alcohols, chiefly myristyl alcohol. The proportion of stearyl to cetyl alcohol varies considerably but usually consists of about 50-70 % stearyl alcohol and 20-35 % cetyl alcohol. It occurs as white or cream coloured unctuous masses, or almost white-coloured flakes or granules which have a faint odour and a bland taste. On heating, cetostearyl alcohol melts to a clear, colourless or pale yellow liquid free of suspended matter (Merkle, 1994).

Cetostearyl alcohol possesses emollient, emulsifying and viscosity enhancing properties and has been used in cosmetics, as well as in oral and topical pharmaceutical preparations. Cetostearyl alcohol is generally regarded as non-toxic, essentially non-irritant material and is not readily absorbed from the gastrointestinal tract. Cetostearyl alcohol has been used in the formulation of oral modified release multiple unit preparations. Wong *et al.* (1992) formulated modified release ibuprofen matrices by a meltable aqueous dispersion technique using cetostearyl alcohol.

In topical preparations cetostearyl alcohol is used as a stiffening agent and emulsifier in both water-in-oil and oil-in-water emulsions. It is also used in the preparation of nonaqueous creams and sticks. The composition of cetostearyl alcohol may vary considerably from different sources which may result in different emulsification behaviour, particularly with respect to emulsion consistency and stability (Merkle, 1994).

2.4 DISSOLUTION

2.4.1 Introduction

The *in vitro* evaluation of the clinical performance of a pharmaceutical dosage form or delivery system and drugs is based, to a large degree, on dissolution testing. Dissolution is

the overwhelming important property of dosage forms that contributes to the rate and extent of drug availability to the body and, as such, is deserving of the effort that has been put forth to develop dissolution systems that provide fundamental information on the dissolution process of many drugs as well as meaningful *in vitro* dissolution system models that can be correlated with some index of an *in vivo* performance. In the present study, dissolution testing was employed in the development, and *in vitro* evaluation, of novel naproxen sodium cetostearyl alcohol microspheres. Thus, further discussion of the fundamentals of dissolution testing is considered justifiable.

The process of dissolution is defined as one by which a solid substance enters in the solvent to yield a solution. Alternatively, dissolution can be defined as a process whereby a solid substance dissolves by a process that is controlled by the affinity between the solid substance and the solvent (Banaker, 1992). A more contemporary term that is preferred by many authors, is the concept of dissolution rate. Dissolution rate may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature, and solvent composition (Abdou, 1989).

The earliest reference to dissolution is credited to Noyes and Whitney who, in 1897, suggested that the rate of dissolution of a solid substance is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. The expression developed by Noyes and Whitney, the Noyes-Whitney equation, correlated the rate of dissolution and the solubility gradient of the solid substance. Interestingly, most modern mathematical expressions of dissolution phenomena still revolve around the basic expression of Noyes and Whitney (Banaker, 1992).

When a pharmaceutical solid dosage form is introduced into biological or simulated biological media, the drug begins to pass into solution from the intact solid. Unless the dosage form is a continuous polymeric device, the solid matrix disintegrates into granules and these granules in turn deaggregate into fine particles. The above process of disintegration, deaggregation and dissolution may occur simultaneously with the release of a drug from the delivery system.

Figure 2.10 outlines the processes involved in the dissolution of solid dosage forms (Martin, *et al.*, 1993).

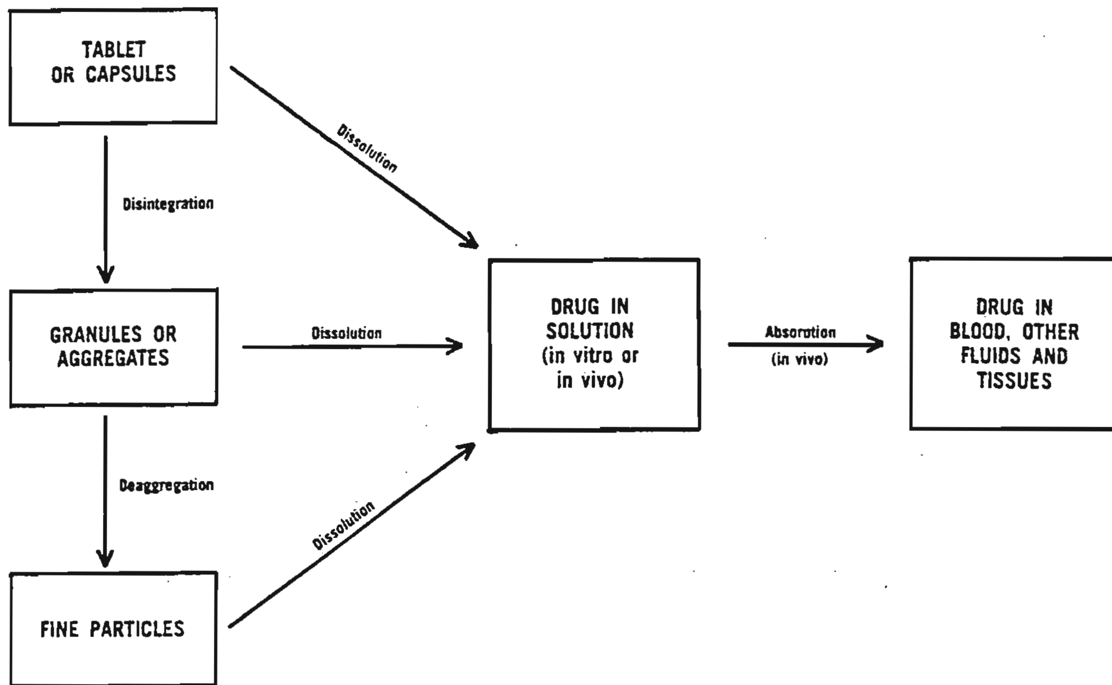


Figure 2.10 : Schematic Illustration of the Dissolution Process of Solid Dosage Forms (Martin *et al.*, 1993, page 331)

Dissolution analysis of pharmaceutical solid dosage forms has emerged as the single most important test that will ensure the quality of the product when carried out appropriately (Prasad *et al.*, 1983). Knowledge of dissolution behaviour and of the factors affecting such behaviour are essential in the design, evaluation, control and therapeutic efficacy of solid dosage forms.

The use of dissolution testing in the preformulation development of modified release delivery systems is being extensively pursued. The culmination of *in vitro* dissolution testing should be the precise prediction of the *in vivo* performance of the delivery system. However, the present

state of the science and technology does not always permit meaningful correlations between *in vitro* dissolution rates and the rate and extent of availability as determined by drug plasma concentrations, and/or urinary excretion of drug or metabolites (Skelly *et al.*, 1990). Thus, the utility of *in vitro* dissolution data as a basis for the design and development of a product to predict *in vivo* performance requires the establishment of a specific *in vitro-in vivo* correlation to be systematically pursued on a product-by-product basis (Tandt *et al.*, 1995).

The application of dissolution testing is not confined to the prediction of *in vivo* performance of a delivery system. Dissolution studies may be carried out to elicit invaluable information which include the following :-

* it is a useful *in vitro* quality control tool that may be utilized to ensure batch to batch uniformity for a particular drug or pharmaceutical product (Moore and Flanner, 1996).

* it aids in the elucidation of the possible mechanism/s of drug release from the delivery system (Govender, 1992).

* to determine the stability of the relevant release characteristics of a pharmaceutical product whilst being subjected to accelerated and long-term stability testing (Skelly *et al.*, 1990).

* *in vitro* dissolution are useful in the design and optimization of pharmaceutical products prior to clinical trials (Lordi, 1986).

* to provide the necessary process control and to facilitate certain regulatory determinations and judgements concerning minor formulation changes, changes in the site of manufacture, etc. (Skelly *et al.*, 1990).

Dissolution methodology is by no means a perfect technique, however, it is here to stay due to the fact that it is the best available tool that can reveal, at least qualitatively, some information about the physiological availability of a drug (Abdou, 1989).

2.4.2 Dissolution Methodology

The ultimate challenge for any dissolution apparatus is its ability to reflect the *in vivo* behaviour of the dosage form during the absorptive phase following oral administration (Mandal *et al.*, 1995). In the quest to achieve this goal there has been an evolution of dissolution apparati that has paralleled the progression in the realization of the importance of dissolution testing in the pharmaceutical industry. In an attempt to design a dissolution apparatus that will enable the generation of *in vitro* data leading to meaningful correlations with the *in vivo* performance of the delivery system, researchers have put forth a multitude of dissolution apparati designs. Carstensen (1978) reported that a good survey of methods was presented by Pernarowski in 1974, who noted the presence of over 150 different apparatus designs.

The various dissolution apparati and techniques are usually classified according to their associated hydrodynamics. Dakkuri and Shah (1982) employed this as the basis of their classification which was divided into natural convection methods and forced convection methods. In natural convection methods, the surrounding medium is continuously replaced by the bulk solution. In comparison, forced convection methods are based on the induction of relative motion between the dissolving unit and the dissolution medium which is accomplished by a stirring, rotating or oscillating mechanism. According to Banaker (1992), forced convection methods can be further subdivided into those with streamline-flow characteristics and those with turbulent-flow characteristics. The great majority of models in the forced convection category belong to the stirred-vessel type. The rotating paddle method, rotating basket method and the rotating bottle method represent the more commonly employed forced convection methods.

There are obvious and insurmountable limitations to the official dissolution testing apparati (i.e. the rotating paddle and rotating basket methods) concerning the maintenance of sink conditions. The flow-through dissolution system model effectively solves the problem of nonsink conditions by supplying an unlimited quantity of fresh dissolution medium (Banaker, 1992). In this method, the dosage form is contained in a small vertical glass

column with a built-in filter, through which a continuous flow of dissolution medium is circulated upward at a specific rate from an outside reservoir using a peristaltic or centrifugal pump. The dissolution fluid is usually collected in a separate reservoir as it leaves the dissolution cell and thereby the dosage form is continuously exposed to fresh solvent, and a perfect sink is maintained (Abdou, 1989). The flow-through model can be used to determine the dissolution rate of both powdery drug substances and final pharmaceutical formulations. Möller (1991) outlined five different types of flow-through models that can be used in the dissolution testing of different types of pharmaceutical formulations.

The compendial methods of dissolution testing are employed most frequently during formulation development to ensure compliance with regulatory requirements. The USP XXIII (1995) currently recognizes seven official methods :-

Rotating basket method	-	Apparatus 1
Rotating paddle method	-	Apparatus 2
Reciprocating cylinder method	-	Apparatus 3
Flow-through method	-	Apparatus 4
Rotating paddle over disk method	-	Apparatus 5
Rotating cylinder method	-	Apparatus 6
Reciprocating disk method	-	Apparatus 7

Apparatus 1-4 are used to investigate drug release from solid oral dosage forms, whereas apparatus 3 and 4 are more specific to modified release preparations. For transdermal dissolution testing, apparatus 5-7 are employed although apparatus 7 may also be used for solid oral dosage forms.

In the present study, the rotating paddle method, the rotating basket method and the rotating bottle method were employed.

2.4.3 Interpretation of Dissolution Data

The proper interpretation and mathematical modelling of dissolution data is vital to the understanding of the mechanisms of drug release. At present, several mathematical relationships governing the release of drug from a dosage form are available. A comprehensive review of some of the approaches available for the interpretation of dissolution data has been presented by Abdou (1989). Some of the more pertinent theories on the mechanisms and interpretation of dissolution data are presented below.

2.4.3.1 Wagner's theory for the interpretation of percent dissolved-time plots

Abdou (1989) presented a detailed discussion of Wagner's theory. This concept relates the pseudo first-order kinetics under sink conditions to the fact that a percent dissolved value at time *t* may be equivalent to the percent surface area generated at the same time. In addition, it showed that the simulated percent dissolved versus time data generated by means of a logarithmic normal distribution function to describe the surface area yielded a pseudo first-order plot. In other words, the first-order kinetics is actually not due to dissolution *per se*, but rather to the distribution of the available surface area. The following equation was proposed for the determination of percent drug dissolved :-

$$\textit{Percent dissolved at time}(t) = \frac{W}{W_\infty}(100) = \frac{\int_{t_0}^{t} S(t)dt}{\int_{t_0}^{\infty} S(t)dt}(100) \quad \textit{(Equation 2.5)}$$

Where W *and* W_∞ = amount in solution at time t

S = surface area at time t

This equation represents the percent surface area generated to time t of total surface area available. Thus the above theory is a justifiable explanation for the first-order kinetics frequently observed in dissolution studies.

2.4.3.2 Dissolution of drugs from matrices - the square root of time model

Higuchi (1963) proposed mathematical relationships for the release of drug from matrices. According to this theory, two systems have to be considered :-

i) When drug particles are dispersed in a uniform homogeneous matrix, which acts as the diffusional mechanism

ii) When drug particles are incorporated in an essentially granular matrix and release is by a leaching action of the penetrating solvent.

In the above study, two geometric systems were considered :-

a) unidirectional leaching or extraction from a simple planar surface

b) three dimensional leaching or extraction from a spherical pellet.

2.4.3.2.1 *Release from a Planar System Having a Homogeneous Matrix*

Under perfect sink conditions, the total amount of drug release can be represented by the following equation :-

$$Q = \sqrt{DC_s(2A - C_s)t} \quad \textit{(Equation 2.6)}$$

Where Q = the amount of drug released after time t per unit exposed area

D = diffusivity of the drug in the homogeneous matrix

A = the total amount of drug present in the matrix per unit volume

C_s = the maximum solubility of the drug in the polymer

2.4.3.2.2 *Release from a Planar System Having a Granular Matrix*

In this case, the leaching mechanism is predominant through diffusion movement utilizing intergranular openings. Thus, the above equation is modified for the effective volume of diffusion and the effective diffusional path for this system and the equation now reads :-

$$Q = \sqrt{\frac{D\varepsilon C_s}{\tau}\left(2A - \varepsilon C_s\right)t} \qquad \textit{(Equation 2.7)}$$

Where ε = the porosity of the matrix

τ = the tortuosity factor of the capillary system

D = the diffusivity of the drug in the permeating fluid

all other terms are as previously defined

2.4.3.2.3 *Release from a Spherical Pellet Having a Homogeneous Matrix*

For the condition A » C_s, and assuming a pseudo steady state during the leaching process, one can consider that a sharp front forms between the partly leached portion of the sphere and the unleached section. Considering that the total amount of the drug contained by the pellet at time *t* is the sum of that in the unleached portion and that in the region no longer saturated with drug, then :-

$$\textit{Total residual amount of drug} = 4\pi\left[\frac{a'^3}{3}A + \frac{C_s}{6}a'\left(a_0^2 + a'a_0 - 2a'^2\right)\right] \qquad \textit{(Equation 2.8)}$$

Where a_0 = the radius of the whole pellet

a' = the radius of the unleached portion

a = the polar radius of any segment of the pellet

2.4.3.2.4 *Release by Leaching from a Granular Spherical Pellet*

To calculate the rate of leaching by an external solvent, such as gastrointestinal fluid, of solid drug dispersed uniformly in a granular matrix of a spherical pellet, assuming that $\alpha = \varepsilon C_s/A$ and is « 1, the following equation can be used :-

$$1 + 2\left(\frac{a'}{a_0}\right)^3 - 3\left(\frac{a'}{a_0}\right)^2 = \frac{6DKC_s}{ra_0^2}t \qquad \textit{(Equation 2.9)}$$

Where the residual fraction $= \left(\frac{a'}{a_0}\right)^3$

2.4.3.3 The baker lonsdale model

Baker and Lonsdale (1974) proposed an equation for modelling drug release from homogeneous spherical matrices :-

$$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty} = \frac{3DtC_s}{r^2 C_0} \qquad \textit{(Equation 2.10)}$$

Where $\frac{M_t}{M_\infty}$ = the fraction of drug released

C_0 = the initial concentration of dispersed drug in the matrix

all other terms are as previously defined.

2.4.3.4 First-order model

This model is frequently used to describe drug release from matrices (Wong *et al.*, 1992). Drug activity within the matrix declines exponentially and the rate of drug release is proportional to the residual activity. This model is expressed by the following equation ;-

$$ln\left(1 - \frac{M_t}{M_\infty}\right) = C - k_1 t \qquad \textit{(Equation 2.11)}$$

Where $\frac{M_t}{M_0}$ = the fraction of drug released at time t

k_1 = first-order dissolution rate constant

2.4.3.5 Hixon crowell cube root law

For a dosage form consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the weight of the particles. The equation, derived by Hixon and Crowell, describes the dissolution from a multiparticulate system from which drug is released concomitantly on the surface of many particles. The cube root law may be expressed by the following equation :-

$$W_0^{1/3} - W_t^{1/3} = \kappa t \qquad \textit{(Equation 2.12)}$$

Where W_0 and W_t = the weight of the particle at time zero and time t, respectively

κ = the dissolution rate constant

Wong *et al.* (1992) expressed the cube root law in terms of the fraction of drug released as follows:-

$$\left(1-\frac{M_t}{M_\infty}\right)^{1/3} = -\kappa t \qquad \textit{(Equation 2.13)}$$

2.4.3.6. The power law

Korsmeyer *et al.* (1983) derived a simple exponential relationship to describe general solute release behaviour from modified release polymeric devices under perfect sink conditions. The power law is expressed by the following equation :-

$$\frac{M_t}{M_\infty} = kt^n \qquad \textit{(Equation 2.14)}$$

Where $\frac{M_t}{M_\infty}$ = fractional release of solute at time t

k = constant incorporating characteristics of the macromolecular network system and the drug

n = diffusional exponent characteristics of the release mechanism

The above expression is only valid for the first 60% of the fractional drug release i.e. $\frac{M_t}{M_\infty} \leq 0.6$. The mechanism of drug release can be determined from the value taken on by the diffusional exponent (Ritger and Peppas, 1987). Fickian diffusion is defined by n = 0.5 and non-fickian diffusion by $0.5 < n < 1.0$. If n = 1.0, then case II transport is dominant and the rate of release is independent of time which is an indication of zero-order drug release. For $n > 1.0$, super case II transport is dominant and the time dependence on release is given by t^{n-1}.

Chapter Three

Naproxen Sodium

3.1 INTRODUCTION

Naproxen sodium, a propionic acid derivative, is a potent non-steroidal anti-inflammatory drug with analgesic and antipyretic activity (Al Shammary *et al.*, 1991). Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of compounds that possess similar therapeutic effects. In addition to sharing common therapeutic effects, they tend to share several unwanted side effects. They are often chemically unrelated, but their pharmacological action depends primarily on the inhibition of prostaglandin biosynthesis (Woodhouse and Wynne, 1987). Consequently, non-steroidal anti-inflammatory drugs have played a major role in the treatment of inflammatory conditions, as well as in analgesia and antipyresis.

Salicylic acid, developed in 1763, was the first non-steroidal anti-inflammatory drug and was used primarily as an antipyretic. Subsequently, in 1899, the most famous descendent of salicylic acid, acetylsalicylic acid (aspirin), was developed. However, the widespread use of aspirin made apparent its toxicological potential which manifested, in the mainstream, with various forms of gastrointestinal intolerance. Efforts to improve upon the side effect profile of aspirin led to the development and ultimate acceptance of the NSAIDs. The first NSAID to be identified, after the discovery of aspirin, was mefenamic acid, which belongs to the group of NSAIDs referred to as the fenamates. The identification of mefenamic acid led to the development of flufenamic acid, meclofenamate and diclofenac, which is one of the most commonly used NSAID of recent (Boynton *et al.*, 1988).

Concurrently, research into the involvement of the indolic hormones, serotonin and tryptophan, in the inflammatory process resulted in the identification of indomethacin.

Indomethacin's superior anti-inflammatory activity has made it a standard of comparison for other NSAIDs (Boynton *et al.*, 1988). However, the toxicological profile of indomethacin, most notably its central nervous system side effects, has limited its widespread use. Members of the indole group with lower toxicity include sulindac and by replacement of the indole ring with a pyrrole ring, the closely related tolmetin and zomepirac.

Further research led to the discovery of ibuprofen, a propionic acid derivative with a much improved side effect profile. The propionic acid derivatives have introduced a new order of anti-inflammatory tolerance. Taken together, the propionic acid class of NSAIDs exhibit a range of activity and individual characteristics more diverse than any other NSAID group (Huskinsson, 1985). Included in this group of NSAIDs are fenoprofen, flurbiprofen, ketoprofen and naproxen. Naproxen is available as the free acid and the sodium salt. Naproxen sodium is reported to have the same pharmacological profile as the parent molecule: naproxen 500 mg and naproxen sodium 550 mg are considered to be bioequivalent. The only difference between the free acid and the salt is the rate of absorption of the two forms. Naproxen sodium is highly water-soluble and dissolves more rapidly in gastric fluid and consequently produces earlier and higher plasma concentrations, hence peak plasma concentrations are achieved in approximately 1 hour with naproxen sodium and 2 hours with naproxen following oral administration. Naproxen has an elimination half-life of 12 to 15 hours which facilitates a twice daily dosage regimen. The normal recommended oral dosage of naproxen sodium is 275 to 550 mg twice daily. The drug is highly protein bound (approximately 99% is bound to serum albumin) and has a low volume of distribution of 0.16 l/kg primarily due to the high degree of protein binding (Todd and Clissold, 1990).

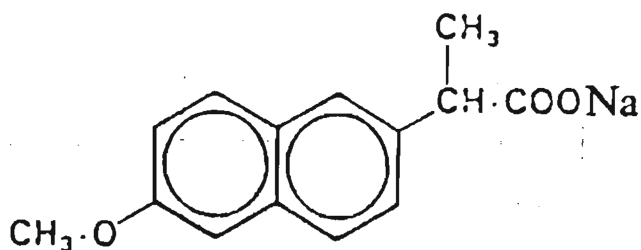
The most recently introduced class of NSAIDs are the oxicams. The oxicams, piroxicam and tenoxicam, are benzothiazine amides which provide anti-inflammatory potency together with extended plasma half-lives. Piroxicam has a half-life of 45 hours which permits once-daily dosing. The obvious advantage of a once-a-day dosing regimen is that it favours patient compliance.

One class of NSAIDs has developed independently of the salicylates. The pyrazalones, phenazone and amidopyrone, were discovered before aspirin was released onto the market. Initially, the pyrazolones were used as antipyretics but later their uses were extended to include the treatment of rheumatic conditions and mild pain. Research into this class of NSAIDs led to the discovery of phenylbutazone and oxyphenbutazone. A major limitation of the pyrazalones is the rare but serious side-effect of agranulocytosis as well as aplastic anaemia. Thus, the use of the pyrazalones has been reserved for the treatment of acute inflammatory conditions, such as gouty arthritis and tenosynovitis of the hip (Boynton *et al.*, 1988).

3.2 NAPROXEN SODIUM

3.2.1 Physico-chemical Aspects

3.2.1.1 Structure :



3.2.1.2 Chemical Name : (-)-Sodium 6-methoxy-α-methyl-2-naphthaleneacetate

3.2.1.3 Empirical Formula : $C_{14} H_{13} Na O_3$

3.2.1.4 Description : A white to creamy white crystalline powder with a bitter taste, odourless or almost odourless.

3.2.1.5	**Molecular weight**	:	252.24
3.2.1.6	**Melting Point**	:	244 - 246 °C
3.2.1.7	**Solubility**	:	Soluble in water; sparingly soluble in ethanol; soluble in methanol; very slightly soluble in acetone; practically insoluble in chloroform. At 25°C and pH 2.0 the solubility of naproxen sodium is 1.0 x 10^{-4}M.
3.2.1.8	**Dissociation constant**	:	pKa 4.2 (25 °C)
3.2.1.9	**Ultraviolet Spectrum**	:	In aqueous acid naproxen exhibited four major peaks, viz. 262 nm, 272 nm, 315 nm, and 328 nm. In aqueous alkali naproxen also exhibited four major peaks, viz. 261 nm, 271 nm, 316 nm, and 330 nm. (Moffat *et al.*, 1986)
3.2.1.10	**Infrared Spectrum**	:	The infrared spectrum of naproxen sodium was investigated using the KBr disk method. Principal peaks were seen at wavenumbers 1724, 1174, 1155, 1223, 1190, 1681 (Moffat *et al.*, 1986).

(USP XXIII, 1995; Lund, 1994)

3.2.1.11 Stability summary

Peswani and Lalla (1990) studied the stability of naproxen sodium in parenteral dosage forms with respect to temperature / heat, oxygen, pH, light and stability to autoclaving. Samples of a newly formulated parenteral preparation of naproxen sodium were stored at 4°, 37°, 60°, 75° and 90°C for a period of 18 weeks. These studies indicated first - order thermal degradation of naproxen sodium and the shelf life of the product, estimated from the Arrhenius plot was found to be 4.2 years. A maximum of 8.6% decomposition was observed at 90°C over a period of eighteen weeks. Oxygen stability studies indicated that the thermal degradation of the drug proceeds at a faster rate if the headspace in the ampoules are not purged with nitrogen prior to sealing. A 7.3% loss of potency was observed over an 18 week period for ampoules sealed under atmospheric conditions. Although the antioxidant, sodium formaldehyde sulfoxylate, was found to be compatible with the drug, its use was thought to be unnecessary, as flooding the ampoules prior to sealing offers sufficient protection against oxidation.

The results of the pH stability studies indicated that the loss in potency for all formulations adjusted to pH 7.5, 8, 9, and 10 was almost equal over a period of twelve weeks. As was anticipated, pH 7.5 showed a greater resistance to oxidation as compared to pH 9 and 10 (Figure 3.1). The formulation was stable to autoclaving even when autoclaved at 121°C and 15 psi for 90 minutes. No colour change or precipitation occurred, however, the pH of the formulation dropped slightly.

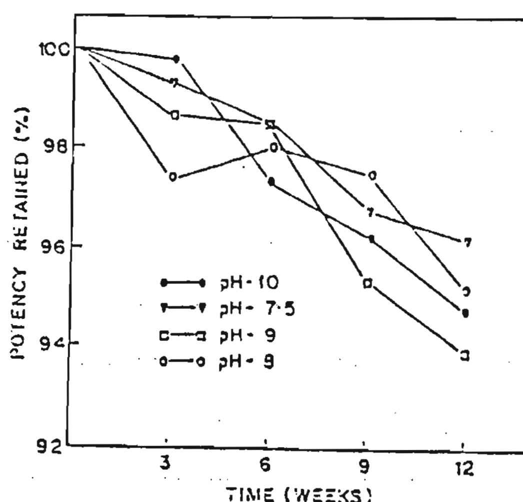


Figure 3.1 : pH Stability studies on Naproxen Sodium formulations.

Often, the triggering force that promotes oxidation is "light" (i.e. certain components of the electromagnetic spectrum). This fact was also evident from the results of the light stability studies on naproxen sodium formulations carried out over a period of two months. Precipitation of the drug from solutions placed in plain glass ampoules was found to be 28% and was accompanied by a drop in pH of about 1.5 pH units, from an initial pH of 8 to approximately 6.5 pH units. However, samples sealed in amber ampoules, although only slightly discoloured, were maintained at almost 100% of the initial potency.

3.2.2 *In vitro - in vivo* Correlation

Three compressed matrix tablet preparations (formulation A, B and C) containing 550 mg naproxen sodium were evaluated as oral controlled release systems, *in vitro* and *in vivo*, by Dahl *et al.* (1990). *In vitro* dissolution results for the three controlled release formulations exhibited identical matrix release kinetics when linear regression was performed on the percent released versus the square root of time profile (r^2 = 0.996). *In vivo* release of the three experimental formulations and conventional naproxen sodium tablets (two 275 mg tablets, Anaprox® , Syntex) were investigated in a crossover study involving six healthy volunteers. Although the controlled release tablets had similar rates and extents of dissolution, the extent of absorption of the preparations varied. The relative bioavailability values, estimated by the ratios of mean total AUC for the controlled release tablets relative to the conventional tablets, were 113% for the controlled release tablets A and C and 102% for controlled release tablet B.

Charles and Mogg (1994) carried out a comparative *in vitro* and *in vivo* bioavailability study of oral naproxen from tablet and caplet formulations involving 14 healthy volunteers in a randomised, crossover study. The *in vitro* parameter of mean dissolution time (MDT of caplet = 5.03 min and MDT of tablet = 15.0 min) differed significantly. However, *in vivo* testing showed the preparations to be bioequivalent. In a study undertaken by Wanwimolruk *et al.* (1991), the relative bioavailability of a controlled release tablet of naproxen

(Naprosyn® CR 500 mg, Syntex) was shown to be 96% of the standard (two 250 mg) Naprosyn® tablets during a randomised, crossover study involving 15 healthy volunteers.

3.2.3 Pharmacodynamic Properties

Naproxen sodium is a potent NSAID with analgesic and antipyretic activity. It is used in the treatment of rheumatoid arthritis and other rheumatic or musculoskeletal disorders such as osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis. It is also recommended as an analgesic for a variety of other painful disorders which include primary and secondary dysmenorrhoea, acute gout and any form of mild to moderate pain. Naproxen is available as the free acid or the sodium salt. Naproxen and naproxen sodium are pharmacologically and therapeutically equivalent at comparable dosages i.e. naproxen 500 mg and naproxen sodium 550 mg are equipotent (Todd and Clissold, 1990).

In animal studies naproxen exhibited dose related anti-inflammatory, analgesic and antipyretic effects. On a weight-for-weight basis naproxen is more potent than aspirin and phenylbutazone, and equal to or less potent than indomethacin. As is common with the NSAIDs, the anti-inflammatory effects of naproxen, and most of its other pharmacological effects, are generally thought to be related to the inhibition of cyclo-oxygenase and a consequent decrease in prostaglandin concentrations in various body fluids and tissues, including the gastric mucosa, synovial fluid, urine and blood.

3.2.3.1 Mechanism of action

The effectiveness of naproxen is largely due to its capacity to inhibit prostaglandin biosynthesis. Most of the pharmacological effects of naproxen, as with other NSAIDs, are believed to be mediated either directly or indirectly by inhibition of prostaglandin synthesis although other mechanisms such as a direct action on inflammatory cells have been postulated.

In vitro, naproxen has been shown to be a potent inhibitor of cyclo-oxygenase (prostaglandin synthetase). Numerous animal experiments have also demonstrated that naproxen inhibits the synthesis or release of prostaglandin and various prostaglandin breakdown products (Todd and Clissold, 1990).

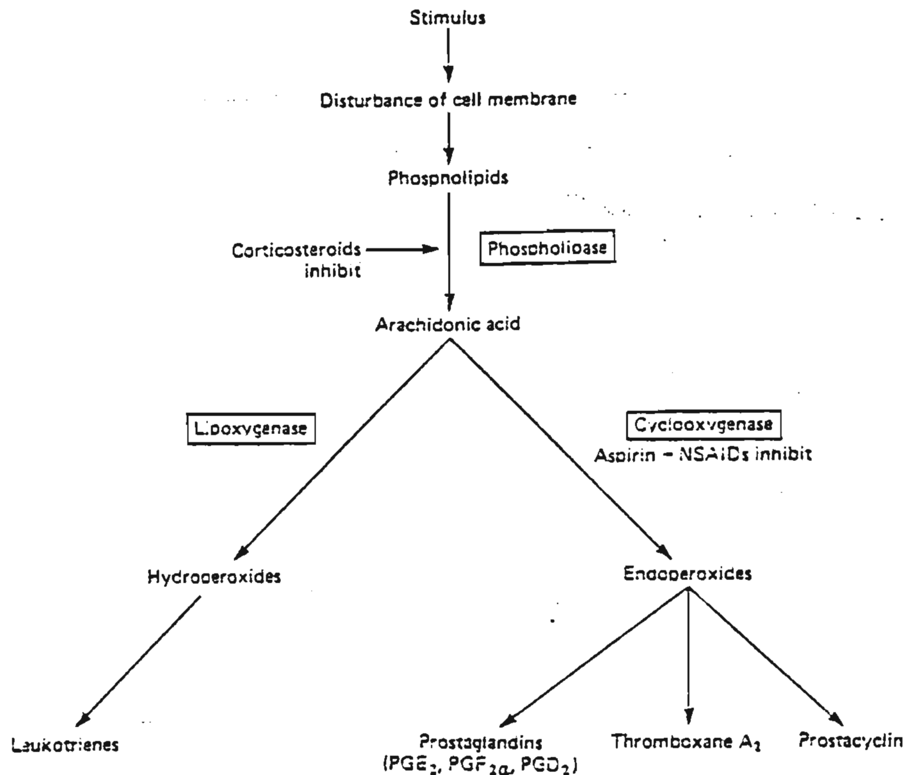


Figure 3.2 : Scheme Showing Inhibition Points of NSAIDs on the Prostaglandin Biosynthesic Pathway (Boynton *et al.*, 1988).

Oral administration of naproxen has produced the following effects : The generation of TxB_2 from arachidonic acid by human platelets is inhibited, TxA_2 and prostacyclin synthesis is reduced (Vesterqvist and Green, 1989), and plasma and urinary TxB_2 concentrations are decreased in healthy subjects (Brater *et al.*, 1985). Naproxen also decreases the synovial fluid concentrations of PGE_2 in patients with rheumatoid arthritis (Seppala *et al.*, 1985).

In adjuvant-induced arthritis in rats, naproxen not only inhibits the inflammatory response but also inhibits cartilage and bone erosion (Ackerman *et al.*, 1984). In common with other NSAIDs, naproxen is also a potent inhibitor of the secondary phase of human platelet aggregation *in vitro* and bleeding time may be increased in some patients who are treated with therapeutic dosages of naproxen (Todd and Clissold, 1990).

3.2.4 Pharmacokinetic properties

3.2.4.1 Absorption

Naproxen sodium exhibits significantly faster dissolution *in vitro* as compared with naproxen (Zecchi *et al.*, 1984). After entering the stomach, naproxen sodium rapidly dissolves in gastric juice but, on dissociation, precipitates out as fine particles of naproxen. Consequently, a larger surface area for absorption is available as compared to the large particles that result from the disintegration of a naproxen tablet (Moyer, 1986). Thus, a conventional tablet formulation of naproxen sodium produces earlier and higher plasma concentrations of naproxen as compared to a similar dosage form of naproxen (Sevelius *et al.*, 1980). Apart from this difference, the pharmacokinetics of the sodium salt and the parent acid are identical provided that equipotent doses are administered (Moyer, 1986).

Following oral administration the drug is completely absorbed, nearly 100% absorption from the gastrointestinal tract has been reported, with steady state plasma concentrations being attained after approximately 4 - 5 doses (Brogden *et al.*, 1975). Although a linear plasma level response occurs with naproxen, a non-linear response occurs when dosed at high levels. Plasma concentrations of naproxen have been shown to increase in direct proportion to the dose administered up to approximately 500 mg, thereafter there is a less than direct proportionality. This observation is attributed to increased clearance of free naproxen due to saturable protein binding and is in no way related to decreased absorption of the drug (Todd and Clissold, 1990). Runkel *et al.* (1972) found that blood levels are readily measurable within 15 minutes of administration suggesting some gastric absorption. Peak plasma levels of

37 µg/l and 79 µg/l were reported after two hours following single oral doses of naproxen of 250 mg and 500 mg respectively.

Concomitant administration of naproxen with antacids has shown to significantly alter the absorption characteristics of the drug. Past studies have shown that sodium bicarbonate enhances the rate of naproxen absorption, magnesium carbonate caused a slight reduction in absorption, and a mixture of magnesium oxide and aluminium hydroxide significantly reduced the rate of naproxen absorption. However, Weber *et al.* (1981) demonstrated that small amounts of Mylanta^{R} (a mixture of aluminium hydroxide, magnesium hydroxide and simethicone) does not alter the bioavailability or the pharmacokinetics of naproxen.

With respect to administration of naproxen with food, studies have demonstrated the lack of effect of a standard meal on the overall extent of absorption or the half-life of naproxen. It has been reported that the rate and absorption of a naproxen controlled release preparation was not substantially altered by the ingestion of food (Mroszczak *et al.*, 1988).

3.2.4.2 Distribution

Rat distribution data suggest very little distribution of naproxen to organ tissue. Naproxen is highly protein bound; approximately 99.9% of the drug in plasma is protein bound thus undoubtedly accounting for the low distribution to other areas of the body, as well as its low rate of metabolism and excretion (Runkel *et al.*, 1972).

Studies carried out by Bruno *et al.* (1988) have shown that, after single oral doses of naproxen sodium, the drug reaches peak synovial fluid concentrations at about 50 - 75% of the peak plasma concentration. This study also showed that peak concentrations in synovial fluid are delayed as compared with plasma and that the elimination from synovial fluid was slow (half-life of 31 ± 12 hours) resulting in appreciable accumulation of the drug in the synovium. Thus, after administration of repeated oral doses of naproxen, peak steady state concentrations are at least equivalent to those in plasma.

The volume of distribution of naproxen is small in humans, about 10 % of the body weight, which is due to the high degree of protein binding. The volume of distribution of naproxen in healthy adults has been reported to range from 0.09 to 0.3 l / kg with an average of 0.16 l/kg (Runkel *et al.*, 1972).

3.2.4.3 Metabolism and elimination

Naproxen is metabolised primarily in the liver to 6-demethyl-naproxen and glucuronide conjugates which are believed to be inactive (Runkel *et al.*, 1972). Following the administration of a radiolabelled dose of naproxen about 95% of the label is recovered in the urine and 3% or less is recovered in the faeces. Approximately 30% of the drug is metabolised to 6-demethyl-naproxen probably by hepatic microsomal oxidation, 10% is excreted as unchanged naproxen and 60% as its glucuronide or other conjugates (Dahl, 1986; Moyer, 1986). The most recent metabolite of naproxen to be identified is the sulphur conjugate of 6-demethyl-naproxen. Kiang *et al.* (1989) isolated and identified low concentrations of a sulphur conjugate of 6-demethyl-naproxen in the plasma of healthy subjects after oral administration of naproxen.

Naproxen has been detected in the milk of lactating mothers at approximately 1% the concentration in the maternal plasma. In a study conducted by Jamali and Stevens (1983), the excretion of naproxen in a nursing mother and its uptake by the infant was evaluated. The researchers concluded that an insignificant amount of naproxen is excreted into breast milk and that the drug can be administered safely to mothers desiring to breast feed.

The elimination half-life of naproxen is between 12 to 15 hours and appears to be independent of plasma concentration or dosage. Naproxen has been shown to have an extended half-life in synovial fluid of 31 $\pm$ 12 hours.Naproxen appears to undergo tubular secretion and the concomitant administration of probenecid reduces naproxen excretion and consequently increases plasma concentration and the elimination half-life of the drug in plasma (Todd and Clissold, 1990).

3.2.4.4 Dosage and Administration

The recommended dose of naproxen sodium for rheumatoid arthritis, osteoarthritis and ankylosing spondylitis is 275 mg or 550 mg twice daily. Lower doses may be adequate for long - term therapy and the dose should be adjusted according to the clinical response. Although symptomatic improvement in arthritis usually occurs within 2 weeks, a trial for 4 weeks should be considered before abandoning therapy. A dose of 10 mg/kg/day in two divided doses has been used in children over 5 years with juvenile arthritis. In acute gout, an initial dose of 825 mg followed by 275 mg every 6 to 8 hours. In all other forms of mild to moderate pain (including primary dysmenorrhoea), an initial loading dose of 550 mg should be administered and should be followed by 275 mg every 6 to 8 hours.

3.2.4.5 Adverse Effects

Naproxen and naproxen sodium have been extensively used for many years and their adverse effects profiles are well established. The drug is generally well tolerated and has a good long term acceptability to patients. The most frequent adverse reactions are predictable extensions of the drugs pharmacology. In common with other NSAIDs the most frequent adverse effects include mild gastrointestinal disturbances and central nervous system (CNS) effects, followed by mild skin reactions. Increased age does not appear to be related to any increase in unwanted effects and there is little evidence to suggest that the nature, severity or frequency of adverse effects is any different with naproxen as compared with other NSAIDs. However, aspirin and indomethacin may produce a higher frequency of gastrointestinal symptoms and CNS effects.

As with any drug which has been used so extensively in clinical practice, a number of rare serious adverse effects have been associated with naproxen, which have also been associated with other NSAIDs. They include : gastrointestinal bleeding or ulceration, pseudoporphyria and other severe cutaneous reactions; acute renal failure including papillary necrosis, interstitial nephritis and hyperkalaemia; agranulocytosis; aplastic anaemia; haemolytic

anaemia; peripheral neuropathy; aseptic meningitis; and corneal opacity. Patients exhibiting aspirin hypersensitivity may show cross-reactivity with naproxen (Todd and Clissold, 1990).

Chapter Four

Materials, Methods and Equipment

The methods of formulation and evaluation of a novel multiple unit naproxen sodium modified release drug delivery system and the equipment utilized in the study are outlined in this section. The materials used in this study and their suppliers are presented in Appendix 1. Figure 4.1 depicts a simplified schematic representation of the sequential methodology employed in the study. Unless otherwise stated, the USP XXIII (1995) will be referred to as the USP.

4.1 QUALITY CONTROL

4.1.1 Naproxen Sodium Powder

4.1.1.1 Identification

4.1.1.1.1 *Infrared Spectrophotometry*

The Shimadzu 8101 Fourier Transform Infrared spectrophotometer was used to obtain the infrared absorption spectrum of naproxen sodium powder and naproxen sodium USP reference standard. The spectrophotometer was used in conjunction with the Shimadzu DR8001 computer software system. The method of analysis, as per the USP, is presented in Appendix 2.

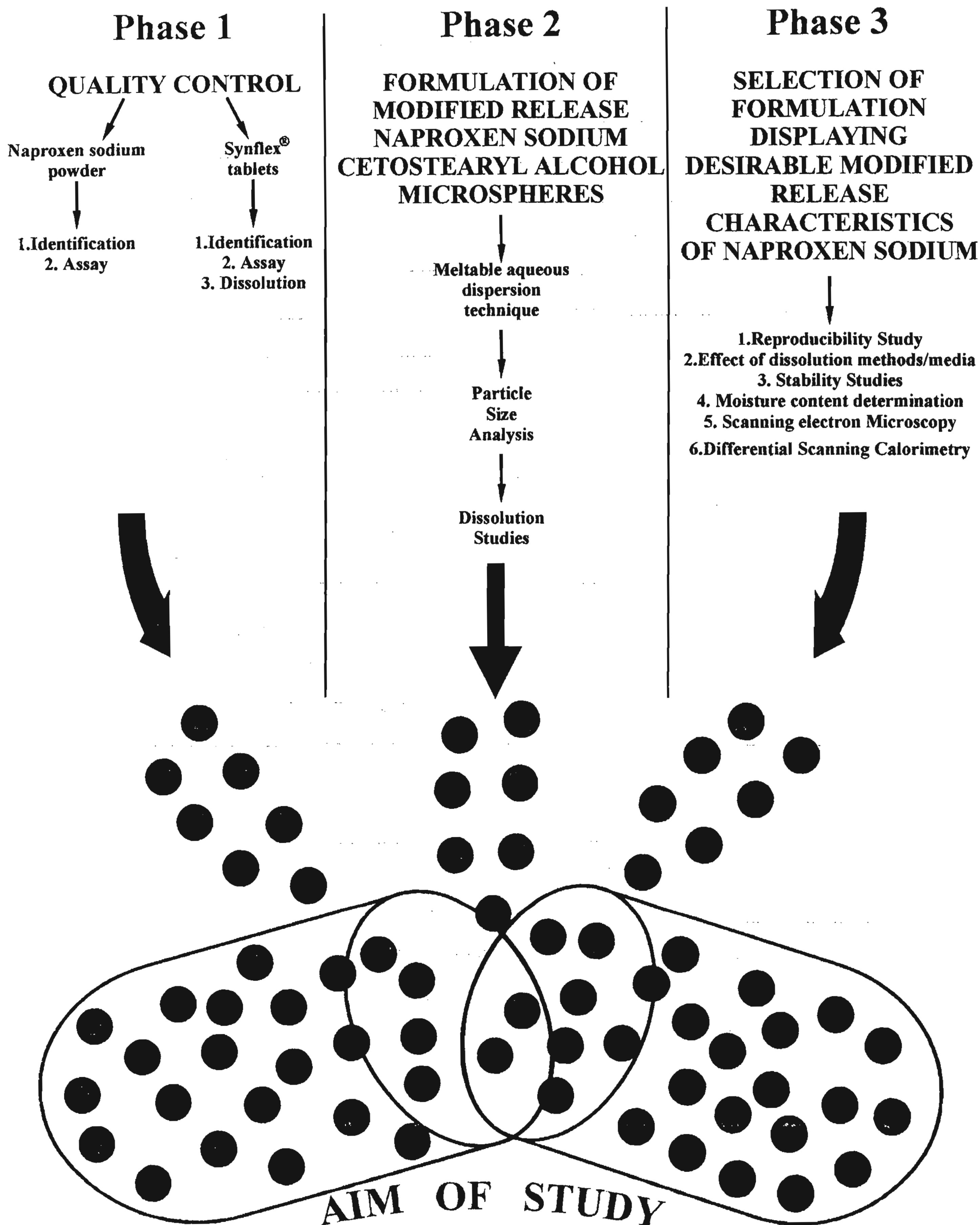


Figure 4.1 : Sequential Methodology of Research Study

4.1.1.1.2 *Ultraviolet Spectrophotometry*

The ultraviolet absorption spectrum of a 1 in 40000 solution of naproxen sodium in methanol (Appendix 2) was obtained with a Beckman DU-64 UV/VIS spectrophotometer using 1 mm quartz cells. All subsequent ultraviolet analyses were performed using the same spectrophotometer and quartz cells.

4.1.1.2 Assay

Naproxen sodium was assayed according to the method presented in the USP (Appendix 2). The USP states that the purity of naproxen sodium should not be less than 98.0% and not more than 102% of naproxen sodium calculated on the dried base.

4.1.2 Synflex® Tablets

4.1.2.1 Identification

Synflex® tablets were identified using the methods described in the USP (Appendix 2).

4.1.2.2 Assay

According to the USP, the purity of naproxen sodium tablets should not be less than 90.0% and not more than 110.0% of the labeled amount of naproxen sodium. The assay procedure is presented in Appendix 2.

4.1.2.3 Dissolution study

The *in vitro* drug release profile of the commercially available, single unit immediate release preparation of naproxen sodium, Synflex®, was determined using the USP monograph for Naproxen Sodium Tablets. The *in vitro* dissolution tests were performed according to the procedure described under 4.4.2.1. However, instead of naproxen sodium-cetostearyl alcohol microspheres, one Synflex® tablet was placed in each of the four dissolution vessels. Phosphate buffer pH 7.4 as described in the USP monograph was the only dissolution medium employed for Synflex® tablets. The analysis of drug content in the dissolution samples was performed using ultraviolet spectrophotometry at the wavelength of maximum absorption of 332 nm. The calibration curve used to quantify the drug release with time in phosphate buffer pH 7.4 was constructed as described in section 4.4.3.1.2. Table 4.1 depicts the dissolution protocol employed for Synflex®.

Table 4.1 : Dissolution Protocol for Synflex®

Operating Parameter	Setting
Apparatus	Rotating paddle
Agitation rate	50 rpm
Medium	phosphate buffer pH 7.4
Volume of medium	900 ml
Sampling times (mins)	5, 10, 15, 20, 25, 30, 35, 40, 45
Sample volume	5 ml
Temperature	37°C

4.2 FORMULATION OF AN ORAL MODIFIED RELEASE PREPARATION OF NAPROXEN SODIUM

Prior to the investigation of the meltable aqueous dispersion technique, the coacervation phase separation technique was employed to formulate ethylcellulose-walled microcapsules. Due to the difficulty encountered in obtaining naproxen sodium, all preliminary investigations were performed with diclofenac sodium.

4.2.1 Coacervation Phase Separation

Microcapsules of diclofenac sodium and naproxen sodium were prepared by a temperature induced coacervation phase separation technique. In preparing a batch, 300 ml of cyclohexane was heated to 50°C in a cylindrical tall-form beaker. Ethylcellulose was added to the warm solution at a stirring rate of 450 rpm. The core material (diclofenac sodium or naproxen sodium) was dispersed in the solution of coating polymer (ethylcellulose) and the temperature was held at 80°C for 1 hour. Phase separation and subsequent coacervation was induced by lowering the temperature to 45°C over a period of 1 hour. The microcapsule wall was rigidified by rapid cooling to 20°C. Microcapsules were allowed to sediment and were separated by decantation, vacuum-filtered and dried at 50°C for 30 minutes in an air-heated Gallenkamp oven, Model OV160.

4.2.1.1 Formulation variables for the coacervation phase separation technique

4.2.1.1.1 *The Effect of Ethylcellulose:Drug Ratios*

Different ratios of ethylcellulose:drug were investigated. Table 4.2 and 4.3 depicts the formulations employed to determine the effect of the different ratios on the drug release profile of diclofenac sodium and naproxen sodium microcapsules.

Table 4.2 : Formulation of Different Batches of Microcapsules with Varying Ratios of Ethylcellulose and Diclofenac Sodium

COMPONENT	DE1 (1:1)	DE2 (1:2)	DE3 (2:3)
Ethylcellulose	9 g	9 g	9 g
Diclofenac sodium	9 g	18 g	13.5 g
Cyclohexane	300 ml	300 ml	300 ml

Table 4.3 : Formulation of Different Batches of Microcapsules with Varying Ratios of Ethylcellulose and Naproxen Sodium

COMPONENT	NE1 (1:2)	NE2 (2:3)	NE3 (1:1)	NE4 (2:1)
Ethylcellulose	3 g	3.6 g	4.5 g	6 g
Naproxen sodium	6 g	5.4 g	4.5 g	3 g
Cyclohexane	300 ml	300 ml	300 ml	300 ml

4.2.1.1.2 *The Effect of Polyisobutylene (PIB)*

The effect of a coacervation inducing agent, PIB, on the drug release profiles of diclofenac sodium microcapsules was investigated. Table 4.4 depicts the formulations employed to investigate the effect of PIB.

Table 4.4 : Formulation of Different Batches of Microcapsules with Varying Concentrations of PIB

COMPONENT	DE2	DE4
Ethylcellulose	9 g	9 g
Diclofenac sodium	18 g	18 g
PIB	0 g (0%)	6 g (2%)
Cyclohexane	300 ml	300 ml

4.2.2 Meltable Aqueous Dispersion Technique

Naproxen sodium-cetostearyl alcohol microspheres were prepared by a technique of hot melt microencapsulation known as the meltable aqueous dispersion technique. The required amount of cetostearyl alcohol was melted on a hot plate. On cetostearyl alcohol becoming molten, naproxen sodium was stirred into it to obtain a homogeneous melt. This mixture was then dispersed in 400 ml of heated (65°C), acidified, deionized water agitated continuously at a predetermined speed. The whole mixture, contained in a cylindrical tall-form beaker, was agitated at the required speed for 10 minutes using a Heidolph Type ST 1 stirrer with a stainless-steel rotor fitted with a three-blade stainless-steel impeller of approximately 30 cm diameter. The height of the stirrer was set at a distance of 3 cm from the base of the glass beaker. After 10 minutes, the beaker was cooled rapidly by draining out the hot water in the bath and replacing it with crushed ice. With constant stirring, the cooling stage took approximately 10 minutes. The resultant hardened spherical particles were filtered, washed and air-dried in a vacuum cupboard overnight. The microspheres were fractionated by sieving and stored in amber bottles.

4.2.2.1 Development of the formulation

Naproxen sodium-cetostearyl alcohol microspheres were prepared as per method outlined by Wong *et al.* (1992). Direct application of this method was not possible and required modification of the formulation. Initially, only naproxen sodium and cetostearyl alcohol were combined and dispersed in pH 3.0 acidified water. This formula yielded microspheres of low drug loading capacity. It was observed that the high water solubility of the drug resulted in loss of drug to the aqueous medium. Hence, the pH of the aqueous medium was varied in order to optimize drug loading. Table 4.5 depicts the formulations employed in the optimization of drug loading.

Table 4.5 : Optimization of Drug Loading Through pH Variation

COMPONENT	NC1	NC4	NC6
Cetostearyl alcohol	10 g	10 g	10 g
Naproxen sodium	10 g	10 g	10 g
pH	3.0	1.5	0.8
Acidified water	200 ml	200 ml	200 ml

However, optimization of the drug loading resulted in agglomeration of the drug-wax matrices. Thus magnesium stearate was incorporated into the formulation as an anti-tackiness agent to prevent agglomeration and clumping of the drug-wax combinations. Various concentrations of magnesium stearate were investigated and a suitable concentration was determined. Table 4.6 outlines the formulations employed to decrease agglomeration of the drug-wax combination.

Table 4.6 : Optimization of Particle Size

COMPONENT	NC21	NC24	NC25
Cetostearyl alcohol	10 g	10 g	10 g
Naproxen sodium	10 g	10 g	10 g
Magnesium stearate	0.2	0.4	0.6
pH	0.8	0.8	0.8
Acidified water	200 ml	200 ml	200 ml

Although the addition of magnesium stearate solved the problem of clumping, the formulation obtained did not possess spherical properties. It was postulated that the addition of a surface active agent or a combination of surfactants would reduce interfacial tension and promote sphericity of the dispersed drug-wax combination. Studies performed showed a combination of surfactants to be desirable. Thus, a combination of Span 20 and Tween 60 were investigated and a suitable combination of the two surfactants were chosen. Due to the hydrophilic nature of Tween 60, it was incorporated into the acidified aqueous medium. Span 20 was added to the drug-wax melt prior to the melt being dispersed in the acidified medium. Thus, the final formula for the preparation of naproxen sodium-cetostearyl alcohol microspheres was derived. Table 4.7 outlines the formulation and process parameters.

Table 4.7 : Formulation and Process Parameters of Naproxen Sodium-Cetostearyl Alcohol Microspheres

COMPONENT	QUANTITY
Cetostearyl alcohol	20 g
Naproxen sodium	20 g
Magnesium stearate	0.8 g
Span 20	0.4 g
Tween 60	0.8 g
Acidified water	400 ml
pH of water	0.6
Agitation rate	900 rpm
Agitation time	20 minutes
Initial temperature	65°C
Final temperature	10°C

4.3 INFLUENCE OF FORMULATION VARIABLES ON DRUG RELEASE FROM NAPROXEN SODIUM-CETOSTEARYL ALCOHOL MICROSPHERES

4.3.1 Effect of pH of the Aqueous Acidified Medium

The pH of the aqueous acidified medium had to be optimized to ensure maximum encapsulation efficiency. Initially, only cetostearyl alcohol and naproxen sodium powder were combined and dispersed in acidified water which had a pH of 3.0. However, due to the high water solubility of naproxen sodium, the encapsulation efficiency was found to be poor. Thus various pH's of the acidified medium were investigated to determine the suitable pH for optimum encapsulation efficiency. In all formulations, 1N hydrochloric

acid was used to adjust the pH of the aqueous medium. The effect of pH on drug release characteristics was investigated and the various formulations are presented in Table 4.8.

Table 4.8 : Formulation of Different Batches of Microspheres with Varying pH of the Dispersion Medium

COMPONENT	NC 80	NC 81	NC 82
Cetostearyl alcohol	20 g	20 g	20 g
Naproxen sodium	20 g	20 g	20 g
Magnesium stearate	0.8 g	0.8 g	0.8 g
Span 20	0.4 g	0.4 g	0.4 g
Tween 60	0.8 g	0.8 g	0.8 g
Acidified water	400 ml	400 ml	400 ml
pH of water	0.8	0.6	0.4

4.3.2 Effect of Magnesium Stearate

Table 4.9 presents the formulations employed in investigating the effect of magnesium stearate on drug release characteristics.

Table 4.9 : Formulation of Different Batches of Microspheres with Varying Quantities of Magnesium Stearate

COMPONENT	NC 83	NC 81	NC 84
Cetostearyl alcohol	20 g	20 g	20 g
Naproxen sodium	20 g	20 g	20 g
Magnesium stearate	0.4 g	0.8 g	1.2 g
Span 20	0.4 g	0.4 g	0.4 g
Tween 60	0.8 g	0.8 g	0.8 g
Acidified water	400 ml	400 ml	400 ml
pH of water	0.6	0.6	0.6

4.3.3 Effect of Cetostearyl alcohol

Table 4.10 presents the formulations employed to investigate the effect of varying the cetostearyl alcohol content of the wax matrices on drug release characteristics.

Table 4.10 : Formulation of Different Batches of Microspheres with Varying Quantities of Cetostearyl Alcohol

COMPONENT	NC 85	NC 81	NC 86
Cetostearyl alcohol	10 g	20 g	40 g
Naproxen sodium	20 g	20 g	20 g
Magnesium stearate	0.8 g	0.8 g	0.8 g
Span 20	0.4 g	0.4 g	0.4 g
Tween 60	0.8 g	0.8 g	0.8 g
Acidified water	400 ml	400 ml	400 ml
pH of water	0.6	0.6	0.6

4.3.3.1 Particle density determination of naproxen sodium-cetostearyl alcohol microspheres by liquid displacement

The density of the batches manufactured with varying quantities of cetostearyl alcohol were determined using the technique of liquid displacement as outlined by Wong *et al.* (1992) with minor modifications.

Initially, the weight of 50 ml of 1N hydrochloric acid (*a*) was determined in a tared stoppered 50 ml pycnometer. The 1N hydrochloric acid was used to minimize any possible dissolution of naproxen sodium. Approximately 1 g of naproxen sodium-cetostearyl alcohol microspheres was accurately weighed and placed in the previously tared pycnometer via a glass weighing boat. The stoppered pycnometer containing the sample was tared. The pycnometer was filled with 1N hydrochloric acid at room temperature and stoppered, taking care not to crush any pellets and to exclude air bubbles by gentle agitation. The exterior of the pycnometer was dried carefully to remove excess liquid and then weighed. This provided the new weight of hydrochloric acid (*b*). The above determination was performed in triplicate for each batch. Thus, the weight of the hydrochloric acid displaced was determined ($a - b$). The density of the hydrochloric acid used was 1.015 $g.cm^{-3}$ (Merck Tables for the Chemical Laboratory). From the weight of hydrochloric acid displaced and its density, the volume of the hydrochloric acid displaced was calculated. Finally, using the volume of hydrochloric acid displaced by the known quantity of sample, the densities of the naproxen sodium-cetostearyl alcohol microspheres from each batch was determined.

4.3.3.2 Calculation of the specific area of naproxen sodium-cetostearyl alcohol microspheres

For naproxen sodium-cetostearyl alcohol microspheres whose densities were determined, the surface area per unit weight can be calculated by assuming the mid-point of a size fraction to be the mean size (Wong *et al.*, 1992).

The following equation was employed :-

$$Mean\ \ Specific\ \ Surface\ \ Area = 3/\rho r \qquad (Equation\ 4.1)$$

where ρ = mean density of the spheres (g.cm^{-3})

r = mean radius of the spheres (cm)

4.3.4 Effect of Particle Size

The influence of particle size of naproxen sodium-cetostearyl alcohol microspheres on the drug release characteristics was investigated. Microspheres of Batch NC81 that was prepared as depicted in Table 4.8 using the manufacturing parameters outlined in Table 4.5 were dried, weighed and subjected to particle size analysis according to section 4.5. Due to the low quantity of microspheres recovered in certain size fractions, it was only possible to perform *in vitro* dissolution studies on three size fractions. On separation of the size fractions, an amount equivalent to 550 mg of naproxen sodium was accurately weighed and subjected to *in vitro* dissolution according to section 4.4.2.1.

4.4 *IN VITRO* DISSOLUTION STUDIES

According to the official monograph for Naproxen Sodium Tablets in the USP, the rotating paddle apparatus was employed to perform *in vitro* dissolution studies. This method was employed with minor modification to characterize drug release from naproxen sodium-cetostearyl alcohol microspheres. Sviensson and Krismundsdóttir (1992) modified the USP dissolution monograph for *in vitro* dissolution of Naproxen Tablets in order to apply the method to new formulated modified release naproxen-ethylcellulose microcapsules. In their method, a stirring rate of 100 rpm was employed. Thus, the USP monograph for Naproxen Sodium Tablets was modified accordingly. The dissolution medium, phosphate buffer pH 7.4, was prepared as specified in Appendix 3. In all dissolution tests, a minimum of four

replicate determinations was performed. The rotating basket and rotating bottle apparatus were also considered to determine the possible dependence of drug release characteristics on dissolution methodologies.

4.4.1 Potency Determination of Naproxen Sodium-Cetostearyl Alcohol Microspheres

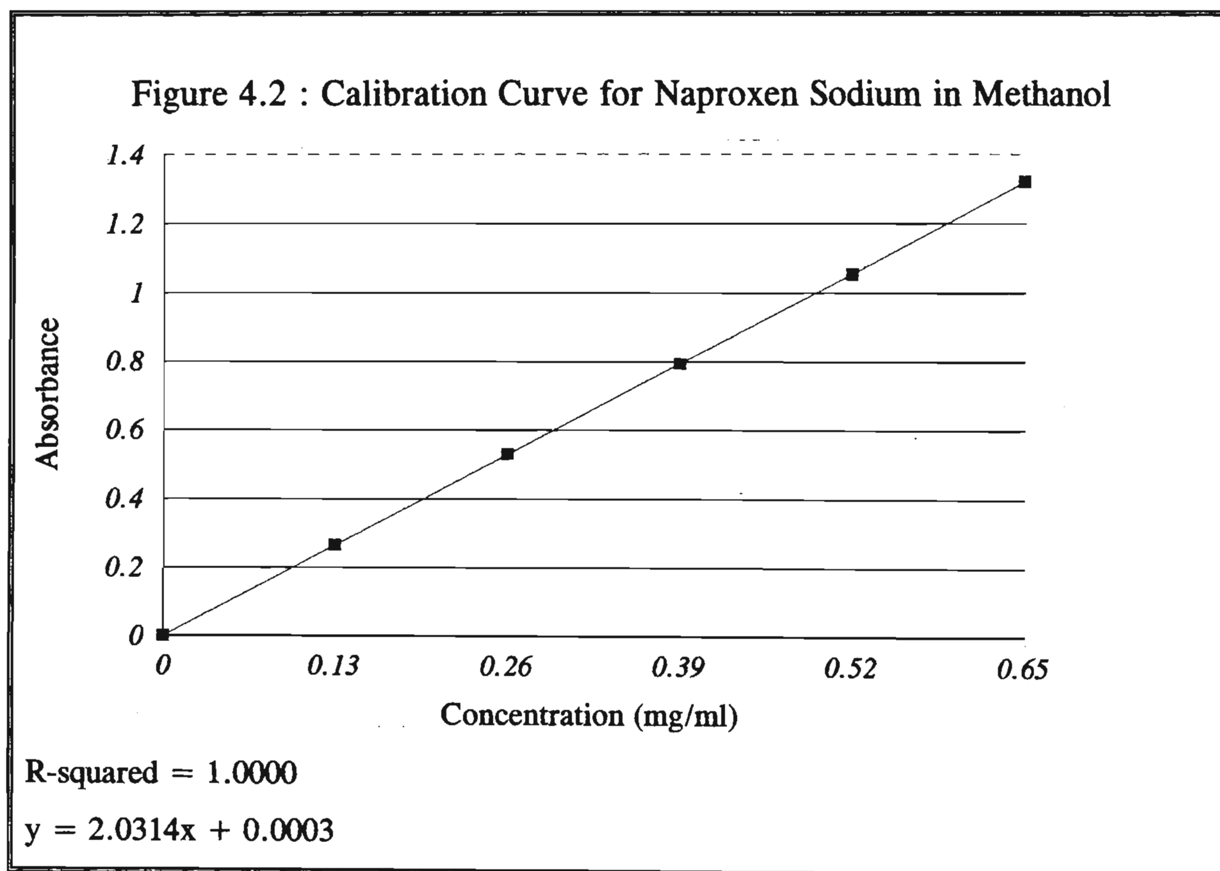
The potency of the naproxen sodium-cetostearyl alcohol microspheres was determined by dissolving the sample in methanol and obtaining the absorbance of the solution by means of the Beckman DU64 spectrophotometer. Initially a stock solution (stock A) of naproxen sodium in methanol was prepared by accurately weighing 0.65 g of naproxen sodium, transferring the mass to a 100 ml volumetric flask, and bringing the solution up to volume with methanol. From stock A, 10 ml was removed and made up to 100 ml in a volumetric flask (stock B). Stock B was scanned spectrophotometrically to determine the wavelength of maximum absorbance of naproxen in methanol. The preparation of a calibration curve of naproxen sodium in methanol involved diluting stock B as obtained above to produce a series of standard solutions containing 0.13, 0.26, 0.39, 0.52 and 0.65 mg/ml. Table 4.11 describes the calibration curve in terms of the wavelength of maximum absorbance and the absorbance values of the standard solutions.

Table 4.11 : Data on the Calibration Curve for Naproxen Sodium in Methanol

NAPROXEN SODIUM CONCENTRATION (mg/ml)	ABSORBANCE IN METHANOL 271 nm
0.13	0.264
0.26	0.529
0.39	0.794
0.52	1.055
0.65	1.321

The absorbance measured for each standard solution was plotted against the concentration of the solution to produce a calibration curve (Figure. 4.2) from which the unknown concentrations of the potency samples were determined.

To determine the potency of a batch of microspheres, approximately 0.1 g of naproxen sodium-cetostearyl alcohol microspheres were accurately weighed and transferred to a 100 ml volumetric flask. Approximately 50 ml of methanol was used to dissolve the microspheres. To aid solution of the microspheres, the contents of the flask was sonicated in a UMC2 ultrasonic bath until the solution was clear. The volumetric flask was brought up to volume with methanol. The absorbance of an aliquot was measured in a 1 mm quartz cell at 271 nm by ultraviolet spectrophotometry. The Quant® II Soft-Pac module was employed to convert the absorbance values of the potency samples to a concentration value on the basis of the calibration curve equation coefficients.



4.4.2 Dissolution Methodology

4.4.2.1 Rotating paddle apparatus

The USP specifications for the rotating paddle apparatus (Apparatus 2) are presented in Appendix 5. In all dissolution testing the Caleva model 7ST dissolution test apparatus was used. Table 4.12 outlines the test conditions employed in these studies.

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, 6.9, 7.4, 8.0
Volume of media	900 ml
Temperature	37 ± 0.5°C
Sampling times (hours)	0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume	5 ml

The dissolution apparatus consisted of six round-bottomed dissolution flasks (1 litre) immersed in a water bath thermostatically maintained at 37 ± 5°C. The stainless-steel paddles were attached to an electrically-controlled drive by means of thumb screws. The dissolution medium (900 ml) was de-aerated and the poured into each dissolution flask. In undertaking a dissolution run, a quantity of naproxen sodium-cetostearyl alcohol microspheres equivalent to 550 mg of naproxen sodium was accurately weighed and emptied into the dissolution vessel containing the dissolution medium.

At the end of each rotation interval, the dissolution apparatus was switched off and a 5 ml aliquot of sample was withdrawn from each dissolution vessel using a 10 ml syringe. The samples were automatically filtered during the withdrawal process by means of a 0.8 µm Millipore® filter attached to the end of each sampling rod immersed in the dissolution medium. Prior to samples being withdrawn and analyzed for drug content, the sampling tubes and rods for each dissolution station were flushed twice by withdrawing and re-injecting the same medium, thus removing any medium or sample that may have been lodged in the tube and rod from the previous withdrawal interval. The samples were then withdrawn and the dissolution apparatus was switched on. An equal volume (5 ml) of fresh dissolution medium was replaced into each vessel via the sampling tube and rod through the attached filter. The whole process of sample withdrawal and replacement was completed in

less than 2 minutes. The samples obtained were immediately analyzed for drug content by ultraviolet spectrophotometry as described under section 4.4.3.

In instances where dissolution studies were performed on encapsulated naproxen sodium-cetostearyl alcohol microspheres, the microspheres were emptied from the gelatin capsule directly into the dissolution vessel. This approach was adopted to prevent any possible interference during drug analysis due to dissolution and disintegration of the capsule shell.

4.4.2.1.1 *Agitation Rates*

To determine the influence of different agitation rates on drug release characteristics, dissolution studies were carried out on batch NC 81. Naproxen sodium-cetostearyl alcohol microspheres were subjected to dissolution testing at agitation rates of 50, 100 and 150 rpm in phosphate buffer pH 7.4 for 8 hours. At the specified sampling intervals, samples were withdrawn according to the technique previously discussed and analyzed for drug content by ultraviolet spectrophotometry.

4.4.2.1.2 *Dissolution Media*

Unless otherwise stated, phosphate buffer pH 7.4 was the dissolution medium utilized in all dissolution testing. To simulate drug release behaviour in the gastrointestinal tract after oral administration *in vitro* dissolution studies were conducted on one formulation viz. Batch NC81. The simulation of the gastrointestinal milieu was achieved with the aid of various buffer solutions of different pH values which were prepared in accordance with the USP (Appendix 4). Ultraviolet spectroscopic scans were performed on naproxen sodium in various dissolution media to determine the wavelength of maximum absorbance in each medium.

Initially, dissolution testing was performed on Batch NC81 in the individual media (pH 1.5, 4.5, 6.9, 7.4, 8.0). Thereafter, a single dissolution run was performed using fresh buffer solution to simulate the gastrointestinal milieu. The method employed to simulate the conditions of, and the duration spent by the dosage form in the gastrointestinal tract was adapted and modified from a study conducted by Dangor (1984). Table 4.13 outlines the sequence of events and duration of the rotation intervals in the various buffers.

Table 4.13 : Protocol for the Simulation of the Gastrointestinal Milieu with Buffer Solutions

BUFFER pH	DURATION OF ROTATION PERIOD
Hydrochloric acid buffer pH 1.5	one hour (1st hour)
Phosphate buffer pH 4.5	one hour (2nd hour)
Phosphate buffer pH 6.9	two hours (3rd and 4th hour)
Phosphate buffer pH 7.4	three hours (5th, 6th and 7th hour)
Phosphate buffer pH 8.0	one hour (8th hour)

At the end of each sample interval, as outlined in Table 4.13, a 5 ml aliquot of sample was withdrawn from each dissolution vessel and analyzed for drug content by ultraviolet spectrophotometry. At the end of each period requiring a change of buffer solution, the apparatus was switched off and the dissolution medium discarded. The microspheres together with the baskets were rinsed in 50 ml of deionized water. Thereafter, the next buffer solution (900 ml), de-aerated and pre-warmed to 37 $\pm$ 0.5°C, was introduced into the dissolution vessels. The baskets containing the microspheres were replaced and the apparatus was switched on. The process was repeated for each buffer media until final sample introduction in the pH 8.0 buffer was performed. This study was conducted over eight hours.

4.4.2.2 Rotating basket apparatus

The USP specifications for the rotating basket apparatus (Apparatus 1) are presented in Appendix 6. The dissolution methodology employed was similar to that described for the rotating paddle method. However, for the rotating basket method, stainless-steel baskets were attached onto stainless-steel rods which were attached to the electrically-controlled drive via thumb screws. Furthermore, the naproxen sodium-cetostearyl alcohol microspheres were accurately weighed and placed into each stainless-steel basket which was screwed onto the stainless steel stirring rod , which in turn was attached on to the electrically-controlled drive by means of thumb screws. Table 4.14 outlines the operating parameters of the rotating basket apparatus.

Table 4.14 : Operating Parameters for the Rotating Basket Apparatus

OPERATING PARAMETER	SETTING
Agitation rates	50, 100, 150 rpm
Medium	Phosphate buffer pH 7.4
Volume of medium	900 ml
Temperature	37 ± 0.5°C
Sampling times (hours)	0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume	5 ml

4.4.2.3 Rotating bottle apparatus

Dissolution testing was also performed using the rotating bottle apparatus, which is a popular non-official method. The studies employing this method were accomplished by using the Hanson Research dissolution apparatus, dissolution drive control, model 3725 and temperature control, model 6041. The apparatus consisted of a dissolution tank through which thermostatically regulated warm water at 37 ± 0.5°C was circulated. A horizontal

rotating four-faced shaft fitted with clamps capable of accommodating twenty 100 ml bottles was supported in the tank. The dissolution drive control was capable of rotational speeds of 35-50 rpm. For the present study, a rotational speed of 50 rpm was selected. Prior to use, the thermostatically controlled dissolution tank was allowed to equilibrate to 37 ± 0.5°C whilst containing six 100 ml amber bottles filled with pre-warmed, de-aerated phosphate buffer pH 7.4.

An accurately weighed quantity of naproxen sodium-cetostearyl alcohol microspheres of Batch NC81 equivalent to 55 mg of naproxen sodium was placed in each of four amber bottles. The bottles were securely capped to prevent leakage of the medium. At the specified sampling intervals, the apparatus was switched off, the bottles were removed and a 5 ml aliquot of sample was withdrawn through a 0.8 μm Millipore® filter from each bottle via a 10 ml syringe. An equivalent volume of fresh dissolution medium was replaced into each bottle. The samples were immediately analyzed for drug content by ultraviolet spectrophotometry. Table 4.15 outlines the operating parameters for the rotating bottle apparatus.

Table 4.15 : Operating Parameters for the Rotating Bottle Apparatus

OPERATING PARAMETER	SETTING
Agitation rate	50 rpm
Medium	Phosphate buffer pH 7.4
Volume of medium	100 ml
Temperature	37 ± 0.5°C
Sampling times (hours)	0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8
Sample volume	5 ml

4.4.3 Analysis of Dissolution Samples

4.4.3.1 Quantitation of naproxen sodium in dissolution media

To quantify the drug content of the dissolution media at the specified time intervals, calibration curves of naproxen sodium in various dissolution media were constructed using the Beckman dissolution testing accessories. Preparation of the calibration curves required the determination of the wavelength of maximum absorbance for naproxen sodium in the various media.

4.4.3.1.1 *Determination of the Wavelength of Maximum Absorbance*

The preparation of a drug solution for the determination of the wavelength of maximum absorbance differed for the various media. For pH 6.9, 7.4 and 8.0, an initial stock solution (stock solution A) containing 0.65 g of naproxen sodium in 100 ml of phosphate buffer was prepared. From stock solution A, a second stock solution (stock solution B) was prepared by taking 10 ml of stock solution A and making up to 100 ml with phosphate buffer to afford a solution of 0.65 mg/ml.

For pH 4.5 a stock solution containing 10 mg of naproxen sodium in 100 ml phosphate buffer pH 4.5 was prepared to afford a solution of 0.1 mg/ml. For pH 1.5, a stock solution containing 5 mg of naproxen sodium in 100 ml of hydrochloric acid buffer was prepared to afford a solution of 0.05 mg/ml. All stock solutions were scanned spectrophotometrically to determine the wavelength of maximum absorbance. The primary peak was employed for pH 1.5 and 4.5 and the wavelength of the secondary peak was employed for pH 6.9, 7.4 and 8.0. The wavelength of maximum absorbance in each medium is reflected in Tables 4.16 and 4.17.

4.4.3.1.2 *Preparation of Calibration Curves for Drug Content Determinations*

The preparation of calibration curves for pH 6.9, 7.4, and 8.0 involved diluting stock solution B obtained in section 4.4.3.1.1 to produce a series of standard solutions containing 0.13, 0.26, 0.39, 0.52 and 0.65 mg/ml of naproxen sodium in 10 ml volumes. The calibration curve for pH 4.5 was prepared by diluting the stock solution obtained in section 4.4.3.1.1 to produce a series of standard solutions containing 0.02, 0.04, 0.06, 0.08 and 0.10 mg/ml, while for pH 1.5 the stock solution obtained in section 4.4.3.1.1 was diluted to produce a series of standard solutions containing 0.01, 0.02, 0.03, 0.04 and 0.05 mg/ml of naproxen sodium in 10 ml volumes. Table 4.16 and 4.17 describes the various calibration curves in terms of the absorbance values and the wavelength of maximum absorbance for the various dissolution media respectively. All calibration curves were generated by employing the Beckman Quant® II Soft-Pac™ module.

Table 4.16 : Data for Calibration Curves Employed for Studies in pH 6.9, 7.4 and 8.0

NAPROXEN SODIUM CONCENTRATION mg/ml	ABSORBANCE VALUES IN DIFFERENT BUFFER SOLUTIONS		
	pH 6.9 (329 nm)	pH 7.4* (332 nm)	pH 8.0 (329 nm)
0.13	0.079	0.076	0.080
0.26	0.159	0.153	0.159
0.39	0.237	0.228	0.237
0.52	0.313	0.309	0.316
0.65	0.393	0.384	0.395

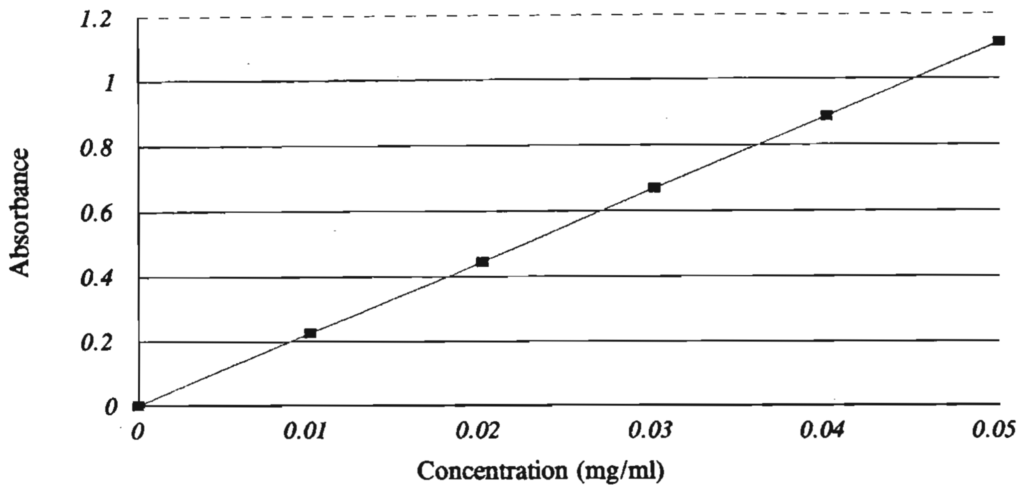
* buffer solution prepared as specified under the USP monograph for Naproxen Sodium Tablets.

Table 4.17 : Data on Calibration Curves for pH 1.5 And 4.5

pH 1.5 (229 nm)		pH 4.5 (260 nm)	
NAPROXEN SODIUM CONCENTRATION mg/ml	**ABSORBANCE**	**NAPROXEN SODIUM CONCENTRATION mg/ml**	**ABSORBANCE**
0.01	0.225	0.02	0.032
0.02	0.444	0.04	0.060
0.03	0.668	0.06	0.090
0.04	0.887	0.08	0.118
0.05	1.110	0.10	0.148

Using each medium as the reference solution, the ultraviolet absorbance of each standard solution was determined at the wavelength of maximum absorbance. The absorbance measured for each standard solution was plotted against the concentration of the solution to produce the calibration curves (Figures 4.3 - 4.7 respectively) from which the unknown concentrations of the dissolution samples were determined. Linear regression correlation coefficients were obtained for all calibration curves.

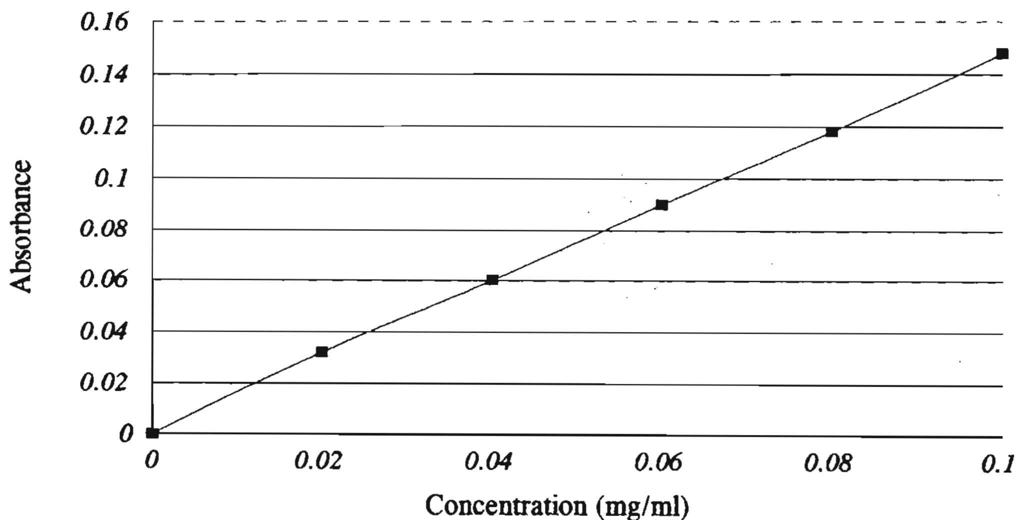
Figure 4.3 : Calibration Curve for Naproxen Sodium in Hydrochloric Acid (pH 1.5)



R-squared = 1.0000

y = 22.171x + 0.0014

Figure 4.4 : Calibration Curve for Naproxen Sodium in Phosphate Buffer (pH 4.5)



R-squared = 0.9997

y = 1.4686x + 0.0012

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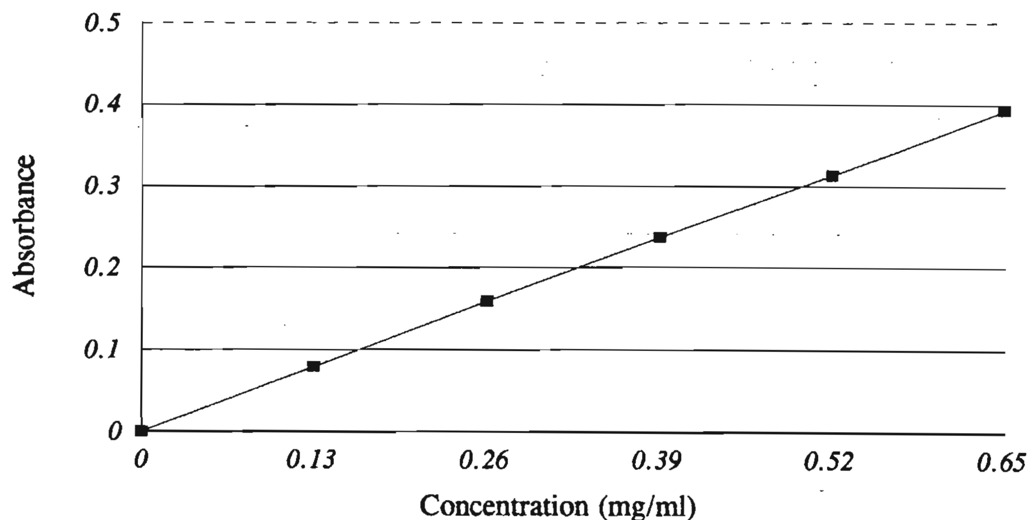
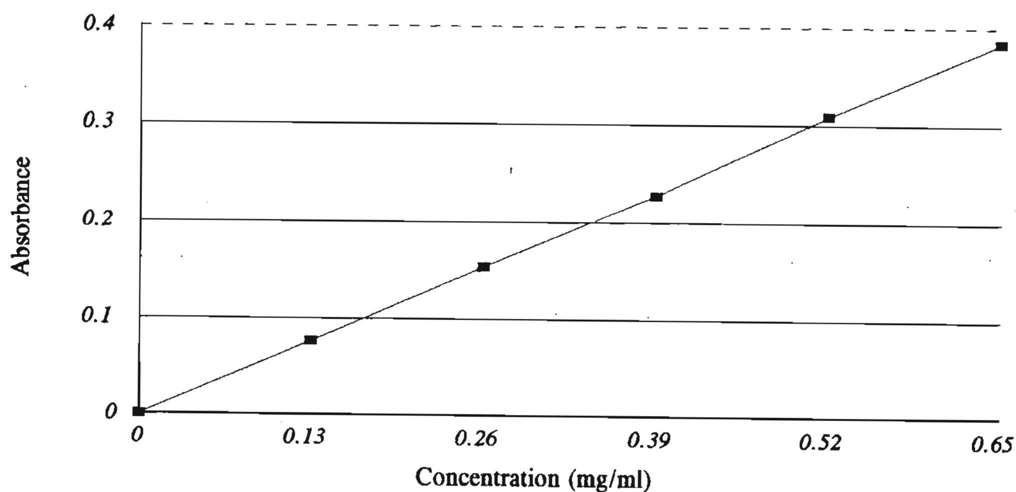
Figure 4.5 : Calibration Curve for Naproxen Sodium in Phosphate Buffer (pH 6.9)



R-squared = 0.9999

y = 0.6033x + 0.0008

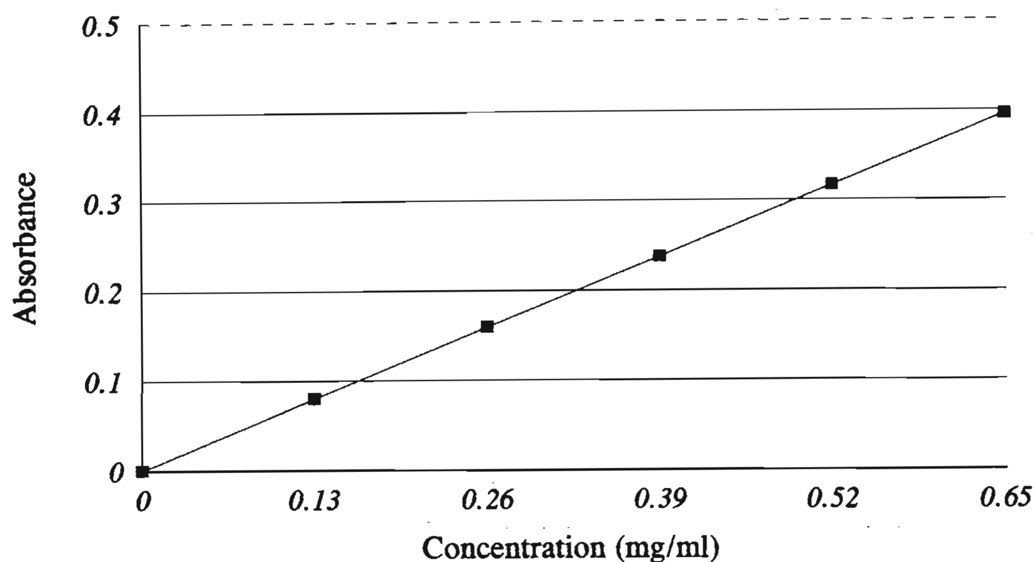
Figure 4.6 : Calibration Curve for Naproxen Sodium in Phosphate Buffer (pH 7.4)



R-squared = 0.9999

y = 0.5921x - 0.0008

Figure 4.7 : Calibration Curve for Naproxen Sodium in Phosphate Buffer (pH 8.0)



R-squared = 1.0000

y = 0.6068x + 0.0006

4.4.3.2 Computation of dissolution data

The Beckman Quant II Soft-Pac™ module computed the calibration curve equation which enabled automatic calculation of the unknown concentration of the dissolution samples. All calibration curves were constructed in units of milligrams per millilitres (mg/ml). Therefore, the values generated for the unknown concentrations of the dissolution samples were in the same units. These drug concentration values did not take into account the quantity of drug lost from each dissolution station due to sample withdrawal. Therefore, the quantity of drug dissolved had to be corrected for aliquots previously removed from the dissolution vessel and replaced with an equal volume of fresh dissolution medium.

The following example serves to illustrate the method of correction employed. Four aliquots of dissolution samples were withdrawn from the dissolution vessel as follows :-

i) At 1 hour, 5 ml of solution containing 0.153 mg/ml of drug was removed;

ii) At 2 hours, 5 ml of a solution containing 0.234 mg/ ml of drug was removed;

iii) At 3 hour, 5 ml of solution containing 0.306 mg/ml of drug was removed;

iv) At 4 hour, 5 ml of solution containing 0.351 mg/ml of drug was removed.

The quantity of drug present in the dissolution vessel at four hours was 315.90 mg (0.351 mg/ml × 900 ml). However, at one hour 0.765 mg (0.153 mg/ml × 5 ml), at two hours 1.170 mg (5 ml × 0.234 mg/ml) and at three hours 1.530 mg (5 ml × 0.306 mg/ml) of drug was removed as aliquots. Therefore, the corrected quantity of drug in solution at the end of 4 hours was 319.37 mg (315.90 mg + 0.765 mg + 1.170 mg + 1.530 mg).

To facilitate the ease of data computation and therefore eliminate undue time loss, and to minimize error during manual computation, the Quattro-Pro® version 6.0 for Windows computer software was used to construct a spreadsheet for the calculation of the percentage of drug released. The stepwise cell format of the spreadsheet is comprehensively represented in Appendix 7.

Selected *in vitro* dissolution data were subjected to statistical analyses, which was accomplished using Simstat® version 3.0 computer software.

4.5 PARTICLE SIZE ANALYSIS

Particle size distribution and mean particle diameter for various batches of naproxen sodium-cetostearyl alcohol microspheres was determined by means of standard sieves as stipulated in the USP.

The various batches of microspheres were weighed, placed on a nest of standard sieves ranging from 150 μm - 2000 μm in ascending order, and then mechanically vibrated for 10 minutes. The mass and percentage (% m/m) of each size fraction of sieved microspheres were determined and used to calculate the average diameter of the batch using the usual statistical formulae for normal distribution on the Quattro Pro® for Windows version 6.0. The standard deviation was used as an indication of the size distribution around the mean.

4.6 ELECTRON MICROSCOPY

Electron microscopic evaluations were performed on the naproxen sodium-cetostearyl alcohol microspheres and on ethylcellulose microcapsules of diclofenac sodium and naproxen sodium by scanning electron microscopy (SEM), energy dispersive x-ray microprobe analysis (EDX) and x-ray mapping.

4.6.1 Scanning Electron Microscopy

SEM was employed not only to evaluate the integrity of the surface morphology and cross-sectional characteristics of the naproxen sodium-cetostearyl alcohol microspheres and the ethylcellulose microcapsules of diclofenac sodium and naproxen sodium, but also to explain the drug release behaviour of these formulations. SEM was also applied to the naproxen sodium-cetostearyl alcohol microspheres prior to and after exposure to the dissolution medium.

Whole intact microcapsules and microspheres were mounted on brass stubs (12 mm in diameter) with double-backed carbon adhesive tape. Cross-sections of the microcapsules and microspheres were achieved by means of an ultramicrotome fitted with a glass knife. These cross-sections were then mounted on brass stubs with carbon adhesive tape in an horizontal plane. The mounted samples were sputter-coated under an argon atmosphere with gold-palladium for five minutes at 1.1 kV and a pressure of 0.1 torr in a Polaron SEM Coating Unit E5000. The Polaron E5000 is a direct contact sputter coating device. In a vacuum, the large inert molecules of an air/argon mixture are excited by establishing an electric field between the negative pole of the gold target and the positive pole of the sample. Particles from the atmosphere bombard the target and dislodge particles from the metal target which then surround the sample as cloud and cause a thin film of gold to be deposited.

Once coating was complete, the samples were removed from the sputter device and viewed under the Joel Scanning Electron Microscope, model 6100. The images were captured on Ilford Pan-F black and white 35 mm film.

4.6.2 Energy Dispersive X-ray Microprobe Analysis

EDX, a technique that is performed in conjunction with SEM, was employed to determine the elemental composition of the naproxen sodium-cetostearyl alcohol microspheres. A particular area or spot of the sample was selected via SEM and, by means of the backscatter detector, the elemental composition of the sample was determined. EDX was made possible via the application of the Noran Voyager® software system.

4.6.3 X-ray Mapping and line scans

X-ray mapping was performed to examine the drug distribution pattern of the microcapsules and microspheres. X-ray mapping is a technique which, like EDX, operates concomitantly

with SEM. The entire surface of a cross-section of the microcapsules and microspheres were scanned for the presence of certain metal ions. To determine the drug distribution pattern, the sodium ion that is present in diclofenac sodium and naproxen sodium was chosen to provide information with regard to the location and distribution of the drug within a single microcapsule or microspheres. A line scan through a cross-section of a microsphere of Batch NC81 was also perfomed to determine the drug distribution pattern.

X-ray mapping was performed on the following samples :-

i) naproxen sodium-cetostearyl alcohol microspheres

ii) naproxen sodium-ethylcellulose microcapsules

iii) diclofenac sodium-ethylcellulose microcapsules

4.7 DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetry was performed on the following samples :-

i) naproxen sodium powder

ii) cetostearyl alcohol

iii) naproxen sodium-cetostearyl alcohol 1:1 physical mixture

iv) Naproxen sodium-cetostearyl alcohol microspheres :-

a) Batch NC81
b) Batch NC85
c) Batch NC86

A Mettler Differential Scanning Calorimeter 20 (Mettler Instrumente AG 1988) equipped with a computerized data capture station was used to perform the analysis. Table 4.18 outlines the measurement conditions used in the study.

Table 4.18 : Operating Parameters for the Mettler Differential Scanning Calorimeter 20

OPERATING PARAMETER	SETTING
Starting temperature	0°C
Heating rate	10°C/min
End temperature	300°C
Reference	air atmosphere
Naproxen sodium mass (mg)	6.855
Cetostearyl alcohol mass (mg)	7.940
Physical mixture 1:1 mass (mg)	7.821
Batch NC81 mass (mg)	7.100
Batch NC85 mass (mg)	7.682
Batch NC86 mass (mg)	7.470

The sample size varied between 6 to 8 mg. All heating sequences were performed at a rate of 10°C/min and the samples were scanned from a starting temperature of 0°C to an end temperature of 300°C. In carrying out a scan, the sample was placed in an aluminum crucible and positioned on the sensor plate within the calorimetric chamber. The reference used for each analysis was air atmosphere. The respective endothermic-exothermic peaks were captured via the Mettler TC 11 TA Processor using the Graphware® computer software.

4.8 STABILITY STUDIES

4.8.1 The Basis of Stability Testing

Naproxen sodium-cetostearyl alcohol microspheres of Batch NC81 were subjected to stability studies over a three month period. From the data derived from drug loading determinations, a quantity of 610 mg of naproxen sodium-cetostearyl alcohol equivalent to 275 mg of naproxen sodium was placed within the body of a gelatin capsule (size 000) and capped firmly. After taking into account the number of capsules required for the various analytical procedures to be performed for the entire duration of the stability study, and after consideration of an excess allowance, a quantity of 60 filled gelatin capsules were placed in each of four amber-coloured bottles.

The following analytical procedures were performed on the encapsulated naproxen sodium-cetostearyl alcohol microspheres :-

i) *In vitro* dissolution testing as per USP

ii) High performance liquid chromatography

iii) Karl Fisher analysis

Dissolution studies were performed on the stability batches at predetermined intervals, for the duration of the stability study, to determine the effect of exposure to the various stability conditions on the drug release characteristics. For the purpose of dissolution testing, two gelatin capsules were emptied into each dissolution vessel in order to achieve a total of 550 mg of naproxen sodium in each dissolution vessel. High performance liquid chromatography was employed to assay the naproxen sodium content in the microspheres and to detect the formation of degradation or breakdown products of naproxen sodium. The data obtained from the accelerated stability testing was utilized to predict the shelf-life of the

naproxen sodium-cetostearyl alcohol microspheres. The Karl Fischer method was employed to determine the moisture content of the microspheres for the duration of the stability study. Data obtained from Karl Fischer analysis was used to quantify the possibility of having developed a hygroscopic drug delivery system and to ascertain the suitability of the storage vessel and closure based on their ability to prevent the ingress of moisture.

4.8.2 The Effect of Storage Conditions on Drug Release, Potency and Moisture Content

Six batches of microspheres were prepared and separated according to the various size ranges. Naproxen sodium-cetostearyl alcohol microspheres of the size range 851 - 1400 μm were subjected to storage under different conditions over a period of three months. Sixty capsules together with 2.0 g of activated silica gel in sachets (as desiccant) were placed in four round, amber bottles which were closed with bakelite screw-top lids. The bottles containing the encapsulated naproxen sodium-cetostearyl alcohol microspheres were each stored under the following storage conditions and monitored at predetermined time intervals:-

i) room temperature (21 ± 1°C)

ii) 40°C

iii) 37°C with 80% relative humidity

iv) low temperature (5 ± 1°C)

4.8.2.1 Storage at room temperature (21 ± 1°C)

Sixty capsules containing naproxen sodium-cetostearyl alcohol microspheres were placed in a tightly closed 200 ml amber bottle. The amber bottle was then placed in a cupboard at room temperature (21 ± 1°C).

4.8.2.2 Storage at 40°C

A thermostatically controlled Heraeus incubator, type FB420, maintained at 40°C was used to store the 200 ml tightly closed amber bottle containing 60 encapsulated naproxen sodium-cetostearyl alcohol microspheres and desiccant.

4.8.2.3 Storage at 37°C with 80% relative humidity

A completely saturated solution of ammonium chloride with a voluminous sediment was prepared in order to obtain a constant humidity of 80% in a well closed desiccator. The saturated solution was prepared in accordance with the Merck Tables for the Chemical Laboratory. The solution was then poured into the glass desiccator and the lid, after being coated with a thin layer of petroleum jelly, was replaced onto the body of the desiccator. A vacuum was created within the desiccator by applying a negative pressure for five minutes. The desiccator was then placed in an air-heated Gallenkamp oven, Model OV 160, maintained at 37°C and was allowed to equilibrate with its surroundings. A well-closed 200 ml amber bottle containing 60 encapsulated naproxen sodium-cetostearyl alcohol microspheres and a desiccant was supported on a circular porous porcelain stage above the saturated solution in the desiccator which was sealed. A vacuum was created within the desiccator by the application of a negative pressure for five minutes, after which time the desiccator was placed in the oven maintained at 37°C.

4.8.2.4 Storage at low temperature (5 ± 1°C)

A well-closed 200 ml bottle containing 60 encapsulated naproxen sodium-cetostearyl alcohol microspheres and desiccant were placed in a cold room maintained at 5 ± 1°C with a Koolmaster thermostat, Model 111570.

4.8.3 Analytical Procedures Employed During Stability Studies

The initial drug release characteristics, potencies and moisture content of the naproxen sodium-cetostearyl alcohol microspheres were determined prior to storage by *in vitro* dissolution testing, high performance liquid chromatography and Karl Fischer analysis, respectively. Capsules stored under the various conditions were removed at the end of 2, 4, 8 and 12 weeks following initial storage for dissolution testing, assay and moisture determination of the naproxen sodium-cetostearyl alcohol microspheres. Thereby, preliminary stability data on newly formulated naproxen sodium-cetostearyl alcohol microspheres could be ascertained.

4.8.3.1 *In vitro* dissolution testing

All *in vitro* dissolution tests performed for the purpose of stability determination were undertaken using the rotating paddle apparatus. The procedure for the dissolution testing was similar to that outlined in Section 4.4.2.1, except that the naproxen sodium-cetostearyl alcohol microspheres were emptied from the capsules directly into each of the four dissolution vessels.

4.8.3.2 High performance liquid chromatography (HPLC)

HPLC studies were conducted according to the procedure outlined in the USP (Appendix 3). The system employed for chromatographic analysis consisted of a Waters 590 programmable HPLC pump interfaced with the Autochrom 162 CSI and a Waters Lambda-Max Model 481 ultraviolet detector which was operated at a wavelength of 254 nm. HPLC separation was conducted in a Z-module radial compression chamber which housed the reversed-phase C_{18} chromatographic column. Prior to the commencement of HPLC analysis, the mobile phase which was prepared according to the specifications of the USP, was filtered and de-gassed using a Millipore® vacuum filtration system fitted with a Millipore® Type HV filter. The chromatographic system was then flushed with mobile phase for a period of two hours. Mobile phase was then circulated through the system to allow for the equilibration of the system. In performing a HPLC run, 20 μl volumes of standard preparation and assay preparation were separately injected into the chromatograph. All sample injections were performed in triplicate. The chromatograms were captured using the Apex Chromatography Workstation version 2.15 computer software system.

The quantity of naproxen sodium (in mg) contained in a single capsule of naproxen sodium-cetostearyl alcohol microspheres was calculated by the following formula :-

$$10C\left(\frac{R_u}{R_s}\right) \qquad \textit{(Equation 4.2)}$$

where C = concentration of USP Naproxen sodium RS in the standard preparation (μl per ml).

R_u and R_s = ratios of the response of the naproxen sodium peak to the internal standard peak obtained for the assay preparation and the standard preparation, respectively.

Table 4.19 outlines the working conditions for the HPLC studies.

Table 4.19 : Operating Conditions for HPLC Studies

OPERATING PARAMETER	SETTING
Mobile phase	Acetonitrile : Water : Glacial acetic acid 50 : 49 : 1
Solvent mixture	Acetonitrile : Water 90 : 10
Internal standard	butyrophenone
Flow rate of mobile phase	4 ml/min
Pressure	680-710 psi
Wavelength of maximum absorbance	254 nm
Sample volume injected	20 µl
Filters	0.45 µm Millex-HV Millipore®

4.8.3.2.1 *Shelf-life Prediction*

To determine the shelf-life of the formulation, the HPLC stability data was applied to an Arrhenius plot. Usually, a degradation of up to 10% of the active ingredient is allowed (90% of the active ingredient is still present)

$$A = A_0 e^{-kt} \qquad \textit{(Equation 4.3)}$$

Where A = amount of active at time t

A_0 = initial amount of active

k = rate constant of degradation

Therefore :

$$\log {}^{A_0}\!/_{A} = {}^{kt}\!/_{2.303} \qquad \text{(Equation 4.4)}$$

It therefore follows that $t_{90} = \log {}^{100}\!/_{90} \times {}^{2.303}\!/_{k}$

$$t_{90} = {}^{0.1054}\!/_{k} \qquad \text{(Equation 4.5)}$$

The rate constants for the degradation of drug at the various storage temperatures are determined from the following equation:

$$C_t = C_0 e^{-kt} \qquad \text{(Equation 4.6)}$$

Where : C_t = concentration of the active present at time t

C_o = initial concentration of the active

A plot of log C_t versus time yields a straight line for a drug that undergoes first order kinetics of degradation. Consequently:

$$k = slope \times 2.303 \qquad \text{(Equation 4.7)}$$

To determine the rate constant of degradation at 25°C, the Arrhenius equation is employed.

$$k = Ze^{-Ea/RT} \qquad \text{(Equation 4.8)}$$

Where: Z = frequency factor

E_a = energy of activation

R = gas constant

T = absolute temperature

Therefore:

$$\log k = \log Z - \frac{Ea}{2.303} \times \frac{1}{T} \qquad \text{(Equation 4.9)}$$

A plot of log k versus 1/T yields a straight line. By extrapolation, the rate constant of degradation at 25°C can be read off. Substitution of this rate constant into equation 4.5 enables the prediction of shelf-life.

4.8.3.3 Karl Fischer analysis

The moisture content of the naproxen sodium-cetostearyl alcohol microspheres were determined prior to and after 2, 4, 8 and 12 weeks of storage at each storage condition using the Orion AF8 Advanced Volumetric Karl Fischer Titrator. Moisture content determinations were performed in triplicate for each sample analyzed. Prior to the analysis of samples, the titrator was calibrated with 25 μl of freshly prepared deionized water. In performing an analysis, the entire contents of a capsule was weighed and placed into the titration chamber. The introduction of methanol, Karl Fischer reagent and the removal of waste from the titration chamber was achieved by means of an automatic, synchronized titrator. Table 4.20 outlines the calibration settings employed for all subsequent titrations.

Table 4.20 : Operating Parameters for Karl Fischer Analysis

OPERATING PARAMETER	SETTING
Stirrer speed	5
Step level	+10
End point level	12
End point time	15 secs
Constant steps/mg	152.16

Chapter Five

Results and Discussion

5.1 QUALITY CONTROL

5.1.1 Naproxen Sodium Powder

5.1.1.1 Identification

5.1.1.1.1 *Infrared Spectrophotometry*

The infrared absorption spectrum of a potassium bromide dispersion of the naproxen sodium powder was concordant with the spectrum of a similar preparation of USP Naproxen Sodium Reference Standard (Appendix 8).

5.1.1.1.2 *Ultraviolet Spectrophotometry*

The identification by ultraviolet spectroscopy indicated a wavelength of maximum absorbance of 271 nm (Appendix 9).

5.1.1.2 Assay

The assay, completed in triplicate (99.27%, 100.03%, 98.84%) gave a mean percentage purity of 99.37 ± 0.60%.

5.1.2 Synflex®

5.1.2.1 Identification

Synflex® tablets were positively identified by detecting the presence of naproxen sodium utilizing the Test for Sodium (USP XXIII, 1995) and high performance liquid chromatographic analysis.

5.1.2.2 Assay

The mean percentage purity of three determinations (101.18%, 102.24%, 102.17%) was found to be 101.86 ± 0.59%.

5.1.2.3 Dissolution

The mean cumulative drug release data and profile of naproxen sodium from Synflex® tablets in phosphate buffer pH 7.4, employing the rotating paddle method (4.4.2.1) are presented in Table 5.1 and Figure 5.1 respectively.

Table 5.1 : Mean Cumulative Percentages of Naproxen Sodium Released from Synflex® Tablets

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD
0.5	91.03 ± 3.04
1	94.52 ± 1.56
1.5	96.31 ± 1.18
2	97.33 ± 1.55
3	98.14 ± 1.19

* *Individual values for 4 replicate determinations are depicted in Appendix 10*

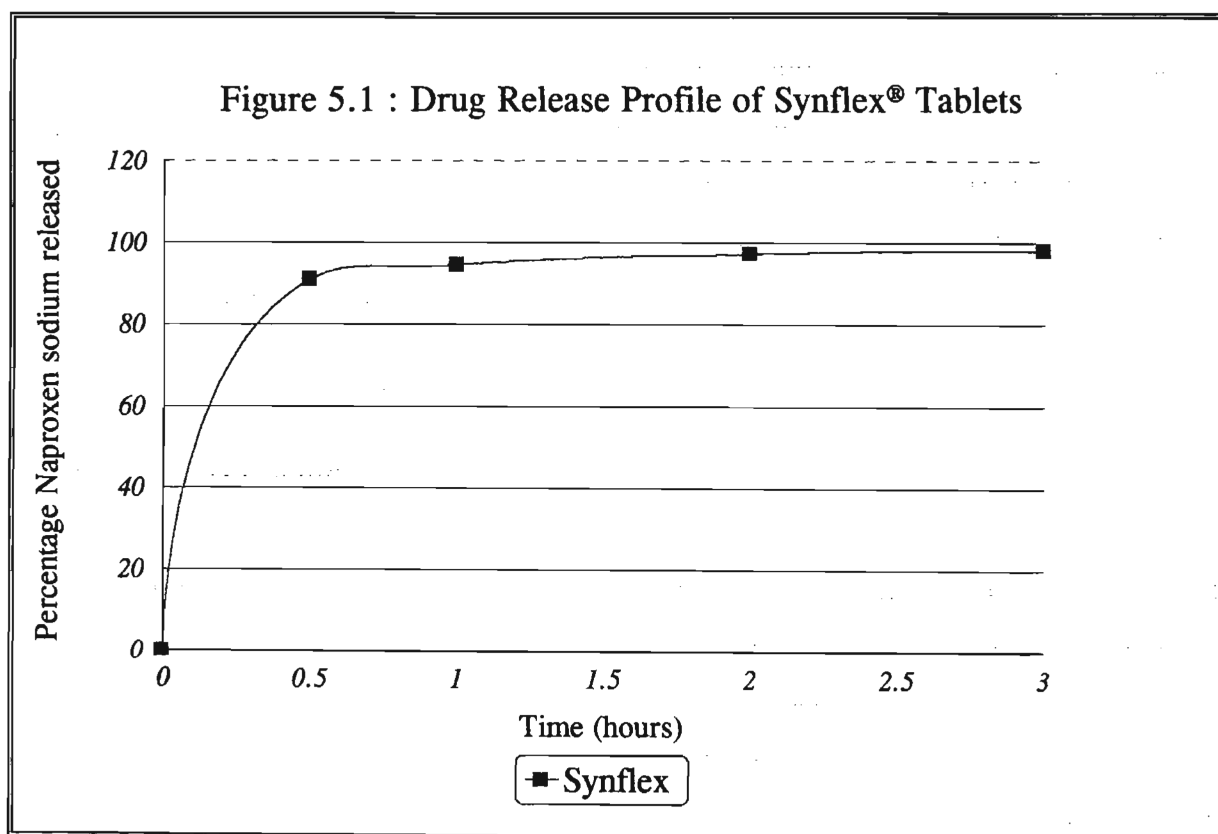


Figure 5.1 : Drug Release Profile of Synflex® Tablets

The dissolution of Synflex® tablets was compliant with USP requirements in that the mean cumulative percentage drug released at the end of 30 minutes in phosphate buffer pH 7.4 was 91.03% of the labelled amount of naproxen sodium. The results indicated that drug release from Synflex® tablets was extremely rapid, thus confirming the immediate release

nature of Synflex® tablets. A maximum of 98.44% of naproxen sodium was released from Synflex® tablets at the end of the 8 hour dissolution period (Appendix 10).

5.2 FORMULATION OF AN ORAL MODIFIED RELEASE PREPARATION OF NAPROXEN SODIUM

5.2.1 Formulation Variables for Coacervation Phase Separation

5.2.1.1 The Effect of Ethylcellulose

The effect of various ethylcellulose:drug ratios on the drug release profiles from diclofenac sodium microcapsules are graphically illustrated in Figure 5.2. It was observed, as anticipated, that drug release was inversely proportional to the polymer : drug ratio.

There was a significant retardation of the release of diclofenac sodium from microcapsules with a polymer:drug ratio of 1:1 (DE1) as compared to microcapsules with a 1:2 (DE2) polymer:drug ratio. The mean cumulative percentage drug released from diclofenac sodium microcapsules with different polymer:drug ratios presented in Table 5.2 shows a difference of 52.79% between the two formulations after 8 hours of dissolution. The difference in the amount of diclofenac sodium released after the 8 hour dissolution period from microcapsules with a polymer:drug ratios of 2:3 (DE3) and 1:2 (DE2) is 11.14%.

Table 5.2 : Mean Cumulative Percentages of Diclofenac Sodium Released from Microcapsules Prepared with Different Polymer:Drug Ratios

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	BATCH DE1 (1:1)	BATCH DE2 (1:2)	BATCH DE3 (2:3)
0.5	2.47 ± 0.17	14.91 ± 1.10	8.32 ± 0.17
1	4.81 ± 0.17	23.65 ± 1.37	16.70 ± 0.34
1.5	6.67 ± 0.15	29.60 ± 1.36	25.82 ± 0.29
2	8.89 ± 0.15	38.34 ± 1.98	35.55 ± 0.66
3	12.67 ± 0.24	50.94 ± 1.74	51.92 ± 0.62
4	15.82 ± 0.38	59.00 ± 1.07	65.44 ± 0.81
5	19.28 ± 0.48	65.98 ± 0.68	76.27 ± 1.67
6	22.99 ± 0.74	71.49 ± 1.41	83.43 ± 0.83
7	26.43 ± 0.71	78.54 ± 0.58	87.78 ± 2.71
8	29.98 ± 0.81	82.77 ± 0.92	93.91 ± 1.30

* *Individual values for 4 replicate determinations are depicted in Appendices 11 - 13 respectively*

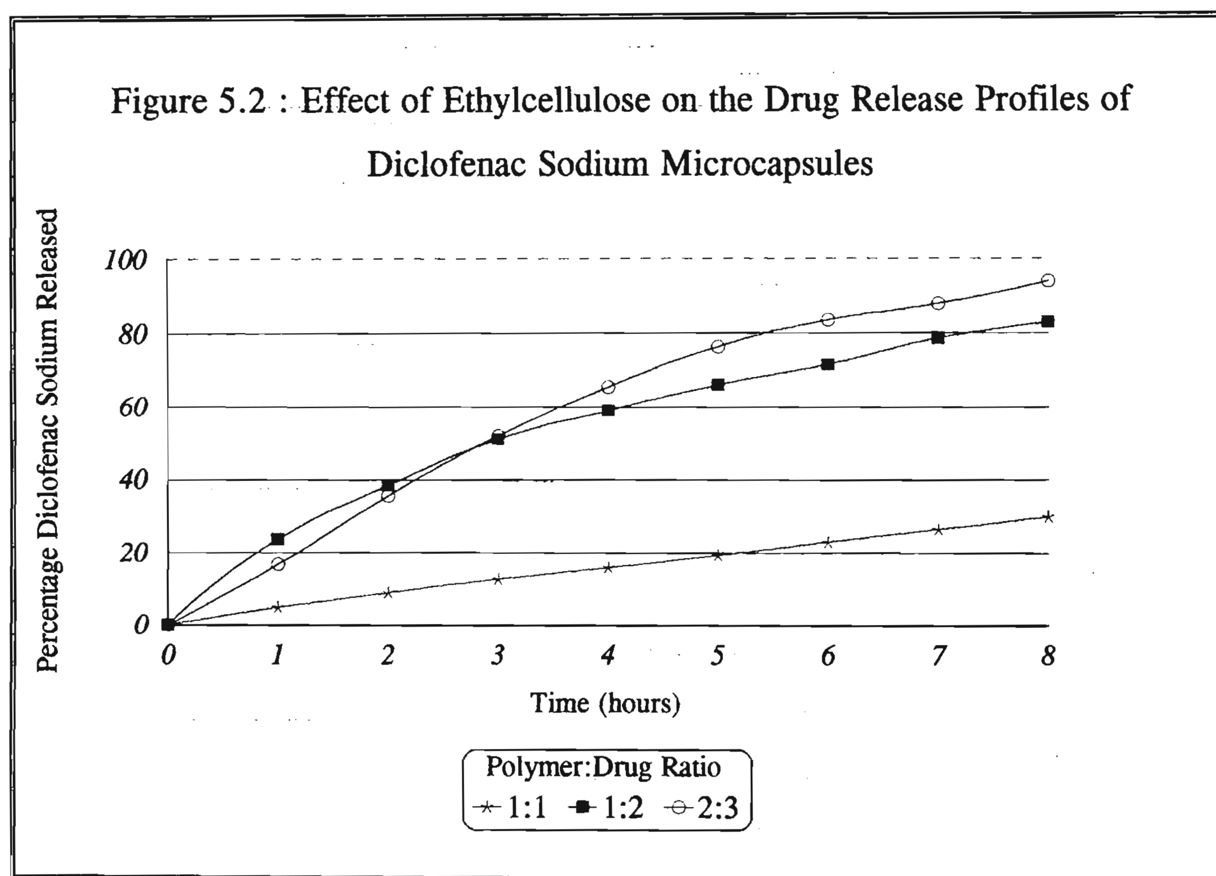
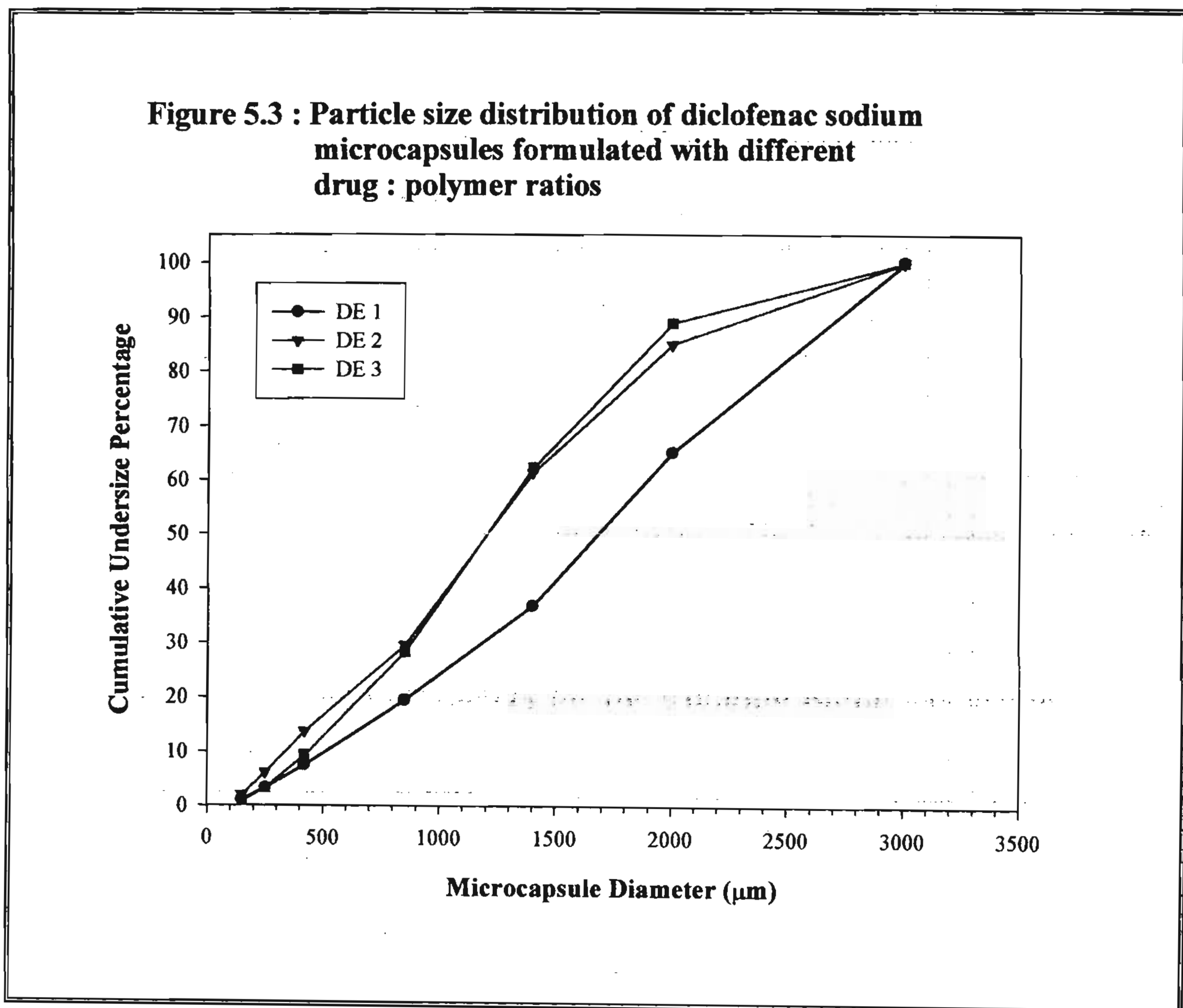


Figure 5.2 : Effect of Ethylcellulose on the Drug Release Profiles of Diclofenac Sodium Microcapsules

In addition to the contribution of ethylcellulose, the release of drug from diclofenac sodium microcapsules can also be related to the particle size distribution of the various formulations. Figure 5.3 graphically illustrates the particle size distribution of the different diclofenac sodium formulations.



The median particle size for Batches DE1, DE2 and DE3 was 1068 μm, 1210 μm and 1210 μm respectively. Batches DE2 and DE3 exhibit the same median particle size and almost similar drug release profiles which serves to confirm the correlation between median particle size and drug release. Therefore it is concluded that the drug release behaviour of diclofenac sodium microcapsules is a function of the particle size distribution and the polymer:drug ratio.

Table 5.3 : Mean Cumulative Percentages of Naproxen Sodium Released from Microcapsules Prepared with Different Polymer:Drug Ratios

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD			
	NE1 (1:2)	NE2 (2:3)	NE3 (1:1)	NE4 (2:1)
0.5	89.91 ± 0.78	85.69 ± 1.67	76.27 ± 0.79	36.58 ± 1.06
1	95.61 ± 2.07	90.67 ± 1.18	89.13 ± 0.16	61.62 ± 0.88
1.5	97.28 ± 2.14	97.79 ± 2.42	93.91 ± 0.53	67.36 ± 1.29
2	100.63 ± 0.83	96.90 ± 1.60	96.76 ± 0.42	73.62 ± 0.83
3	101.38 ± 1.69	101.88 ± 0.87	99.05 ± 0.57	80.28 ± 0.24
4	103.77 ± 1.54	104.97 ± 0.40	100.41 ± 0.54	83.75 ± 1.40
5	104.13 ± 0.62	107.50 ± 0.94	101.32 ± 0.23	84.77 ± 1.48
6	105.10 ± 0.89	109.02 ± 0.77	102.02 ± 0.22	86.25 ± 0.81

* *Individual values for 4 replicate determinations are depicted in Appendices 14 - 17 respectively*

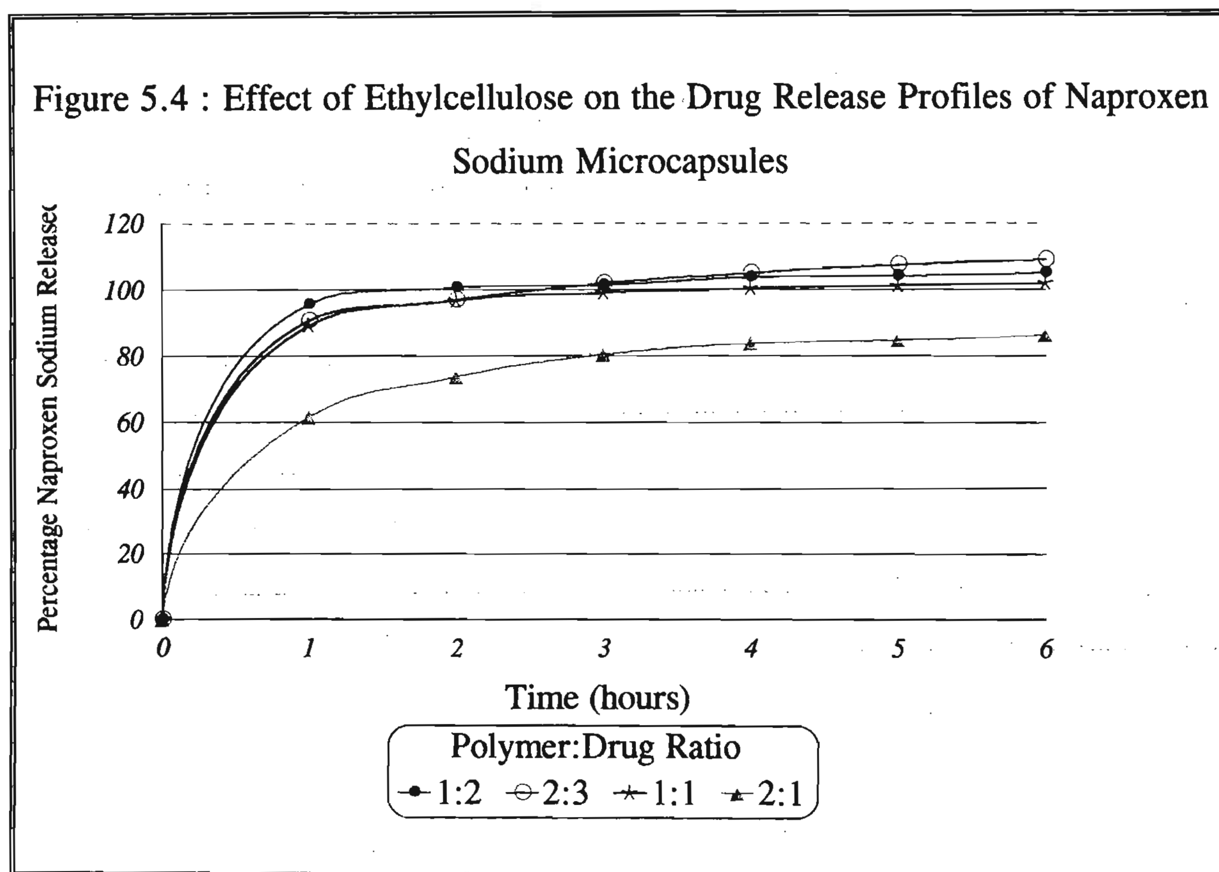


Figure 5.4 : Effect of Ethylcellulose on the Drug Release Profiles of Naproxen Sodium Microcapsules

No significant differences in the drug release profiles were observed for naproxen sodium microcapsules formulated with polymer:drug ratios of 1:2 (NE1) , 2:3 (NE2) and 1:1 (NE3). However, a significant difference of the release profile was observed between the above formulations and naproxen sodium microcapsules formulated with a 2:1 (NE4) polymer:drug ratio. The mean cumulative percentage released from naproxen sodium microcapsules with various polymer:drug ratios presented in Table 5.3 shows a maximum difference of 22.25% between the formulations with a polymer:drug ratio of 2:3 (NE2) and 2:1 (NE4).

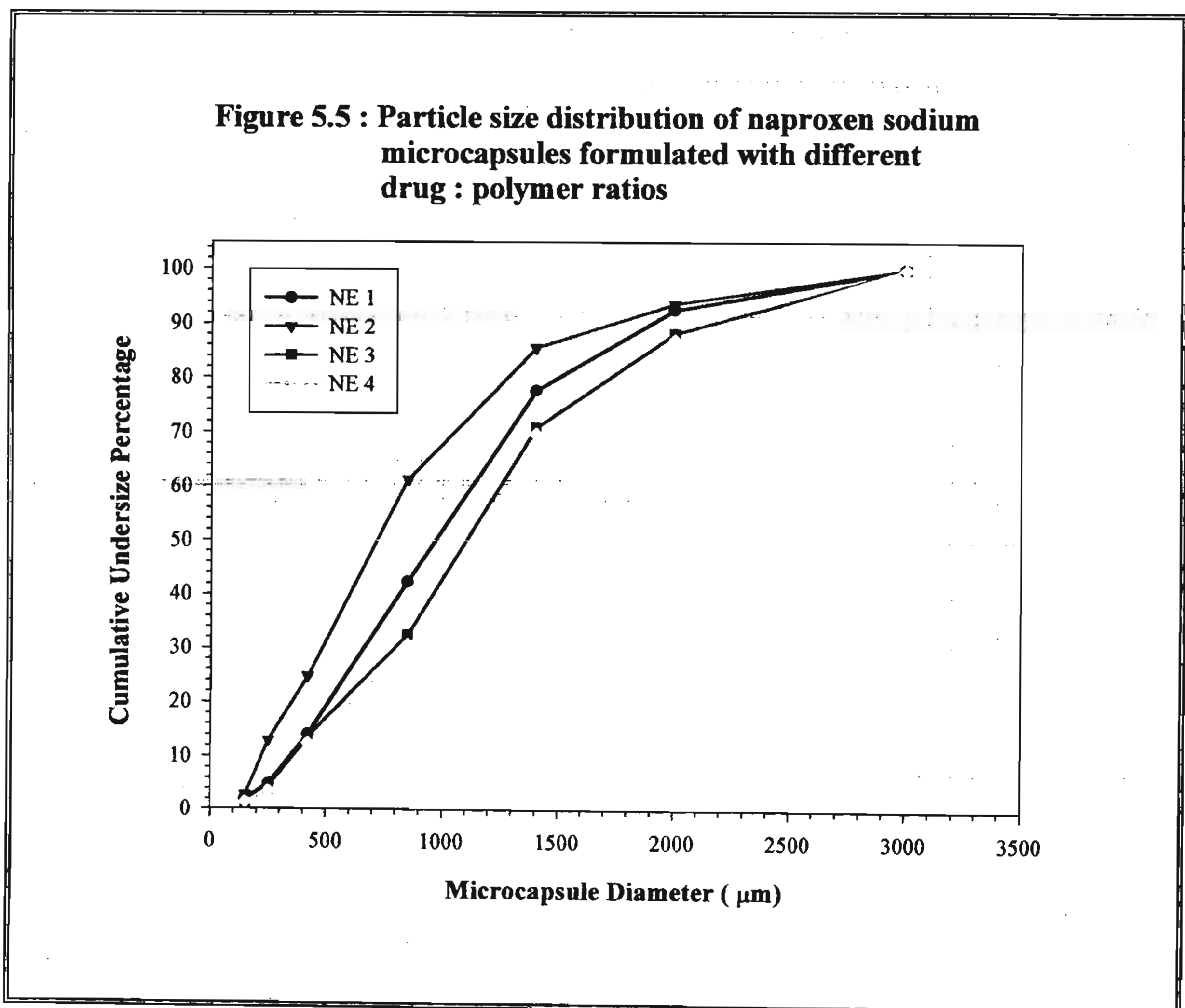


Figure 5.5 : Particle size distribution of naproxen sodium microcapsules formulated with different drug : polymer ratios

A cumulative frequency polygon was constructed for naproxen sodium microcapsules formulated with various polymer:drug ratios (Figure 5.5). The median particle size for Batches NE1, NE2, NE3 and NE4 was 970 μm, 720 μm, 1100 μm and 1120 μm

respectively. Therefore it may be concluded that the particle size contributes to a degree in the retardation of the release of naproxen sodium from ethylcellulose-walled microcapsules.

The findings of these studies are supported by studies carried out by Chemtob *et* al. (1986) and Aly *et al.* (1993). The above studies reported that an increase in the polymer:drug ratio resulted in a decrease in the release profile of a drug from ethylcellulose-walled microcapsules. Aly *et al.* (1993) noted a significant difference between formulations with a 1:1 and 2:1 polymer:drug ratio and no significant difference between formulations with a 1:1 and 1:2 polymer:drug ratio. These results support the findings of the present study.

Scanning electron microscopy studies carried out on ethylcellulose-walled microcapsules revealed that the microcapsules were irregularly shaped with rounded edges and uneven surfaces (Figure 5.6). Individual ethylcellulose-coated particles of drug could be observed and larger microcapsules were seen as aggregates of individually-coated drug particles (Figure 5.7). These results are in accordance with the results reported in other studies (Oya Alpar and Walters, 1981; Chemtob *et al.* 1986; Sviensson and Kristmundsdöttir, 1992).

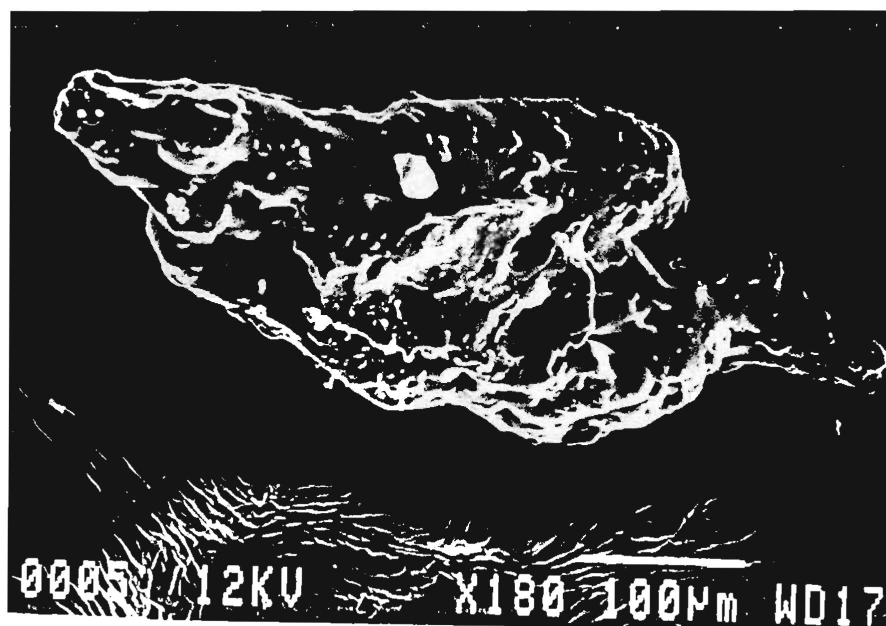


Figure 5.6 : Single Naproxen Sodium Microcapsule of Batch NE3

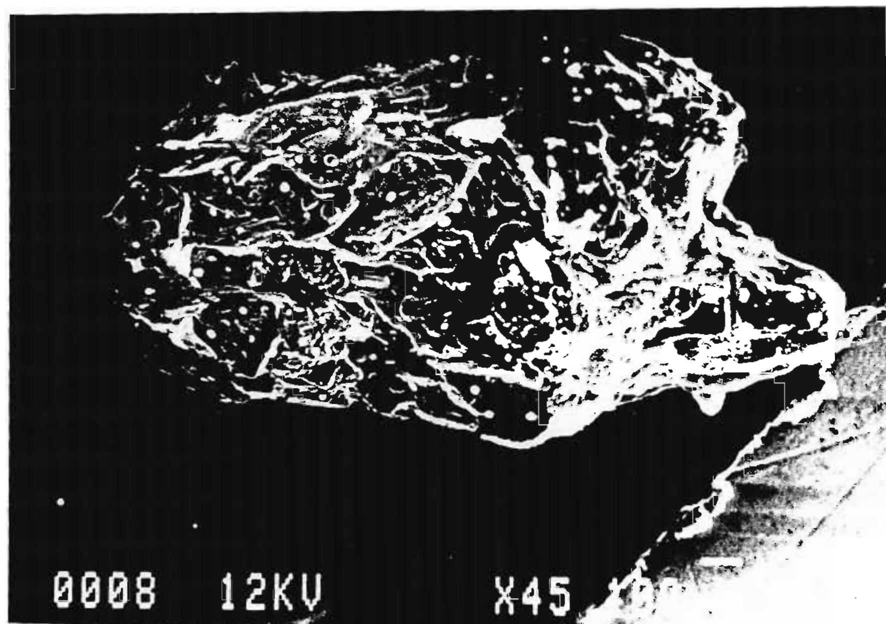


Figure 5.7 : Naproxen Sodium Microcapsule Depicted as an Aggregate of Individually-Coated Drug Particles

5.2.1.2 The Effect of Polyisobutylene (PIB)

The coacervation-inducing agent used in the present study, PIB, is a linear molecule of high molecular weight and functions as a protective colloid. The mean drug release data and profiles for the study utilizing PIB are depicted in Table 5.4 and Figure 5.8 respectively.

The addition of PIB to the formulation resulted in an increase in the release of diclofenac sodium from the ethylcellulose-walled microcapsules. A marked difference in the drug release profiles was observed between the batch prepared with 2% $^m/_m$ PIB and the batch prepared with 0% $^m/_m$ PIB. The $t_{80\%}$ for the formulation with 2% $^m/_m$ PIB was approximately 3 hours whereas this value was approximately 8 hours for the formulation with 0% $^m/_m$ PIB. These observations are consistent with the findings of Benita and Donbrow (1982), Chemtob *et al.* (1986), and Sviensson and Kristmundsdöttir(1992).

Table 5.4 : Mean Cumulative Percentages of Naproxen Sodium Released from Microcapsules Prepared with Different Quantities Of PIB

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD	
	DE2 (0%)	DE4 (2%)
0.5	14.91 ± 1.10	26.03 ± 3.67
1	23.65 ± 1.37	43.91 ± 6.51
1.5	29.60 ± 1.36	58.83 ± 8.21
2	38.34 ± 1.98	69.27 ± 7.44
3	50.94 ± 1.74	82.03 ± 6.50
4	59.00 ± 1.07	91.87 ± 5.19
5	65.98 ± 0.68	93.19 ± 3.14
6	71.49 ± 1.41	95.43 ± 2.34
7	78.54 ± 0.58	101.15 ± 0.53
8	82.77 ± 0.92	101.95 ± 0.68

* *Individual values for 4 replicate determinations are depicted in Appendices 12 and 18 respectively*

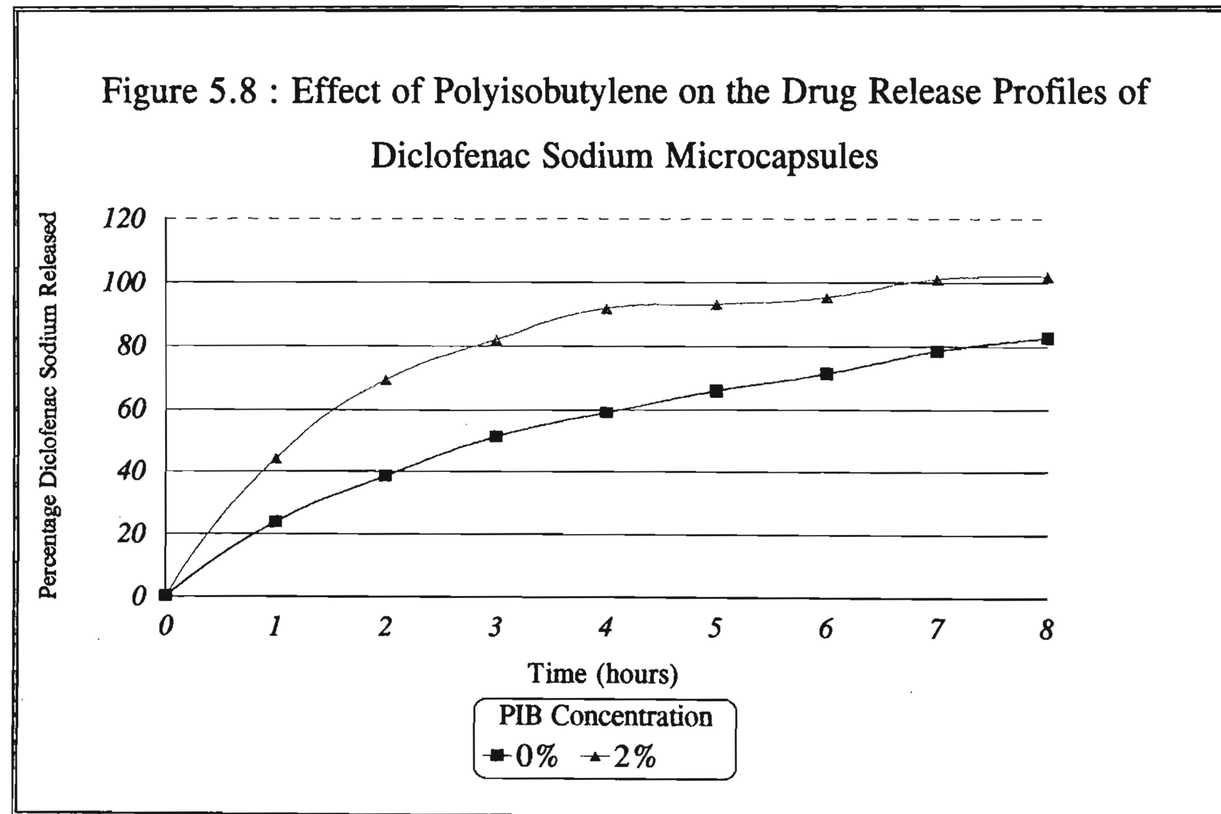


Figure 5.8 : Effect of Polyisobutylene on the Drug Release Profiles of Diclofenac Sodium Microcapsules

Microscopic evaluation of the microcapsules revealed that the surface of the microcapsules prepared without a protective colloid displayed a multiple-pore structure. Microcapsules prepared in the presence of PIB displayed a smooth, compact surface although the microcapsules remained irregularly shaped (Figure 5.9).

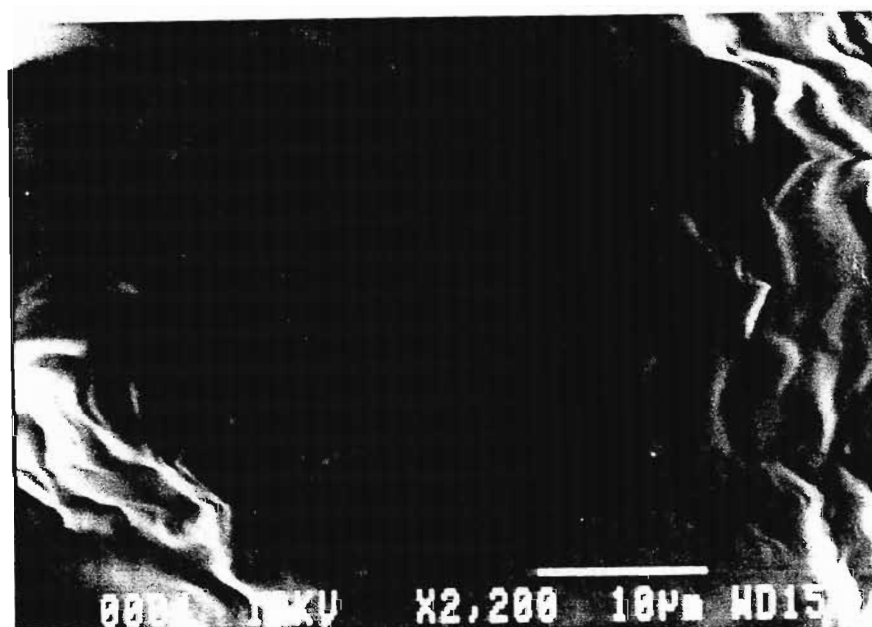
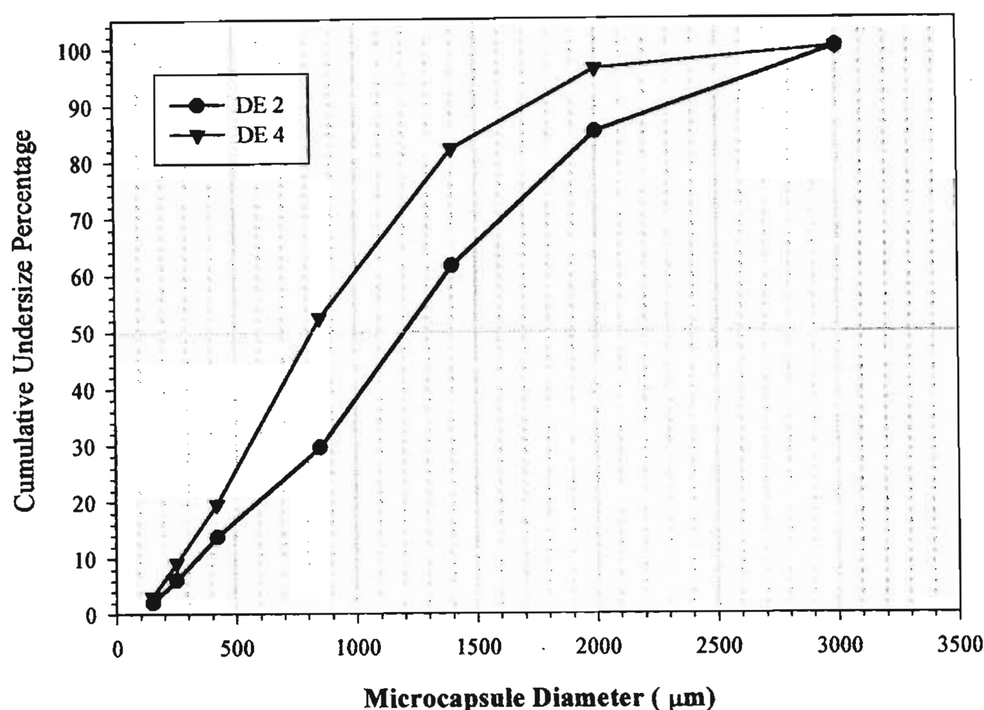


Figure 5.9 : Surface of a Diclofenac Sodium Microcapsule of Batch DE4

The results of particle size analysis indicated that the presence of PIB resulted in an overall decrease in the size distribution of the batch of microcapsules. The effect of PIB on the size distribution of the batches of microcapsules prepared with different concentrations of PIB is presented in Figure 5.10. The median particle size for Batches DE2 and DE4 was extrapolated from the cumulative frequency polygon and was calculated to be 1210 μm and 820 μm respectively. The increase in the release of drug from the microcapsules prepared in the presence of PIB can be attributed to a decrease in the overall size distribution of the microcapsules. A decrease in the size of microcapsules leads to an increase in the surface area of the microcapsule which results in an increase in the effective releasing area of the batch of microcapsules.

Figure 5.10 : Particle size distribution of diclofenac sodium microcapsules as a function of polyisobutylene concentration



5.2.2 Formulation Variables for the Meltable Aqueous Dispersion Technique

5.2.2.1 Optimization of drug loading

The potency of the naproxen sodium-cetostearyl alcohol microspheres was found to be influenced by the pH of the liquid manufacturing vehicle. Due to the high water solubility of the drug, the pH of the aqueous manufacturing vehicle markedly influenced the potency of the formulation. Initially, the pH of the aqueous manufacturing vehicle was adjusted to pH 3.0 with 1N hydrochloric acid. The encapsulation efficiency of the resultant microspheres was calculated to be 3.09% of the theoretical amount of drug. Subsequently,

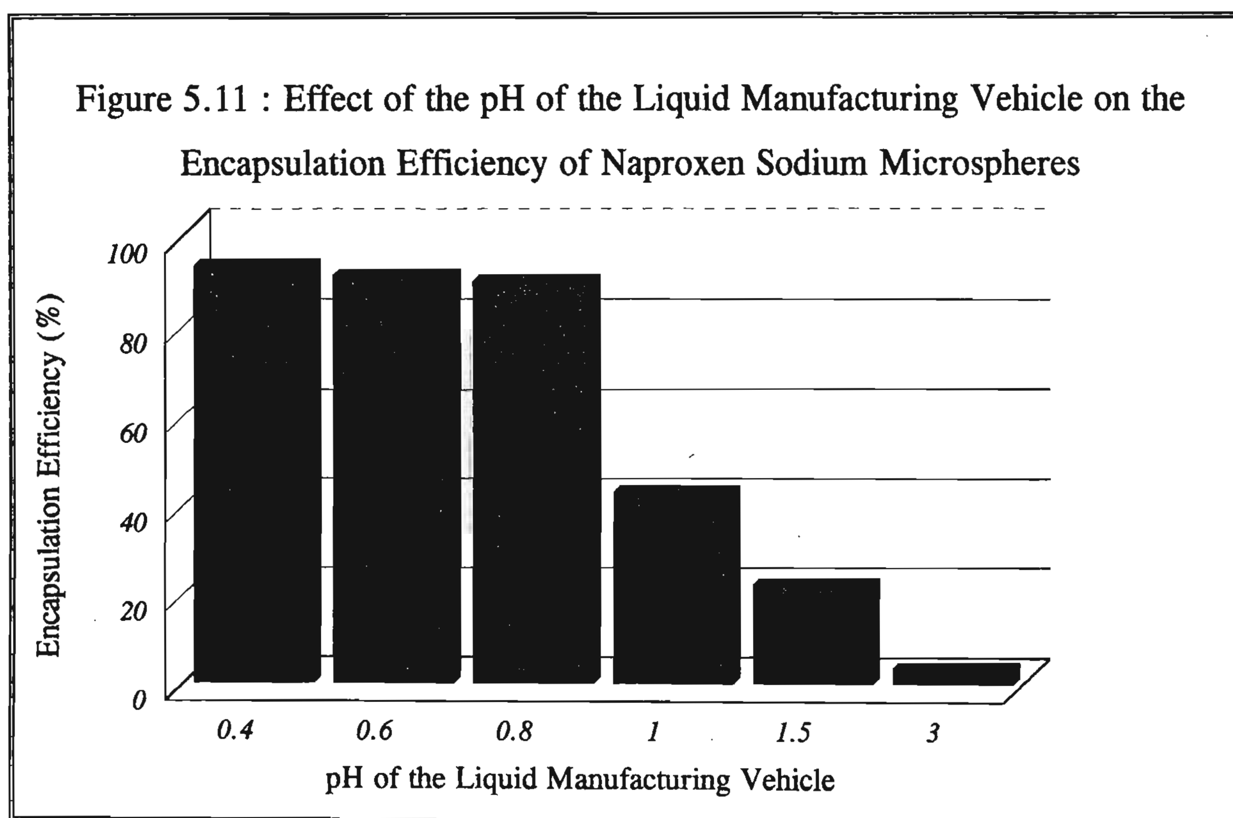
various pH's of the aqueous manufacturing vehicle was employed to optimize the encapsulation efficiency of the formulation. Table 5.5 depicts the encapsulation efficiency of the various batches that were formulated with different pH's of the aqueous manufacturing vehicle.

Table 5.5 : Influence of pH of the Aqueous Manufacturing Vehicle on the Potency of Naproxen Sodium-Cetostearyl Alcohol Microspheres

pH	ENCAPSULATION EFFICIENCY (%)				
	*S1	*S2	*S3	*S4	MEAN ± S.D
0.4	92.66	92.80	92.84	93.17	92.87 ± 0.22
0.6	91.25	90.41	90.40	90.45	90.63 ± 0.42
0.8	88.59	89.64	89.64	90.01	89.47 ± 0.61
1	42.70	42.49	42.83	42.46	42.62 ± 0.18
1.5	21.61	22.03	21.47	21.55	21.67 ± 0.25
3	3.10	3.14	3.05	3.07	3.09 ± 0.04

* *Individual values of 4 replicate determinations employed to calculate the mean*

Figure 5.11 : Effect of the pH of the Liquid Manufacturing Vehicle on the Encapsulation Efficiency of Naproxen Sodium Microspheres



The data presented in Table 5.5 clearly shows that the pH of the aqueous manufacturing vehicle has a marked effect on the potency of the formulation. An inversely proportional relationship exists between pH and encapsulation efficiency. This inverse relationship is illustrated in Figure 5.11. A decrease in the pH of the aqueous manufacturing vehicle results in an increase in the potency of the formulation. This observation can be correlated to the solubility of the drug in the aqueous manufacturing vehicle. Naproxen sodium displays pH-dependent solubility characteristics in aqueous media (Lund, 1994). As the pH of the aqueous medium is decreased, there is a corresponding decrease in the solubility of naproxen sodium in the medium. Consequently, a larger amount of drug is entrapped by the wax matrix. A decrease in the pH of the aqueous manufacturing vehicle below 0.8 resulted in a minimal increase in the encapsulation efficiency. This limiting effect at low pH's can be observed in Figure 5.11.

5.2.2.2 Optimization of particle size and shape

Visual observation of preliminary batches depicts the formation of large aggregates as the pH of the aqueous manufacturing vehicle was decreased. At the pH's employed to ensure an adequate encapsulation efficiency, irregularly-shaped particles with a diameter greater than 2 mm were produced. The results of the particle size analysis performed on Batch NC6 are presented in Figure 5.12. From the cumulative frequency polygon, the median (2230 μm) was extrapolated. Consequently, magnesium stearate was added to the formulation as an anti-tackiness agent to prevent aggregation and clumping. The addition of 1% magnesium stearate to the formulation markedly decreased the median particle size of the formulation.

Figure 5.12 : Particle size distribution of naproxen sodium microspheres formulated as a function of various formulation variables

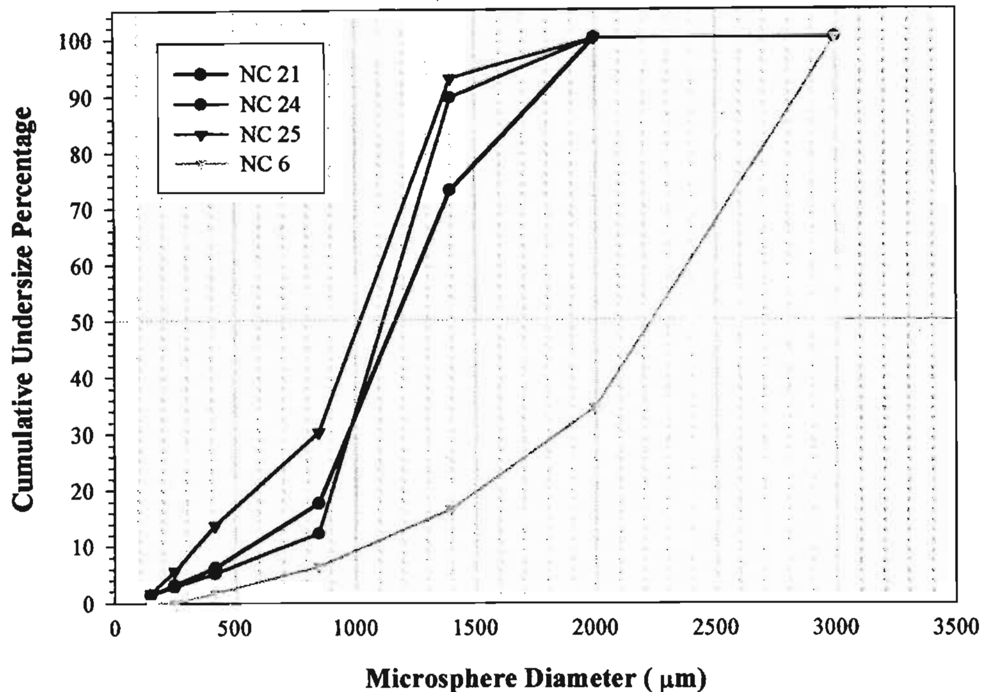


Figure 5.12 clearly depicts the effect on the particle size distribution for batches formulated with varying quantities of magnesium stearate. An increase in the concentration of magnesium stearate results in a decrease in the particle size distribution of the formulation. The median for Batches NC 21, NC 24 and NC 25 was determined to be 1180 μm, 1120 μm and 1030 μm, respectively.

The use of magnesium stearate as an anti-tackiness agent was also reported by Govender (1992). Johansson (1984) noted that magnesium stearate displayed the ability to form a hydrophobic film around granules. The same study showed that there were pronounced differences in anti-adhesive properties with increasing magnesium stearate concentrations initially with a convergence of values at high concentrations.

Desai *et al.* (1993) and Riepma *et al.* (1993) have also reported on the film forming properties of magnesium stearate.

The addition of magnesium stearate to the formulation resolved the problem of aggregation, but, the particles formed were irregularly shaped. Therefore, a combination of two surfactants (Span 20 and Tween 60) were added to the formulation in an attempt to produce spherical units. Various combinations of the two surfactants were evaluated and a combination of 1% $^m/_m$ Span 20 and 2% $^m/_m$ Tween 60 was selected for the formulation since this combination afforded a spherical preparation. Studies utilizing the hot melt microencapsulation technique with the incorporation of surfactants have been undertaken by various researchers (Benita *et al.*, 1986; Giannola *et al.*, 1993; Giannola *et al.*, 1995). These studies have shown that the optimum surfactant concentration when utilizing the polysorbates and the sorbitan esters is less than 3% $^m/_m$.

5.2.2.3 Effect of pH of the aqueous manufacturing vehicle

The pH of the aqueous manufacturing vehicle was observed to play a dual role in the formulation. Firstly, a decrease in the pH resulted in an increase in the encapsulation efficiency of the microspheres. It was also noted that a decrease in the pH served to retard the release of the drug from the formulation. Thus, it was imperative to determine the effect of the pH of the aqueous manufacturing vehicle on the release of the drug from the formulation.

The mean drug release data and profiles of the batches prepared with varying pH of the aqueous manufacturing vehicle are presented in Table 5.6 and Figure 5.13 respectively.

Table 5.6 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Prepared in Media of Varying pH

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	NC80 (pH 0.8)	NC81 (pH 0.6)	NC82 (pH 0.4)
0.5	24.97 ± 0.27	16.68 ± 0.31	18.12 ± 0.88
1	35.50 ± 0.17	24.05 ± 0.40	25.91 ± 1.47
1.5	44.82 ± 0.34	31.10 ± 0.34	33.05 ± 1.86
2	52.59 ± 0.34	37.20 ± 0.32	39.16 ± 1.83
3	64.17 ± 0.34	47.84 ± 0.51	47.36 ± 1.99
4	73.93 ± 0.37	56.69 ± 0.50	54.49 ± 2.42
5	81.90 ± 0.59	64.45 ± 0.72	61.00 ± 2.33
6	87.05 ± 0.26	72.41 ± 0.65	65.26 ± 2.09
7	91.94 ± 0.49	78.04 ± 0.65	69.83 ± 2.33
8	94.61 ± 0.24	83.21 ± 0.59	73.97 ± 2.30

* *Individual values for 4 replicate determinations are depicted in Appendices 19 - 21 respectively*

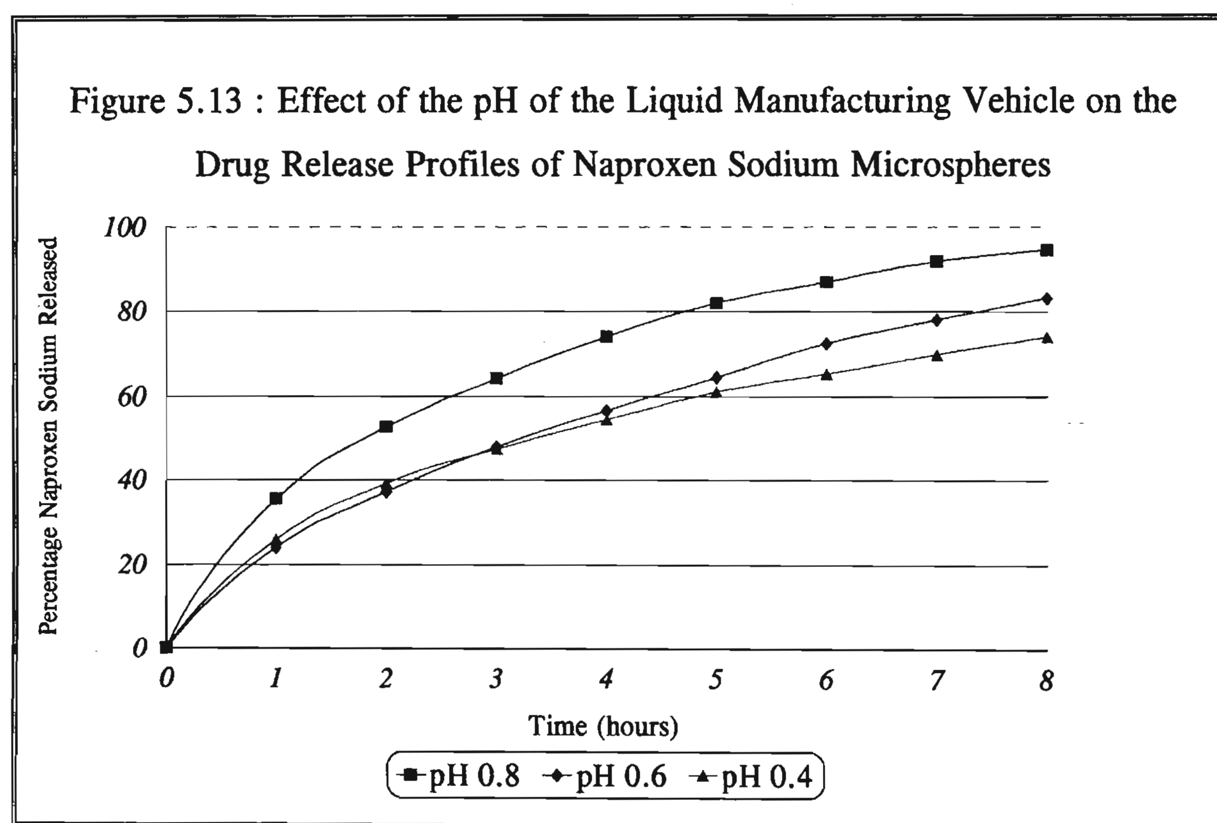


Figure 5.13 : Effect of the pH of the Liquid Manufacturing Vehicle on the Drug Release Profiles of Naproxen Sodium Microspheres

The drug release data reflects the marked effect that the pH of the acidified medium has on drug release characteristics. As the pH of the aqueous manufacturing vehicle is decreased, there is a corresponding decrease in the release profile of naproxen sodium. For the range investigated, a drug release difference of 20.64% was observed at the termination of the eight hour dissolution testing.

Figure 5.14 : Particle size distribution of naproxen sodium microspheres as a function of the pH of the acidified medium

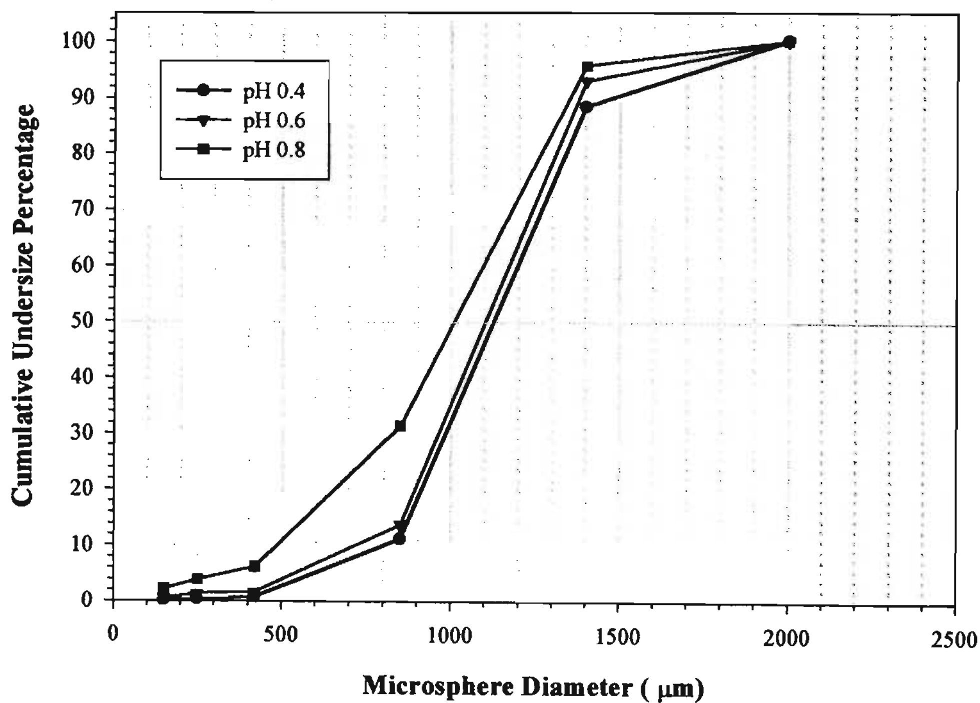


Figure 5.14 graphically illustrates the effect of the pH of the aqueous manufacturing vehicle on the particle size distribution of the various formulations. The median particle size for Batches NC80, NC81 and NC82 was 1010 μm, 1100 μm and 1120 μm respectively. An inversely proportional relationship is observed to exist between the pH of the aqueous

manufacturing vehicle and the median particle size. It is concluded that the increase in the median particle size contributes to the decrease in the drug release profile that was observed as the pH of the aqueous manufacturing vehicle was decreased.

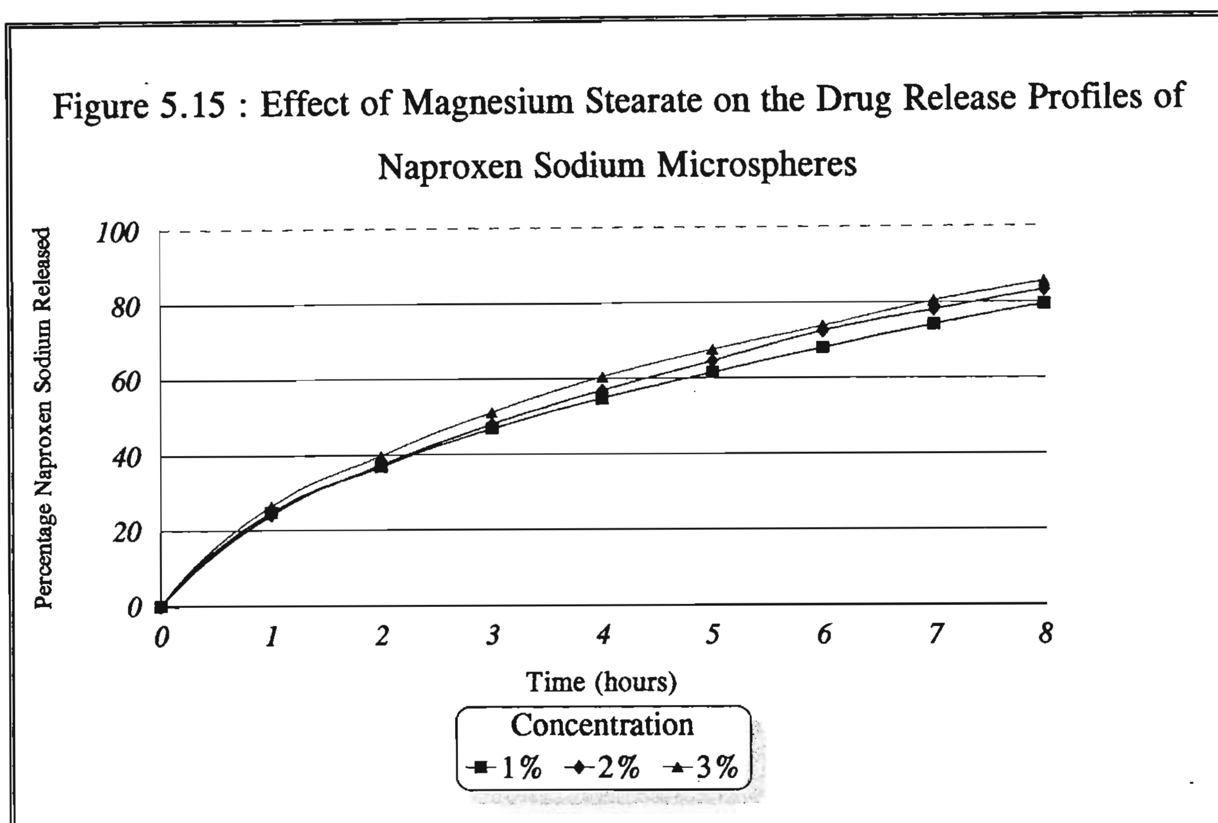
5.2.2.4 Effect of magnesium stearate

The effect of magnesium stearate on the drug release profiles and particle size distribution of the selected formulation was investigated. The mean drug release data and profiles of the batches prepared with 1, 2 and 3% $^{m}/_{m}$ concentrations of magnesium stearate are presented in Table 5.7 and Figure 5.15 respectively.

Table 5.7 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Prepared with Different Magnesium Stearate Concentrations

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	NC81 (2%)	NC83 (1%)	NC84 (3%)
0.5	16.68 ± 0.31	17.67 ± 0.16	18.12 ± 0.36
1	24.05 ± 0.40	24.76 ± 0.21	26.45 ± 0.29
1.5	31.10 ± 0.34	31.11 ± 0.08	33.71 ± 0.59
2	37.20 ± 0.32	36.81 ± 0.23	39.70 ± 0.70
3	47.84 ± 0.51	46.71 ± 0.39	51.05 ± 0.90
4	56.69 ± 0.50	54.53 ± 0.10	60.21 ± 0.92
5	64.45 ± 0.72	61.37 ± 0.29	67.49 ± 0.84
6	72.41 ± 0.65	67.92 ± 0.32	73.87 ± 1.05
7	78.04 ± 0.65	74.10 ± 0.65	80.33 ± 1.00
8	83.21 ± 0.59	79.49 ± 0.30	85.38 ± 1.18

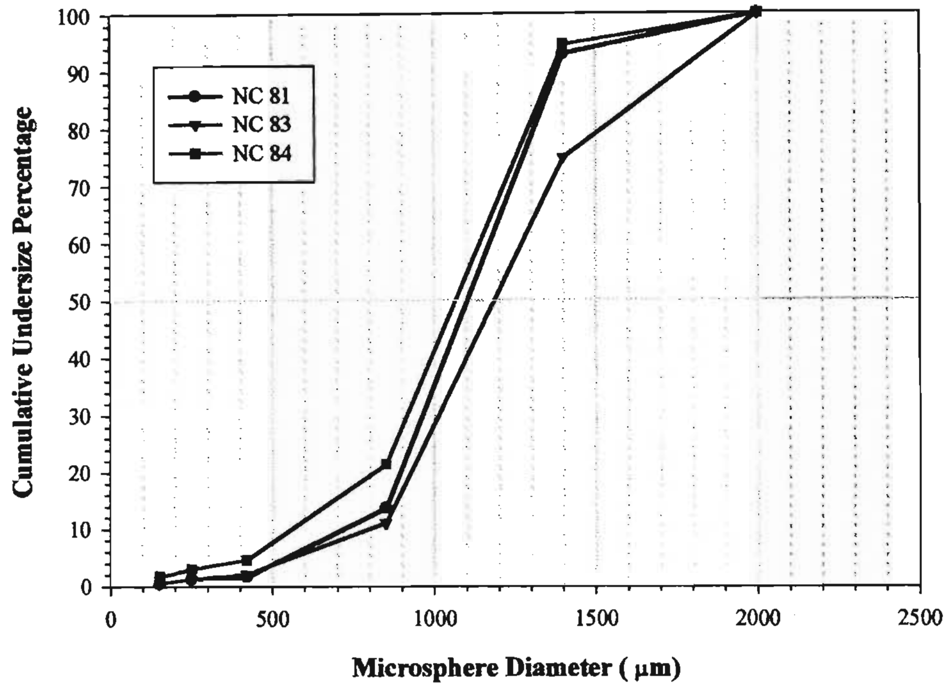
* *Individual values for 4 replicate determinations are depicted in Appendices 20, 22, and 23 respectively*



As the concentration of magnesium stearate was increased from 1 to 3% $^{m}/_{m}$, there was a simultaneous increase in the drug release profiles. However, this difference in the drug release profiles was observed to be minimal and may be considered to be pharmaceutically insignificant. The maximum difference in drug release at eight hours, for the range of concentrations investigated, was 5.89%.

Figure 5.16 illustrates the effect of magnesium stearate on the particle size distribution of the various formulations. From the graph, the median particle size of Batches NC81, NC 83 and NC84 were extrapolated and determined to be 1100 μm, 1190 μm and 1060 μm respectively. The increase in the drug release that was observed with an increase in the magnesium stearate concentration may be attributed to a decrease in the median particle size that was observed as the concentration of magnesium stearate was increased.

Figure 5.16 : Particle size distribution of naproxen sodium microspheres as a function of magnesium stearate concentrations



Govender (1992) reported a decrease in drug release with an increase in the concentration of magnesium stearate. The results of the present study is in direct contrast to these findings. Various other studies have reported on the retardant effect of magnesium stearate on drug release (Johansson, 1984; Desai *et al.*, 1993 and Perumal, 1996). Since magnesium stearate is a hydrophobic substance, a decrease in drug release with increasing magnesium stearate concentrations would be expected. Energy dispersive x-ray microprobe analysis performed in conjunction with scanning electron microscopy confirms the presence of a minute amount (0.83%) of magnesium ions in the microspheres (Figure 5.43). Therefore the expected decrease in the drug release profile with increasing magnesium stearate concentrations was not observed.

5.2.2.5 Effect of cetostearyl alcohol

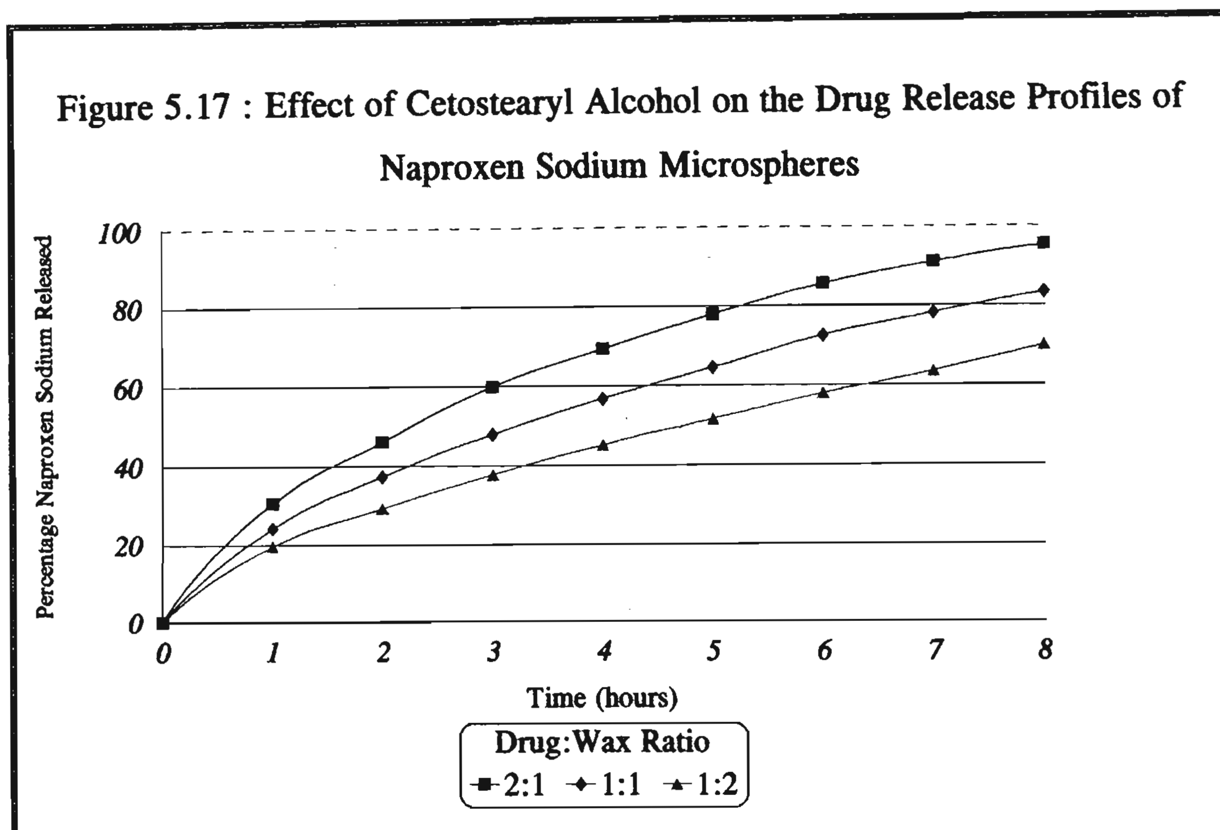
It was anticipated that by varying the relative amounts of naproxen sodium and cetostearyl alcohol, the rate of drug release may be affected. Therefore, the influence of different ratios of naproxen sodium:cetostearyl alcohol was investigated. The mean drug release data and profiles of the respective batches are presented in Table 5.8 and Figure 5.17 respectively.

Table 5.8 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Prepared with Different Drug:Wax Ratios

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	NC81 (1:1)	NC85 (2:1)	NC86 (1:2)
0.5	16.68 ± 0.31	20.41 ± 0.25	13.80 ± 0.58
1	24.05 ± 0.40	30.42 ± 0.44	19.48 ± 0.80
1.5	31.10 ± 0.34	39.35 ± 0.37	24.50 ± 0.94
2	37.20 ± 0.32	46.03 ± 0.21	29.09 ± 1.10
3	47.84 ± 0.51	59.82 ± 0.17	37.60 ± 1.57
4	56.69 ± 0.50	69.15 ± 0.32	45.04 ± 1.68
5	64.45 ± 0.72	77.75 ± 0.09	51.55 ± 2.02
6	72.41 ± 0.65	85.41 ± 0.39	57.92 ± 2.07
7	78.04 ± 0.65	90.87 ± 0.32	63.43 ± 2.20
8	83.21 ± 0.59	95.20 ± 0.41	69.87 ± 2.51

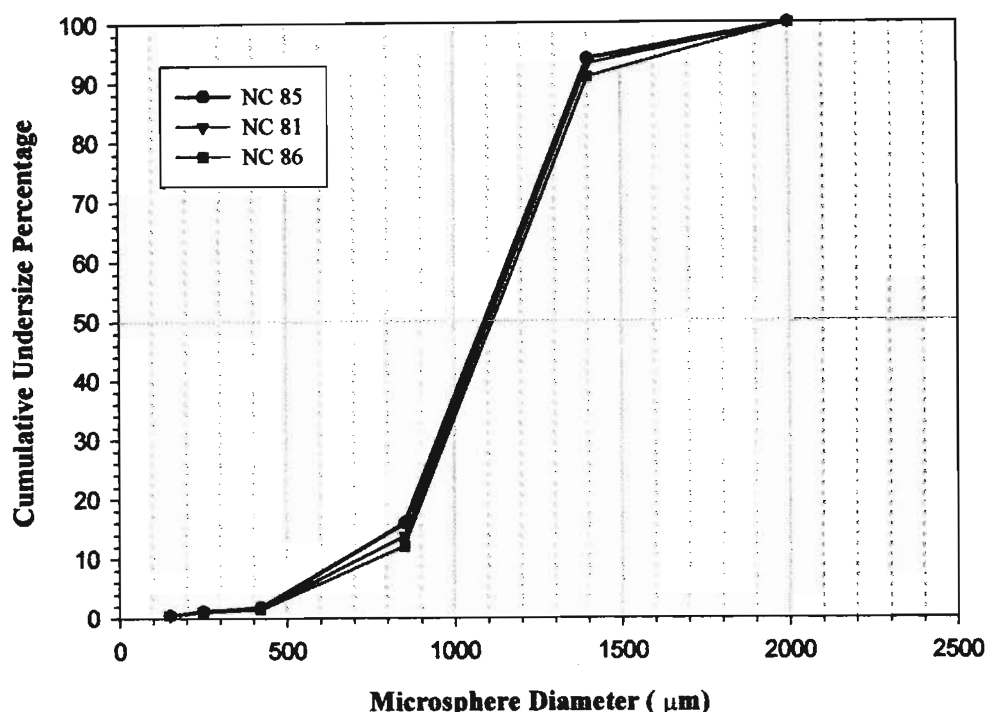
* *Individual values for 4 replicate determinations are depicted in Appendices 20, 24, and 25 respectively*

A decrease in the ratio of naproxen sodium:cetostearyl alcohol resulted in a decrease in the release of naproxen sodium from the microspheres. This was attributed to the presence of a more compact wax matrix and hence a greater degree of drug immobilization in the cetostearyl alcohol wax matrix. Consequently, diffusion of drug from the matrix would be retarded. A marked difference in drug release was observed between batches prepared from drug:wax ratios of 2:1 and 1:2 (Figure 5.17). The $t_{80\%}$ for the formulation with a 2:1 drug:wax ratio was approximately 5.5 hours whereas the $t_{80\%}$ for the formulation with a 1:2 drug:wax ratio was extrapolated to exist at approximately 10 hours.



Particle size analysis performed on the various batches show that the median particle size is not greatly affected by the drug:wax ratio. Figure 5.18 depicts the cumulative frequency polygons for batches prepared with varying quantities of cetostearyl alcohol. The median particle size for Batches NC81, NC85 and NC86 was determined to be 1100 μm, 1090 μm and 1120 μm respectively. A moderate increase in the median particle size is observed with an increase in the drug:wax ratio. This increase in the median particle size may also contribute to the retardation of drug release observed with decreasing drug:wax ratios.

Figure 5.18 : Particle size distribution of naproxen sodium microspheres for batches prepared with varying quantities of cetostearyl alcohol.



Wong *et al.* (1992) investigated the effect of varying amounts of drug and wax on the release of ibuprofen from cetostearyl alcohol matrices. The study reflected an increase in the release rates with increasing drug loading. However, it was observed that microspheres prepared with 20% $^{w}/_{w}$ and 30% $^{w}/_{w}$ ibuprofen loadings have unusually high release rates. The authors attributed this to the formation of a eutectic mixture between ibuprofen and cetostearyl alcohol. The findings of the present study correlate well with the study carried by Wong *et al.* (1992). It is postulated that the concentrations of cetostearyl alcohol and naproxen sodium employed in the present study were not in close proximity to the eutectic point, therefore a direct correlation between the drug:wax ratio and drug release was possible.

5.2.2.5.1 *Densities of Naproxen Sodium-Cetostearyl Alcohol Microspheres*

The densities of the naproxen sodium-cetostearyl alcohol microspheres formulated with varying drug:wax ratios were determined and are presented in Table 5.9. These density values were subsequently used to calculate the specific surface areas of the microspheres. It is observed from Table 5.9 that as the concentration of drug in the microspheres increase, there is a corresponding increase in the density of the microspheres. Wong *et al.* (1992) reported an increase in the density of cetostearyl alcohol pellets as the ibuprofen composition increased.

The density of microspheres formulated with a 1:1 drug:wax ratio was 0.956 g/cm^3. Consequently, it is anticipated that the microsphere will float in the stomach fluid. However, visual observation of the dissolution process in simulated gastrointestinal milieu reveals that the microspheres sediment to the base of the dissolution vessel after 30 minutes of dissolution. It is postulated that the perfusion of the dissolution medium into the microsphere and the failure of the system to release drug at a low pH results in an increase in the apparent density of the microsphere. Therefore it is concluded that the microspheres will not behave as a floatable dosage form *in vivo*.

Table 5.9 : Sequential Data Employed for the Determination of the Naproxen Sodium-Cetostearyl Alcohol Microsphere Densities

BATCH * (drug:wax)	SAMPLE WEIGHT (g)				PRE-HCl WEIGHT (g)**	POST-HCl WEIGHT (g) ***				HCl WEIGHT DISPLACED (g)				VOLUME OF HCl DISPLACED (cm³)				DENSITY (g/cm³)			
	W1	W2	W3	MEAN ± SD		W4	W5	W6	MEAN ± SD	W7	W8	W9	MEAN ± SD	V1	V2	V3	MEAN ± SD	D1	D2	D3	MEAN ± SD
NC81 *(1:1)	1.0005	1.0002	1.0002	1.0003 ± 0.0002	50.191	48.956	48.956	48.957	48.956 ± 0.001	1.235	1.235	1.234	1.235 ± 0.001	1.047	1.047	1.046	1.047 ± 0.001	0.956	0.955	0.956	0.956 ± 0.001
NC85 *(2:1)	1.0005	1.0005	1.0007	1.0006 ± 0.0001		49.027	49.026	49.027	49.027 ± 0.001	1.164	1.165	1.164	1.164 ± 0.001	0.986	0.986	0.987	0.986 ± 0.001	1.015	1.015	1.014	1.015 ± 0.001
NC86 *(1:2)	1.0003	1.0002	1.0001	1.0002 ± 0.0001		48.902	48.902	48.901	48.902 ± 0.001	1.289	1.289	1.290	1.289 ± 0.001	1.092	1.092	1.093	1.092± 0.001	0.916	0.916	0.915	0.916 ± 0.001

* *Drug:wax ratios used to prepare the respective batches*

** *Weight of hydrochloric acid (1N HCl) in tared pycnometer*

*** *Weight of HCl in tared pycnometer-sample vessel*

5.2.2.5.2 *Specific Surface Areas of the Naproxen Sodium-Cetostearyl Alcohol Microspheres*

Surface area determinations of naproxen sodium-cetostearyl alcohol microspheres were conducted to quantify their relationship with their respective densities.

Table 5.10 depicts the calculated mean specific surface area values for batches of microspheres prepared with varying drug:wax ratios. The mean diameter was the same for all determinations since microspheres of the size range 851-1400μm was employed for all determinations.

Table 5.10 : Correlation Between Density and Mean Specific Surface Area

BATCH *(drug:wax)	MEAN DENSITY (g/cm^3)	MEAN SPECIFIC SURFACE AREA (cm^2/g)
NC86 (1:2)	0.916 ± 0.001	58.22 ± 0.001
NC81 (1:1)	0.956 ± 0.001	55.78 ± 0.001
NC85 (2:1)	1.015 ± 0.001	52.24 ± 0.001

* *Drug:wax ratio used to prepare the respective batches*

It is clearly evident that an increase in the density of the microspheres resulted in a decrease in the mean specific surface area. However, the expected correlation between the mean specific surface area and drug release was not observed. Different quantities of microspheres were used in the dissolution studies so as to maintain the quantity of naproxen sodium constant. When a constant amount of drug is employed in dissolution testing, a correlation between mean specific surface area and drug release may not be elucidated. Therefore, surface area was corrected for using the correction factor $W_1\rho_2/W_2\rho_1$ where W_1 and W_2 are the weights of the microspheres with a 1:1 drug:wax ratio and microspheres

with any other drug:wax ratio, respectively, and ρ_1 and ρ_2 denote the corresponding densities (Wong *et al.*, 1992).

Table 5.11 : Corrected Densities and Mean Specific Surface Area Values

BATCH *(drug:wax)	MEAN DENSITY (g/cm^3)	MEAN SPECIFIC SURFACE AREA (cm^2/g)
NC86 (1:2)	1.416	37.66
NC81 (1:1)	0.956	55.78
NC85 (2:1)	0.724	73.66

* *Drug:wax ratio used to prepare the respective batches*

From Table 5.11, it is clearly evident that a direct relationship exists between the corrected mean specific surface area and drug release.

5.2.2.6 Effect of particle size

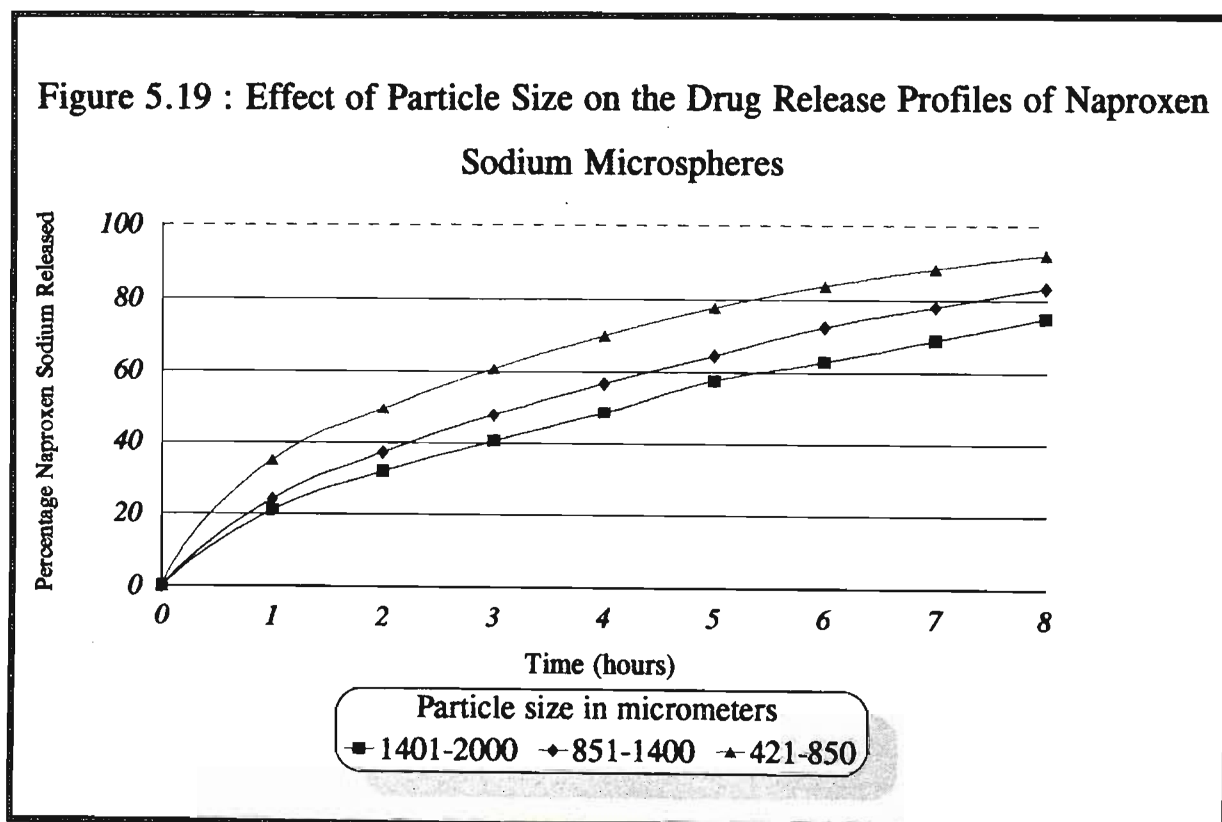
Batch NC81 was selected for the purpose of examining the influence of microsphere size on the *in vitro* drug release rate. The mean drug release data and profiles for the various size ranges of microspheres of Batch NC81 are presented in Table 5.12 and Figure 5.19 respectively.

Table 5.12 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres of Different Mean Diameters

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	421 - 850 μm	851 - 1400 μm	1401 - 2000 μm
0.5	24.07 ± 0.31	16.68 ± 0.31	14.55 ± 0.31
1	34.96 ± 0.60	24.05 ± 0.40	20.93 ± 0.19
1.5	42.23 ± 0.72	31.10 ± 0.34	26.65 ± 0.34
2	49.52 ± 0.75	37.20 ± 0.32	31.91 ± 0.50
3	60.65 ± 0.88	47.84 ± 0.51	40.51 ± 0.49
4	69.86 ± 0.90	56.69 ± 0.50	48.67 ± 0.61
5	77.73 ± 0.95	64.45 ± 0.72	57.57 ± 0.52
6	83.63 ± 0.75	72.41 ± 0.65	62.79 ± 0.50
7	88.38 ± 0.89	78.04 ± 0.65	68.78 ± 0.49
8	92.09 ± 0.88	83.21 ± 0.59	74.96 ± 0.56

* *Individual values for 4 replicate determinations are depicted in Appendices 26, 20, and 27 respectively*

Figure 5.19 : Effect of Particle Size on the Drug Release Profiles of Naproxen Sodium Microspheres



An inverse relationship was observed to exist between particle size and the rate of drug release. Microspheres in the size range 421-850 μm displayed a rapid release profile whilst microspheres of size range 1401-2000 μm released drug at a slower rate. The effect of particle size on drug release is attributed to a decrease in the effective releasing area as particle size increases. Furthermore, in the case of larger particles, the diffusional path length is increased. Consequently, larger microspheres release drug at a slower rate than smaller microspheres.

Perumal (1996) reported similar findings with regard to the release of drug from microspheres of different size ranges. Other studies that support the findings of the present study include studies carried out by Dubernet *et al.* (1987), Das and Gupta (1988) and Al-Kassas *et al.* (1993). Particle size analysis revealed that approximately 80% of the microspheres from Batch NC81 were contained in the size range 851-1400 μm. The drug release data for this size range showed that 24.05 ± 0.40% and 83.21 ± 0.59% of naproxen sodium was released in 1 and 8 hours respectively. Therefore, the size range 851-1400 μm was selected for further investigations.

5.3 SELECTION OF A FORMULATION DISPLAYING DESIRABLE MODIFIED RELEASE CHARACTERISTICS

The application of the meltable aqueous dispersion technique to naproxen sodium required modification of the formulation and optimization of different variables. Consequently, various batches were considered for the preparation of different batches of naproxen sodium-cetostearyl alcohol matrices. In keeping with the objectives of the study, a formulation was selected for evaluation and characterization.

Batch NC81 was selected to evaluate the meltable aqueous dispersion technique and to characterize the release profile of the drug. The selection of Batch NC81 was justified on the basis of the following results:-

1) Batch NC6 consisted of a large particle size due to aggregation of wax globules during the formulation process. Furthermore, these particles were irregularly-shaped. Thus Batch NC6 was considered to be undesirable since the irregular shape of the wax matrices would lead to erratic release of drug. Furthermore, a particle size greater than 2 mm would not be suitable to achieve the objectives of a multiple-unit preparation.
2) A formulation containing 2% $^{m}/_{m}$ magnesium stearate was discovered to be suitable since it afforded a median particle size of 1100 μm and a larger fraction of the formulation contained within the size range 851-1400 μm. Batches formulated with 1% $^{m}/_{m}$ magnesium stearate had a larger median particle size and a wider particle size distribution whereas, batches formulated with 3% $^{m}/_{m}$ magnesium stearate had a smaller median particle size and a wider particle size distribution.
3) A formulation containing 2% $^{m}/_{m}$ Tween 60 and 1% $^{m}/_{m}$ Span 20 was selected since this combination afforded a preparation of adequate sphericity.
4) Apart from the implications on drug release, a 1:1 drug:wax ratio was suitable for the preparation technique. A 2:1 ratio of drug:wax resulted in a highly viscous dispersion of drug in the melted wax which resulted in problematic introduction of the melt into the aqueous manufacturing vehicle. Conversely, a 1:2 drug wax ratio produced a dispersion of low viscosity which aided pouring during formulation. However, the low viscosity led to sedimentation of the drug resulting in an uneven distribution of drug in the microspheres. Furthermore, due to the larger dose required, a drug:wax ratio lower than 1:1 would be cumbersome to administer.
5) Batch NC81 released 24.05 ± 0.40% in 1 hour and 83.21 ± 0.59% in 8 hours.

5.4 REPRODUCIBILITY STUDY

To confirm the reproducibility of the meltable aqueous dispersion technique, a study was conducted whereby drug release characteristics of different lots of Batch NC81 were compared. The mean drug release data and profiles of Batches NC81, NC81a and NC81b are depicted in Tables 5.13 and 5.14 and Figures 5.20 and 5.21 respectively.

Table 5.13 : Comparison of the Drug Release Profiles of Batches NC81a and NC81b with Control Batch NC81

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	NC81	NC81a	NC81b
0.5	16.68 ± 0.31	16.18 ± 0.10	17.96 ± 0.21
1	24.05 ± 0.40	24.74 ± 0.21	26.20 ± 0.27
1.5	31.10 ± 0.34	32.65 ± 0.39	33.91 ± 0.09
2	37.20 ± 0.32	38.15 ± 0.47	39.99 ± 0.37
3	47.84 ± 0.51	48.99 ± 0.49	50.31 ± 0.27
4	56.69 ± 0.50	59.82 ± 0.61	59.83 ± 0.35
5	64.45 ± 0.72	66.97 ± 0.44	67.93 ± 0.19
6	72.41 ± 0.65	73.35 ± 0.63	75.01 ± 0.01
7	78.04 ± 0.65	78.78 ± 0.46	81.31 ± 0.19
8	83.21 ± 0.59	83.46 ± 0.79	86.00 ± 0.27

* *Individual values for 4 replicate determinations are depicted in Appendices 20, 28, and 29 respectively*

Figure 5.20 : Comparison of the Drug Release Profiles of Lots NC81a and NC81b with Control Batch NC81

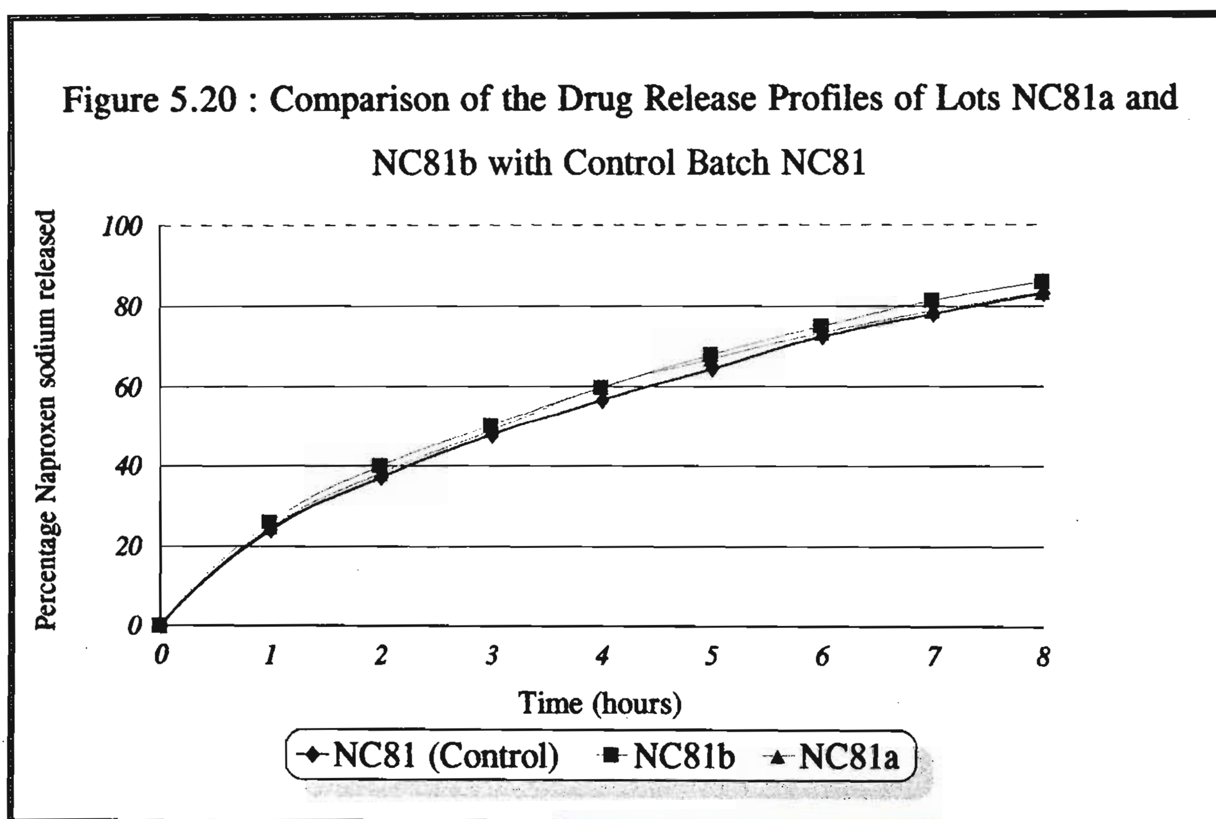
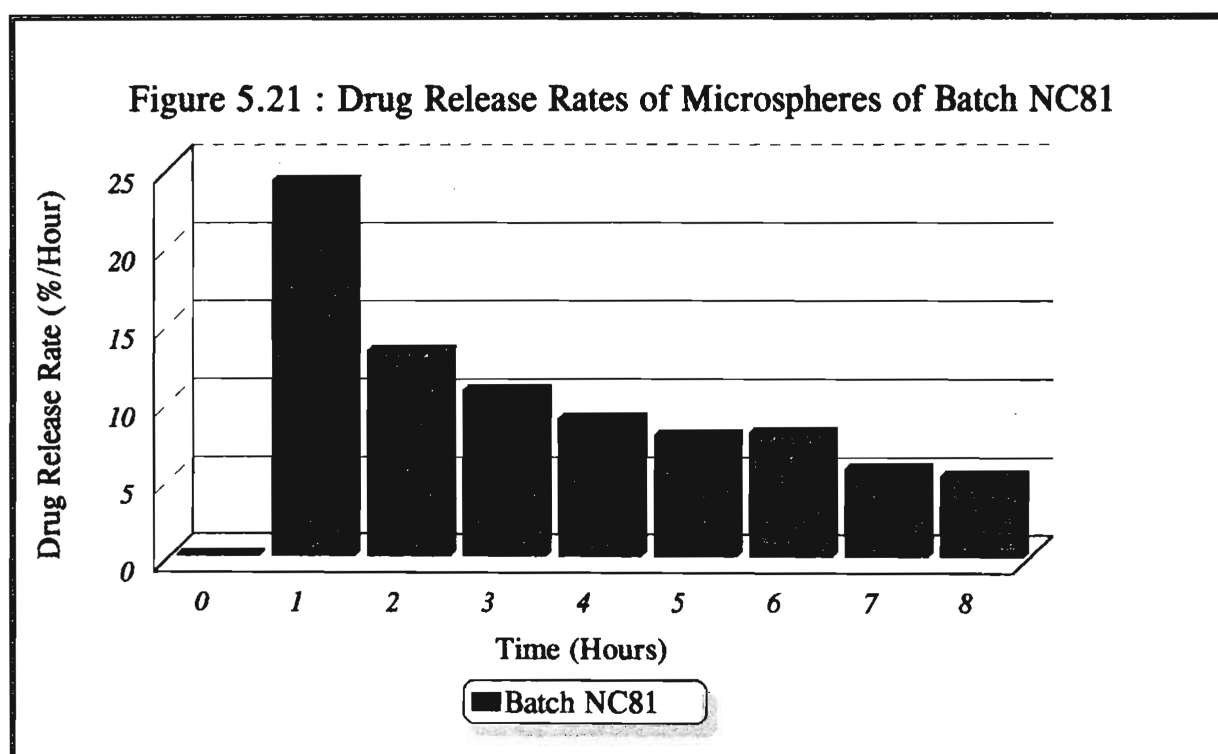


Table 5.14 : Drug Release Rates of Batch NC81

TIME (HOURS)	*MEAN DRUG RELEASED RATES ± SD (%/HOUR) BATCH NC81
1	24.06 ± 0.40
2	13.15 ± 0.28
3	10.64 ± 0.31
4	8.85 ± 0.09
5	7.76 ± 0.29
6	7.96 ± 0.09
7	5.63 ± 0.00
8	5.17 ± 0.35

* *Individual values for 4 replicate determinations are depicted in Appendix 30*



The drug release rates of Batch NC81 reveals initially high drug release rates which become virtually similar after the fourth hour of release (Table 5.14 and Figure 5.21). The data presented in Table 5.13 reflect intra- and inter-batch variation that lie within the acceptable limits. The largest difference between the mean cumulative percentage drug released for

the batches employed at a specific sampling interval was 3.48% which was observed in the fifth hour of dissolution. This difference may be considered to be pharmaceutically insignificant.

Furthermore, statistical evaluation of the data revealed that the differences in the drug release characteristics were insignificant ($p > 0.05$). Thus, the differences among the preparations fell within the maximum allowable limits. Therefore, it was concluded that the meltable aqueous dispersion technique was reproducible in the production of drug-loaded cetostearyl alcohol microspheres.

5.5 VALIDATION OF THE MELTABLE AQUEOUS DISPERSION TECHNIQUE

5.5.1 Influence of Dissolution Variables

5.5.1.1 Influence of different dissolution methods

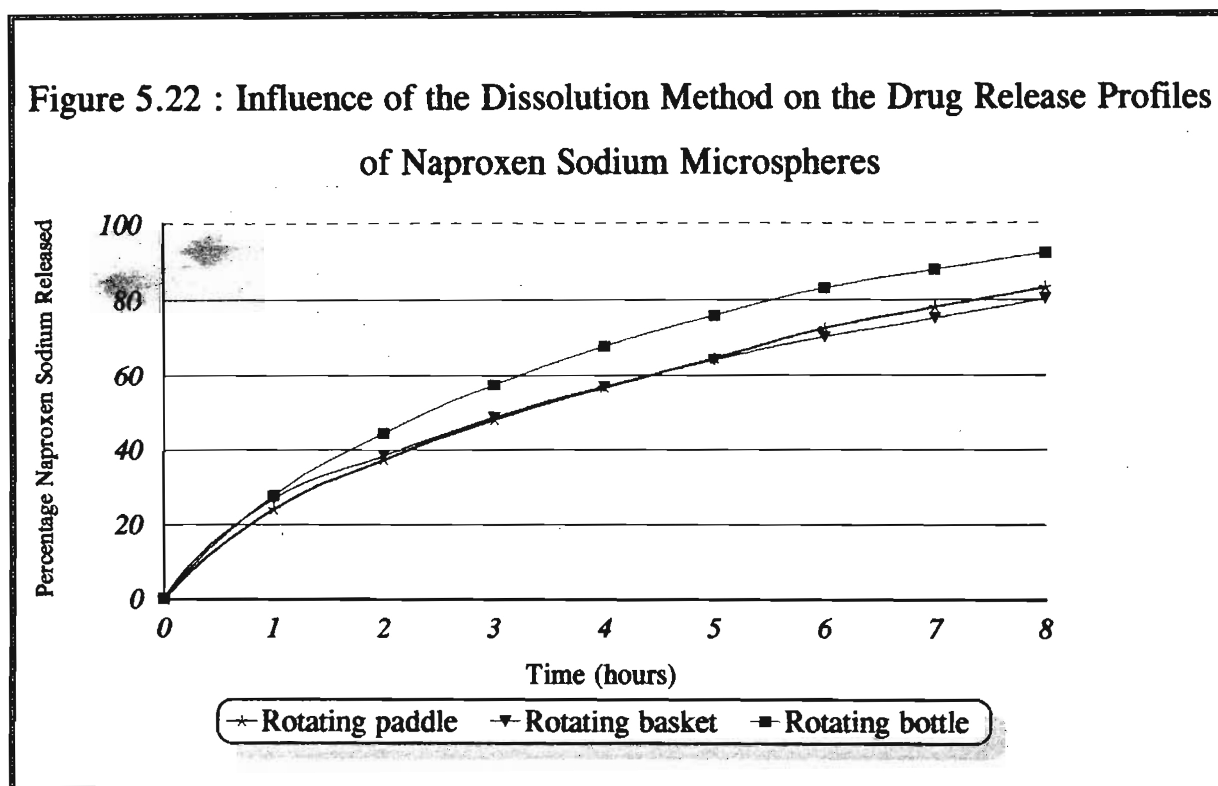
Data reflecting the dependency of the drug release characteristics of the naproxen sodium-cetostearyl alcohol microspheres (Batch NC81) employing three dissolution methods, viz. the rotating paddle, basket and bottle methods, are presented in Tables 5.15 and 5.16 and Figures 5.22 and 5.23 respectively.

Table 5.15 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Employing Different Dissolution Methods

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	ROTATING PADDLE (100 RPM)	ROTATING BASKET (100 RPM)	ROTATING BOTTLE (50 RPM)
0.5	16.68 ± 0.31	18.85 ± 0.21	17.53 ± 1.32
1	24.05 ± 0.40	26.73 ± 0.81	27.65 ± 1.57
1.5	31.10 ± 0.34	34.32 ± 0.66	36.23 ± 1.65
2	37.20 ± 0.32	38.28 ± 0.58	44.17 ± 1.54
3	47.84 ± 0.51	48.39 ± 0.57	57.34 ± 1.71
4	56.69 ± 0.50	56.96 ± 0.39	67.51 ± 1.62
5	64.45 ± 0.72	63.94 ± 0.59	75.77 ± 1.74
6	72.41 ± 0.65	70.05 ± 0.73	82.98 ± 1.24
7	78.04 ± 0.65	75.01 ± 0.59	87.81 ± 1.12
8	83.21 ± 0.59	80.29 ± 0.37	92.29 ± 1.22

* *Individual values for 4 replicate determinations are depicted in Appendices 20, 31, and 32 respectively*

Figure 5.22 : Influence of the Dissolution Method on the Drug Release Profiles of Naproxen Sodium Microspheres



Examination of the drug release profiles attained by the application of different dissolution methods show that the dissolution method influences the release of drug from naproxen sodium-cetostearyl alcohol microspheres. The release of naproxen sodium was more rapid with the rotating paddle method as compared to the rotating basket method. However, this difference may be considered to be pharmaceutically insignificant since the difference in the quantity of drug released at the end of the eight hour dissolution period was 2.92%. Prasad *et al.* (1983) reported faster drug release with the rotating paddle method as compared to the rotating basket method.

A comparison between the rotating basket method and the rotating bottle method reveals a similarity between the two drug release profiles until the third hour of dissolution. After this period, the release of drug increased for the rotating bottle method. The largest difference of 12.93% between the two profiles was observed at the six hour sampling interval. Similar results were noted in a study carried out by Govender (1992). This study reflected statistically significant differences in drug release between the rotating paddle, bottle and basket methods.

Table 5.16 depicts the drug release rates for the different dissolution methods. The release rates for all three dissolution methods reveal a distinct trend, that is, a high initial drug release rate which gradually tails off. Furthermore, the drug release rates from all dissolution methods were observed to be relatively similar.

Table 5.16 : Mean Drug Release Rates of Naproxen Sodium from Microspheres Using Different Dissolution Methods

TIME (HOURS)	*MEAN DRUG RELEASED RATES ± SD (%/HOUR)		
	ROTATING PADDLE (100 RPM)	ROTATING BASKET (100 RPM)	ROTATING BOTTLE (50 RPM)
1	24.06 ± 0.40	26.74 ± 0.81	27.66 ± 1.56
2	13.15 ± 0.28	11.54 ± 0.47	16.51 ± 0.20
3	10.64 ± 0.31	10.11 ± 0.16	13.17 ± 0.36
4	8.85 ± 0.09	8.57 ± 0.36	10.17 ± 0.37
5	7.76 ± 0.29	6.98 ± 0.28	8.27 ± 0.49
6	7.96 ± 0.09	6.12 ± 0.34	7.20 ± 0.59
7	5.63 ± 0.00	4.96 ± 0.33	4.83 ± 0.55
8	5.17 ± 0.35	5.27 ± 0.33	4.49 ±0.54

* *Individual values for 4 replicate determinations are depicted in Appendices 30, 33, and 34 respectively*

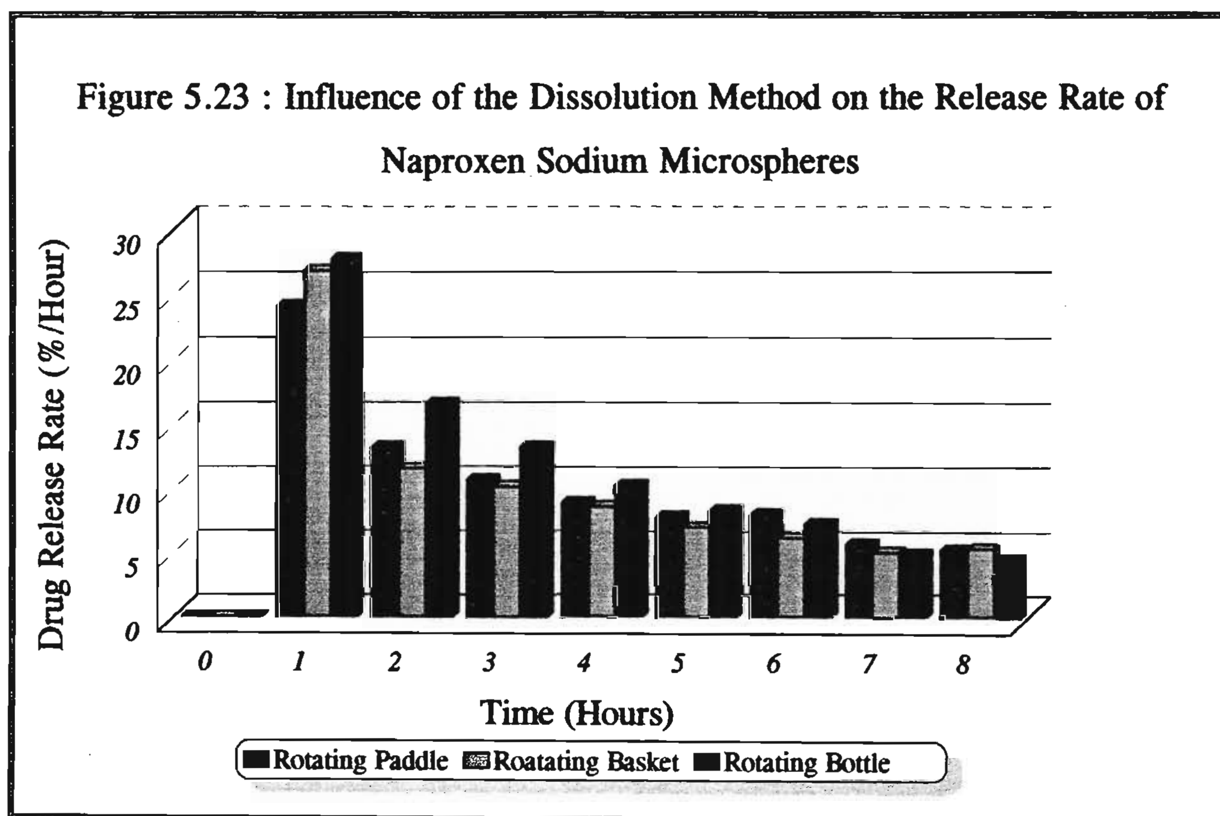


Figure 5.23 : Influence of the Dissolution Method on the Release Rate of Naproxen Sodium Microspheres

The largest difference between the various methods was observed using the rotating basket and rotating bottle methods. The drug release data depicts a difference of 12.93% that exists at the six hour sampling interval. Drug release dependency of dissolution methods were presented by Ammar and Khalil (1996). This study showed that the release of rifampicin from various commercially available preparations was dependent on the dissolution method employed.

5.5.1.2 Influence of Agitation Rates

The influence of different agitation rates, employing the rotating paddle and rotating basket methods, was investigated. The drug release data for the different agitation rates employed within the specific methods is presented in Tables 5.17 and 5.18 and Figures 5.24 and 5.25 respectively.

Table 5.17 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres at Different Rotating Paddle Agitation Rates

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	50 rpm	100 rpm	150 rpm
0.5	18.07 ± 0.19	16.68 ± 0.31	21.29 ± 0.74
1	25.62 ± 0.16	24.05 ± 0.40	30.33 ± 0.64
1.5	32.55 ± 0.33	31.10 ± 0.34	38.80 ± 0.65
2	38.50 ± 0.34	37.20 ± 0.32	46.09 ± 0.76
3	48.94 ± 0.21	47.84 ± 0.51	56.78 ± 0.95
4	57.51 ± 0.39	56.69 ± 0.50	65.72 ± 0.66
5	64.82 ± 0.56	64.45 ± 0.72	72.26 ± 0.91
6	71.47 ± 0.72	72.41 ± 0.65	77.64 ± 0.43
7	76.97 ± 0.60	78.04 ± 0.65	82.23 ± 0.54
8	82.22 ± 1.19	83.21 ± 0.59	86.44 ± 0.54

* *Individual values for 4 replicate determinations are depicted in Appendices 35, 20, and 36 respectively*

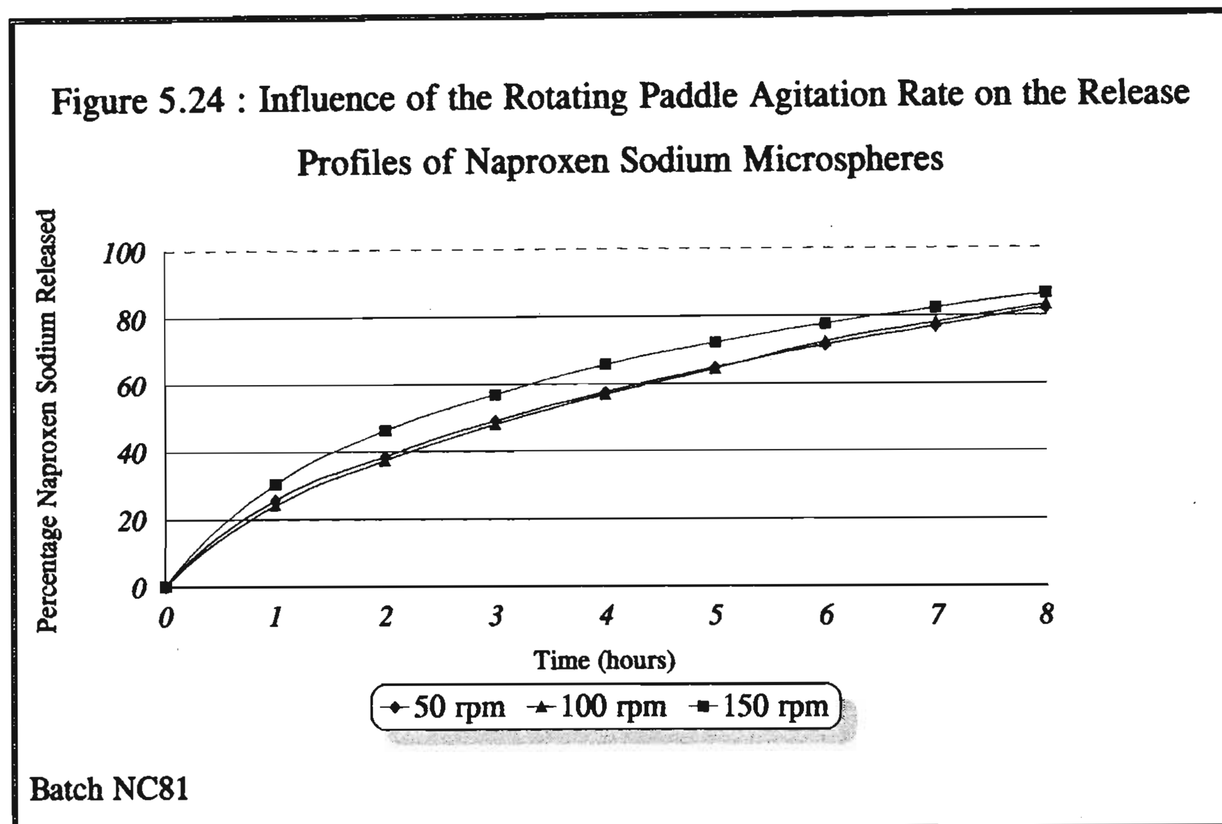


Figure 5.24 : Influence of the Rotating Paddle Agitation Rate on the Release Profiles of Naproxen Sodium Microspheres

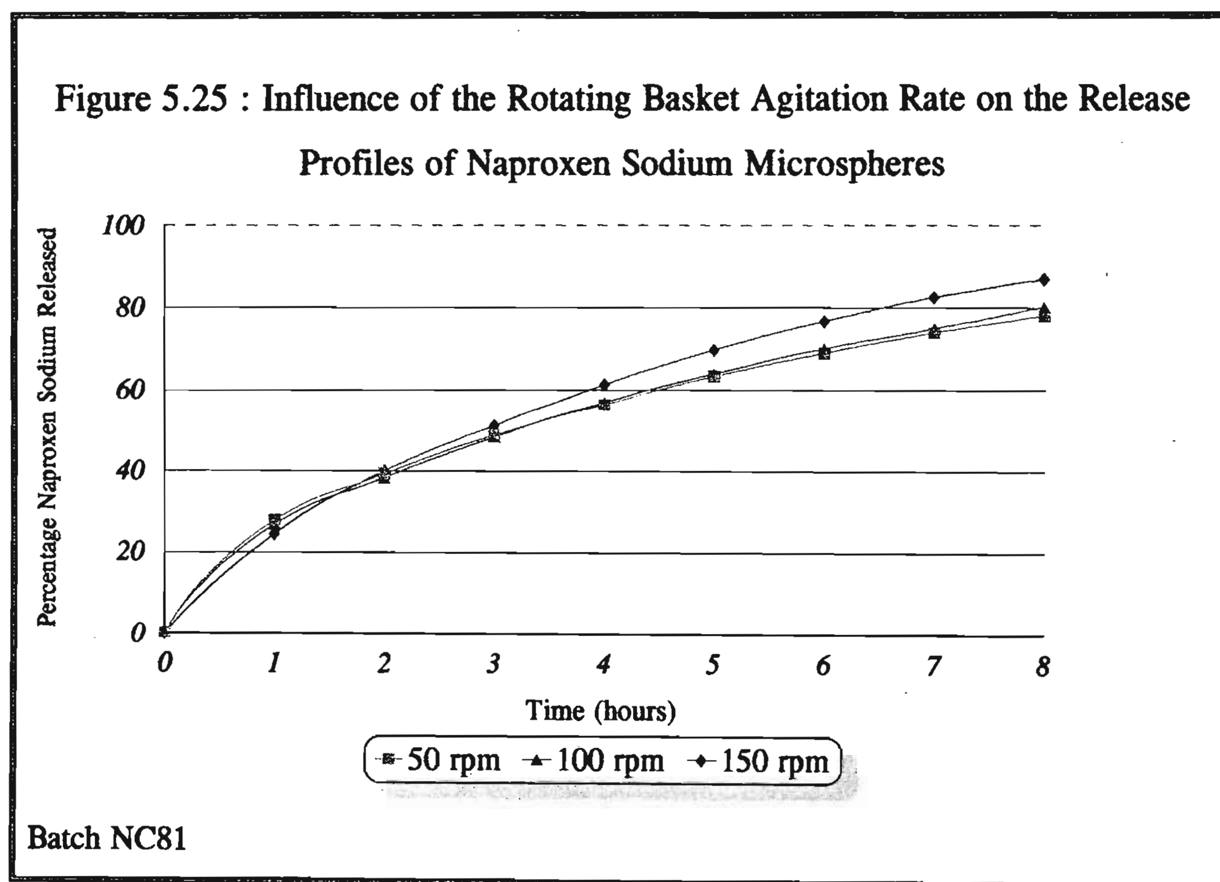
Employing different agitation rates for the rotating paddle method resulted in the production of almost similar drug release profiles. The effect of the different agitation rates on drug release using the rotating paddle method was negligible and may be considered to be pharmaceutically insignificant. Furthermore, statistical evaluation of the data revealed that the differences in the drug release characteristics were insignificant ($p > 0.05$). In contrast, the drug release profiles depicting the effect of the different agitation rates on drug release utilizing the rotating basket method show a distinct difference in the amount of drug released at the various sampling intervals.

Table 5.18 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres at Different Rotating Basket Agitation Rates

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	50 rpm	100 rpm	150 rpm
0.5	19.26 ± 0.25	18.85 ± 0.21	14.78 ± 0.19
1	27.76 ± 0.43	26.73 ± 0.81	24.32 ± 0.36
1.5	33.96 ± 0.34	34.32 ± 0.66	32.51 ± 0.70
2	39.22 ± 0.44	38.28 ± 0.58	39.97 ± 0.61
3	48.89 ± 0.37	48.39 ± 0.57	51.19 ± 0.62
4	56.40 ± 0.52	56.96 ± 0.39	61.29 ± 0.89
5	63.25 ± 0.61	63.94 ± 0.59	69.73 ± 0.76
6	68.87 ± 0.44	70.05 ± 0.73	76.74 ± 0.85
7	74.03 ± 0.42	75.01 ± 0.59	82.55 ± 0.67
8	78.11 ± 0.45	80.29 ± 0.37	87.05 ± 0.53

* *Individual values for 4 replicate determinations are depicted in Appendices 37, 31, and 38 respectively*

Figure 5.25 : Influence of the Rotating Basket Agitation Rate on the Release Profiles of Naproxen Sodium Microspheres



Batch NC81

A comparison of the drug release data obtained at different agitation rates at the end of eight hours of dissolution for each method is presented in Table 5.19.

Table 5.19 : Drug Release Differences from Different Dissolution Methods at 50 and 150 rpm at the End of 8 Hours of Dissolution

METHODS	Rotating paddle		Rotating bottle	
AGITATION RATES (RPM)	50	150	50	150
% DRUG RELEASED (8th HOUR)	82.22	86.44	78.11	87.05
DRUG RELEASE DIFFERENCE (8th HOUR)	4.22		8.94	

Table 5.19 clearly depicts that the agitation rate employed in the dissolution study using the rotating basket method affects the drug release data markedly whereas such an effect is minimal when the rotating paddle method is utilized. A study performed by Veiga and Alvarez de Eulate (1994) employing the rotating paddle apparatus showed minimal differences in drug release as a function of agitation rate with most of the drug release profiles being superimposable and comparable. Pillay (1996) also showed that drug release differences as a function of agitation rate was more pronounced with the rotating basket method as compared to the rotating paddle method.

It was also noted that the rotating basket method afforded the fastest drug release at an agitation rate of 150 rpm when compared to the rotating paddle method. Initially, the rotating paddle method displayed a higher drug release rate. However, after the sixth hour of dissolution a larger quantity of drug was released with the rotating basket method. At agitation rates of 50 and 100 rpm, the rotating paddle method provides a higher drug release than the rotating basket method. This effect can be attributed to the boundary layers that

are present at the interface of the dissolution media and the walls of the basket which results in the resistance to diffusion of drug into the bulk dissolution medium. At high rotational speeds, there is an effective breakup of these boundary layers thereby allowing for the transfer of the drug molecules into the bulk dissolution medium.

5.5.1.3 Influence of dissolution media

5.5.1.3.1 *pH-dependent Characteristics*

The dissolution characteristics of naproxen sodium from cetostearyl alcohol microspheres (Batch NC81) were investigated in buffers of varying pH (hydrochloric acid buffer pH 1.5 and phosphate buffers pH 4.5, 6.9, 7.4 and 8.0) employing the rotating paddle method. The mean drug release data and profiles obtained for individual dissolution runs in the different buffer solutions are presented in Table 5.20 and Figure 5.26 respectively.

Table 5.20 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Using Different Buffer Solutions

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD				
	pH 1.5	pH 4.5	pH 6.9	pH 7.4	pH 8.0
0.5	2.09 ± 0.21	1.16 ± 0.18	13.96 ± 0.27	17.58 ± 0.16	21.28 ± 0.32
1	2.80 ± 0.23	3.08 ± 0.21	20.01 ± 0.17	26.90 ± 0.16	32.23 ± 0.54
1.5	3.80 ± 0.13	3.92 ± 0.16	25.57 ± 0.25	33.54 ± 0.19	40.84 ± 0.53
2	4.23 ± 0.29	4.55 ± 0.16	30.21 ± 0.34	40.68 ± 0.21	47.12 ± 0.72
3	5.07 ± 0.10	5.64 ± 0.13	38.19 ± 0.41	53.56 ± 0.23	58.59 ± 0.72
4	5.34 ± 0.58	6.20 ± 0.21	44.61 ± 0.41	61.21 ± 0.23	67.25 ± 0.80
5	6.31 ± 0.16	6.85 ± 0.13	50.46 ± 0.49	67.44 ± 0.23	72.49 ± 0.88
6	6.88 ± 0.52	7.42 ± 0.16	56.42 ± 0.41	72.29 ± 0.16	76.97 ± 0.56
7	6.92 ± 0.19	7.83 ± 0.31	59.47 ± 0.44	77.69 ± 0.23	80.25 ± 0.48
8	7.12 ± 0.51	8.57 ± 0.24	62.25 ± 0.54	82.65 ± 0.25	82.69 ± 0.40

* *Individual values for 4 replicate determinations are depicted in Appendices 39 - 43 respectively*

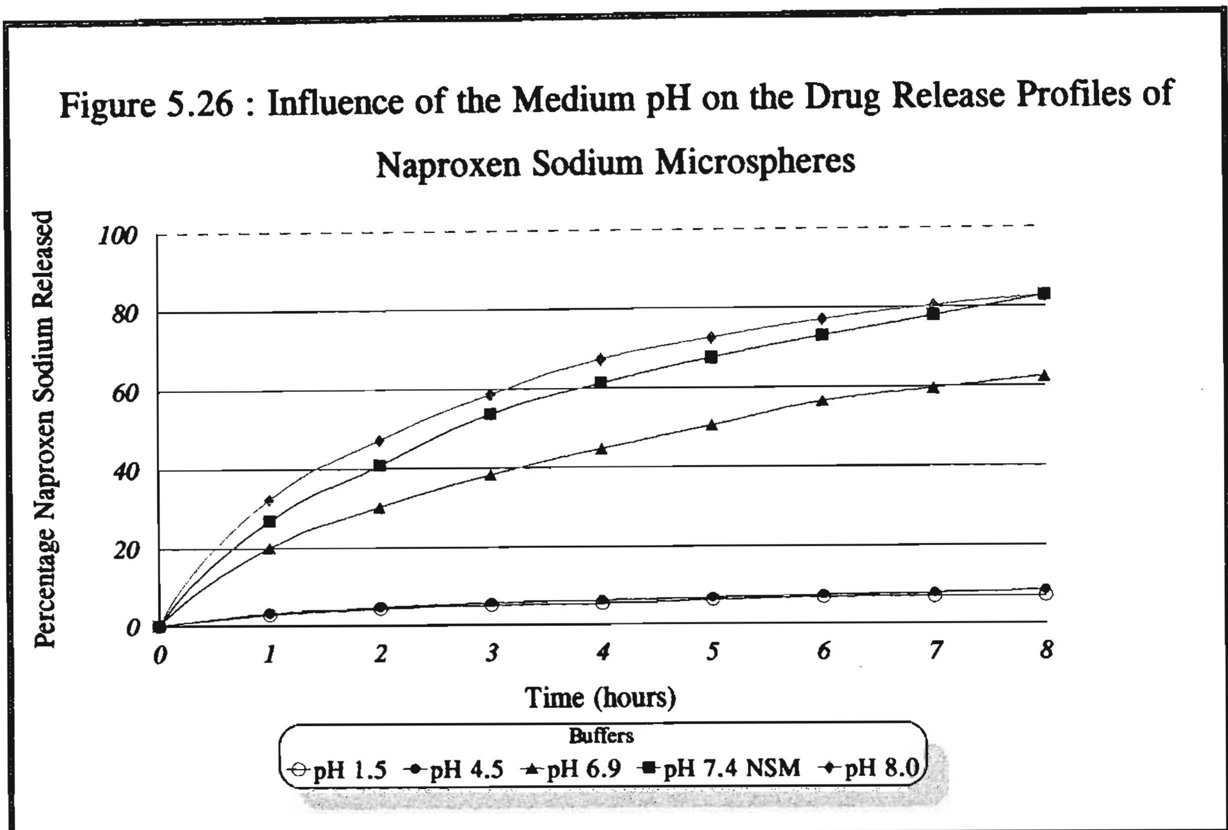


Figure 5.26 : Influence of the Medium pH on the Drug Release Profiles of Naproxen Sodium Microspheres

The results above show significant differences in the dissolution profiles obtained from dissolution studies carried out in media of the various pH values. The release of drug is markedly retarded in acidic media with only 7.12% of drug being released at the end of eight hours at pH 1.5 and 8.75% of drug being released in the pH 4.5 dissolution medium. In comparison, more than 80% of naproxen sodium was released at the end of eight hours when the dissolution was performed at pH 7.4 and pH 8.0. These results clearly depict the pH dependency of drug release from the formulation.

The pH dependency of drug release can be explained in terms of the Henderson-Hasselbach equation (Martin *et al.*, 1993). According to the above equation, the dissolution rate of a weak acid increases with increasing pH whilst the dissolution of a weak base decreases with increasing pH. Naproxen sodium is a weakly acidic drug, therefore dissolution of the drug will be retarded in acidic media and rapid in basic media. Thus, the increased release rates observed in phosphate buffer (pH 7.4 and 8.0) as compared to the suppressed release

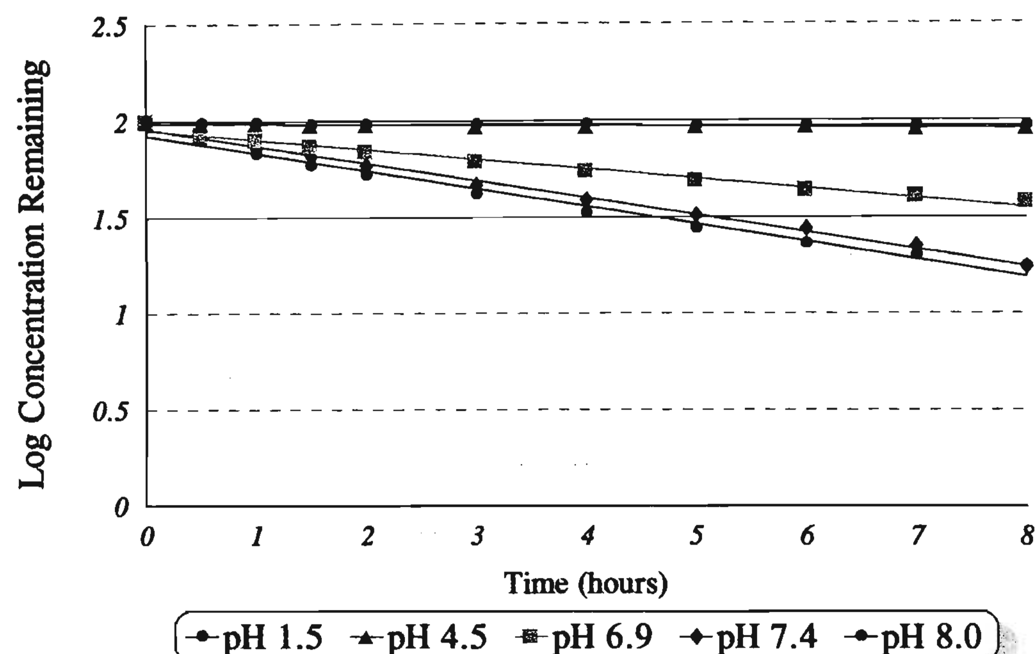
observed in hydrochloric acid buffer (pH 1.5) is supported by the Henderson-Hasselbach theory.

Table 5.21 : Effect of pH on the First Order Drug Release Rate Constant of Naproxen Sodium from the Microspheres

pH OF DISSOLUTION MEDIUM	RELEASE RATE CONSTANT (K) ($HOUR^{-1}$)	CORRELATION COEFFICIENT r^2
1.5	0.008	0.798
4.5	0.009	0.858
6.9	0.116	0.980
7.4	0.207	0.995
8.0	0.213	0.981

The pH dependent drug release behaviour is further highlighted by the acceleration of the drug release rate constant (Table 5.21) with an increase in the pH of the dissolution media. The increase in the first order rate constant is clearly evident in the increase in the slope of the first order plots with an increase in the pH of the dissolution media (Figure 5.27).

Figure 5.27 : Determination of the First Order Rate Constants for Batch NC81 Under Different pH Conditions



Visual observation during the dissolution process, as well as results obtained from scanning electron microscopy, suggest that the wax matrix does not undergo dissolution when exposed to phosphate buffer. Consequently, the pH dependent drug release characteristics of the formulation can be attributed, in its entirety, to the dependency of the solubility of the drug on the pH of the medium.

5.5.1.3.2 *Drug Release in Simulated Gastrointestinal Milieu*

The pH dependent drug release characteristics of the formulation prompted the investigation of the drug release profiles of Batch NC 81 in various dissolution media that simulated the gastrointestinal milieu following oral administration. The mean cumulative percentages of drug released in phosphate buffer (pH 7.4) and the drug release data obtained for the

dissolution study carried out in media of various pH gradients are presented in Table 5.22 and Figure 5.28 respectively.

Table 5.22 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres in Phosphate Buffer pH 7.4 Relative to Various Dissolution Media that Simulated the Gastrointestinal Milieu

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD		
	PHOSPHATE BUFFER pH 7.4	VARIOUS pH GRADIENTS	
0.5	17.58 ± 0.16	1.76 ± 0.08	pH 1.5
1	26.90 ± 0.16	2.67 ± 0.16	
1.5	33.54 ± 0.19	3.99 ± 0.31	pH 4.5
2	40.68 ± 0.21	4.89 ± 0.16	
3	53.56 ± 0.23	22.36 ± 0.73	pH 6.9
4	61.21 ± 0.23	32.97 ± 1.28	
5	67.44 ± 0.23	50.44 ± 1.56	pH 7.4
6	72.29 ± 0.16	61.50 ± 2.02	
7	77.69 ± 0.23	70.82 ± 2.42	
8	82.65 ± 0.25	82.19 ± 2.74	pH 8.0

* *Individual values for 4 replicate determinations are depicted in Appendices 42 and 44 respectively*

The drug release data and profiles indicate a significant decrease in drug release in the dissolution media of various pH gradients in the first two hours (4.89 ± 0.16%) as compared to dissolution performed in phosphate buffer pH 7.4 which released 40.68 ± 0.21% of drug in the same time period. A significant increase in the drug release profile was observed after the two hour dissolution period. This was due to the retardation of drug release in the hydrochloric acid buffer pH 1.5 and phosphate buffer pH 4.5, as compared to the release in phosphate buffers (pH 6.9, 7.4 and 8.0). Accordingly, there was a rapid release of drug on exposure to phosphate buffer pH 6.9. The total amount of drug released in 12 hours for microspheres subjected to dissolution in the simulated gastrointestinal milieu was 99.46 ± 3.31% (Appendix 44).

Figure 5.28 : Naproxen Sodium Release Profiles in Phosphate Buffer pH 7.4 and in Media Simulating the Gastrointestinal Milieu

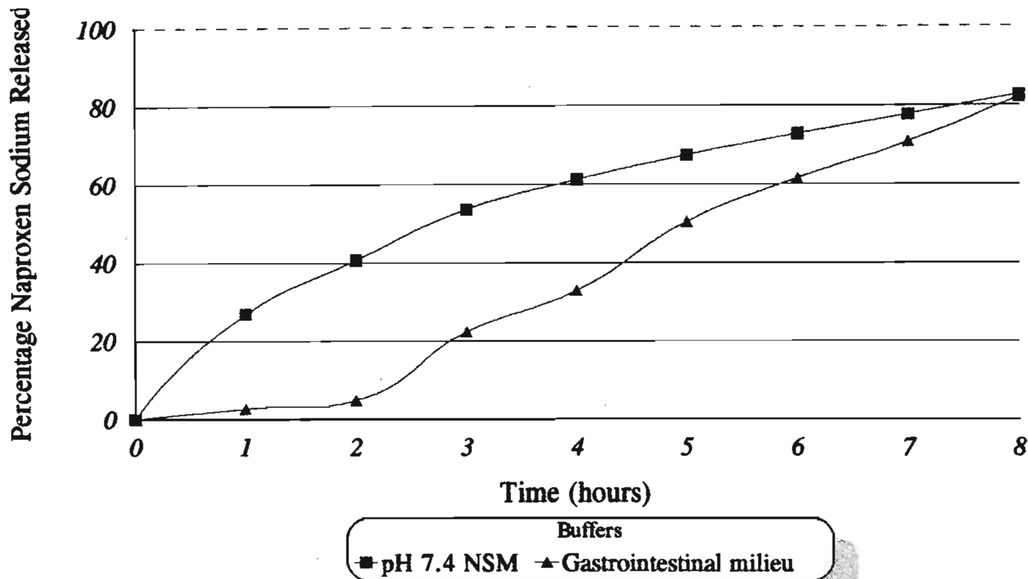


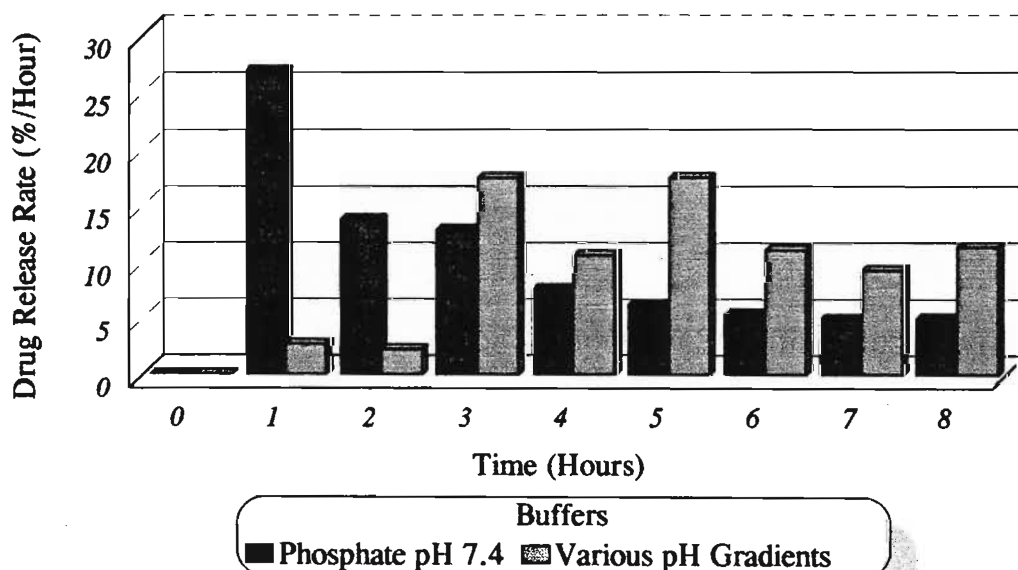
Table 5.23 and Figure 5.29 also demonstrate that although the release rates of naproxen sodium in the various pH gradients depicted an initial lag period during which the drug release rates were slower than in phosphate buffer pH 7.4, the drug release rates after two hours were greater in the simulated gastrointestinal milieu than in phosphate buffer pH 7.4. The maximum drug release rate (17.47 %/hr) in the various pH gradients was achieved in the third and fifth hour as compared to a maximum drug release rate of 26.89 %/hr which was achieved in the first hour for the dissolution study performed in phosphate buffer pH 7.4.

Table 5.23 : Mean Release Rates of Naproxen Sodium Released from Microspheres in Phosphate Buffer pH 7.4 Relative to Various Dissolution Media that Simulated the Gastrointestinal Milieu

TIME (HOURS)	*MEAN DRUG RELEASED RATES ± SD (%/HOUR)		
	PHOSPHATE BUFFER pH 7.4	VARIOUS pH GRADIENTS	
1	26.89 ± 0.17	2.68 ± 0.16	pH 1.5
2	13.79 ± 0.08	2.22 ± 0.10	pH 4.5
3	12.88 ± 0.25	17.47 ± 0.57	pH 6.9
4	7.65 ± 0.19	10.61 ± 0.67	
5	6.23 ± 0.23	17.47 ± 0.36	pH 7.4
6	5.36 ± 0.21	11.06 ± 0.69	
7	4.90 ± 0.09	9.32 ± 0.47	
8	4.96 ± 0.16	11.37 ± 0.42	pH 8.0

* *Individual values for 4 replicate determinations are depicted in Appendices 45 and 46 respectively*

Figure 5.29 : Naproxen Sodium Release Rates in Phosphate Buffer pH 7.4 and in Media Simulating the Gastrointestinal Milieu



5.5.2 Electron Microscopy

5.5.2.1 Scanning electron microscopy (SEM)

SEM studies were performed on cetostearyl alcohol microspheres to determine surface and cross-sectional morphology. Furthermore, SEM studies conducted on microspheres after various dissolution sampling intervals were used to elucidate possible mechanisms of drug release from naproxen sodium-cetostearyl alcohol microspheres.

5.5.2.1.1 *Naproxen Sodium-Cetostearyl Alcohol Microspheres*

Figure 5.30 depicts a single microsphere of Batch NC81. The microsphere appears to be almost completely spherical with a continuous, 'rough' and uneven surface appearance.

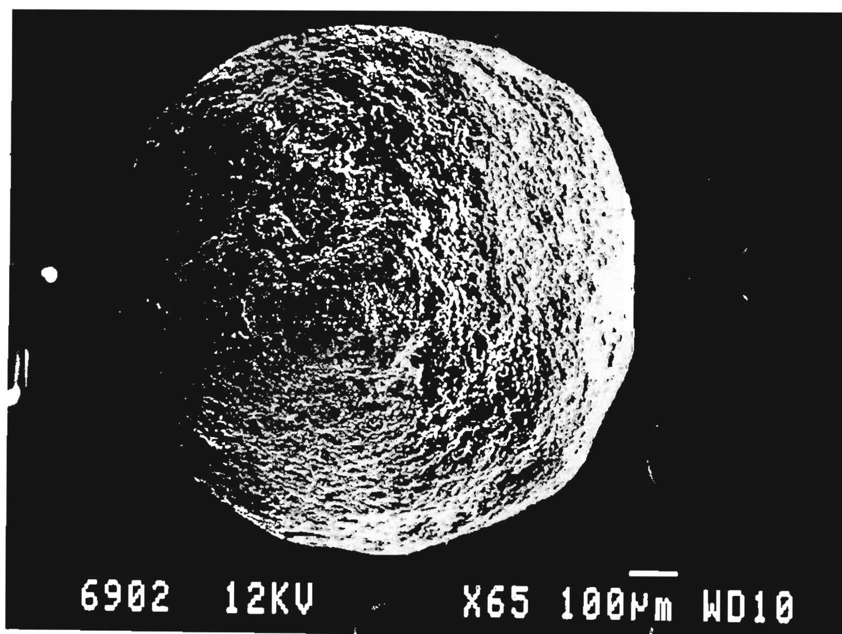


Figure 5.30 : Single Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81

Furthermore, the surface displayed a porous nature, with minute pores randomly located on the surface of the microsphere. At higher magnifications, as illustrated in Figure 5.31 , the surface appears to be granular and 'flakes' of cetostearyl alcohol are clearly visible.

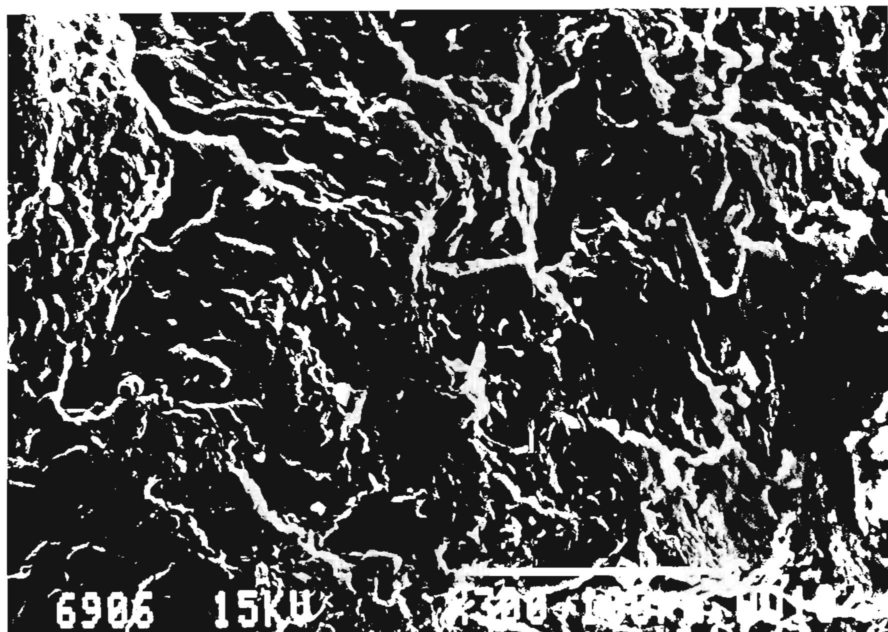


Figure 5.31 : Surface of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81

The surface appearance of the microsphere is attributed to the rapid cooling protocol adopted in the manufacturing process. The porous nature of the microspheres is confirmed at higher magnifications. Al-Kassas *et al.* (1993) showed that surface morphology is markedly affected by the rate of cooling. Rapid cooling resulted in microspheres that exhibit more cracks and channels than those formed at slower cooling times.

A cross-section through a single microsphere is illustrated in Figure 5.32. The cross-sectional micrograph reveals the presence of two distinct regions; the outer region appears to be compact while the inner region appears to be made up of loosely bound crystals.

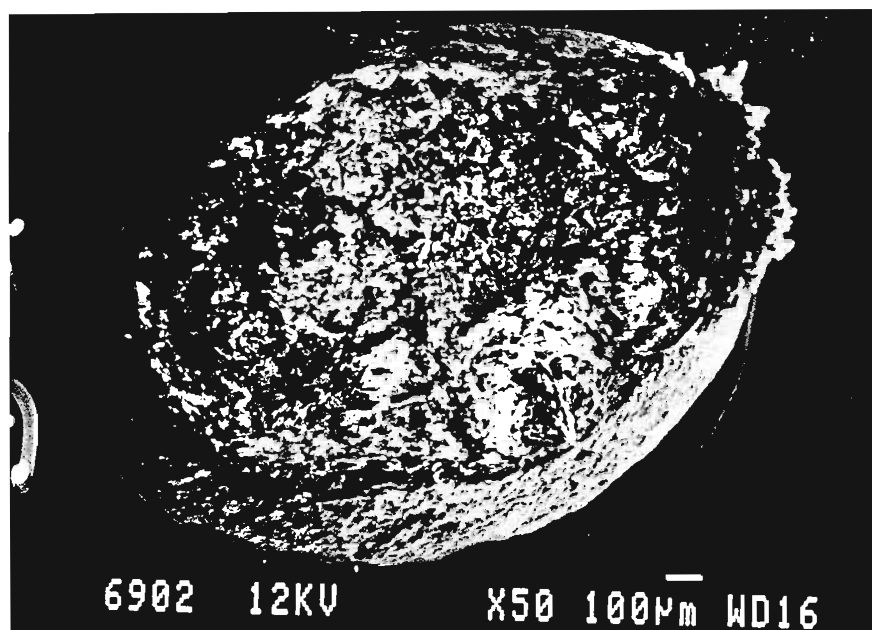


Figure 5.32 : Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81

The inner region is probably comprised of a greater amount of drug than cetostearyl alcohol therefore it has a crystalline appearance. Other studies employing wax matrices have shown similar findings with regard to microsphere shape and surface morphology (Benita *et al.*, 1986; Wong *et al.*, 1992 and Giannola *et al.*, 1993)

5.5.2.1.2 *Microspheres Stored at Elevated Temperatures*

SEM was performed on microspheres stored at 37°C with 80% relative humidity and at 40°C for a period of 12 weeks to determine the effect of storage at elevated temperatures on the surface morphology of the microspheres. The scanning electron micrograph of a single microsphere subjected to a temperature of 40°C for the 12 week period revealed a more smooth yet uneven surface appearance (Figure 5.33).

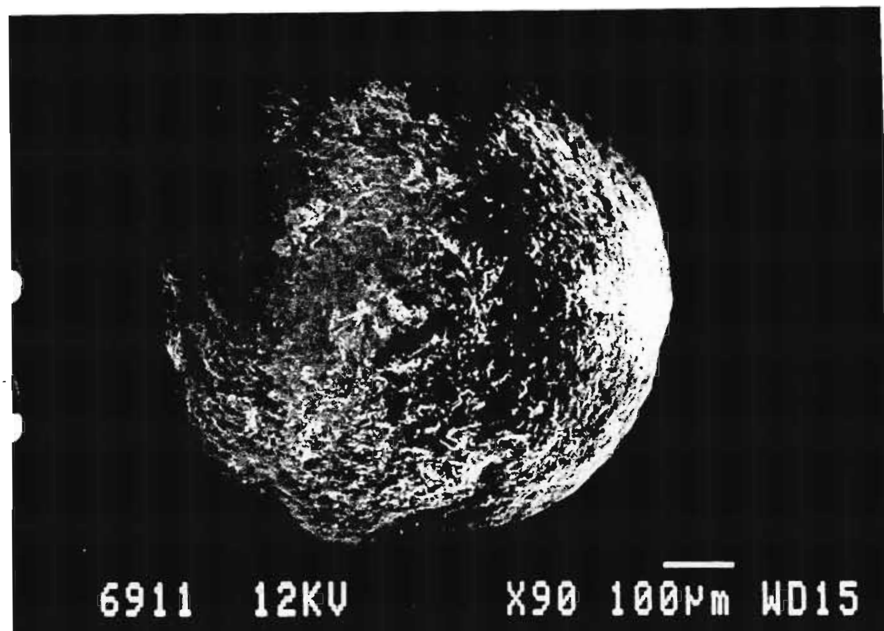


Figure 5.33 : Single Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after Storage at 40°C for 12 Weeks

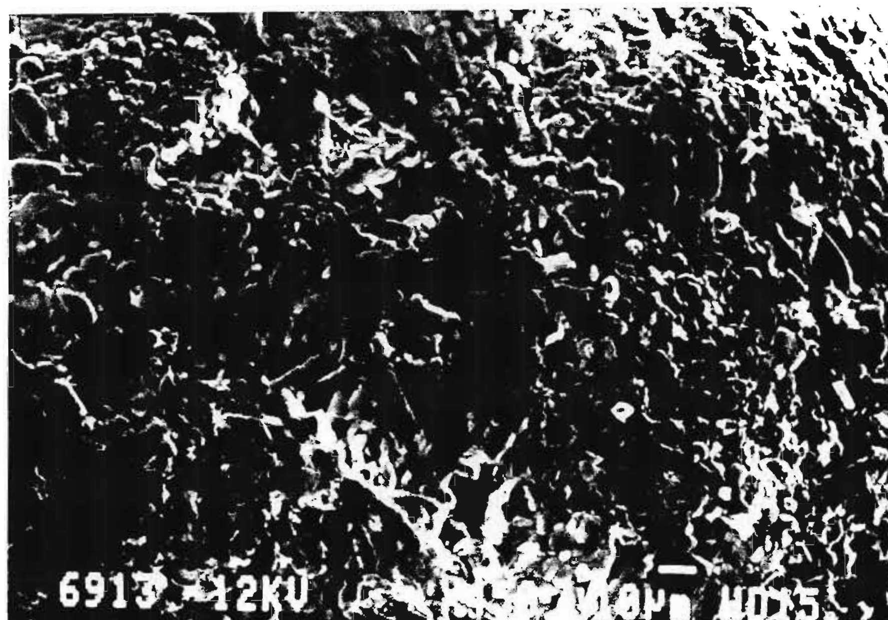


Figure 5.34 : Surface Morphology of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after Storage at 40°C for 12 Weeks

Microspheres stored at 37°C with 80% relative humidity showed similar surface changes as those observed with the microspheres stored at 40°C (Figure 5.34). A comparison between the microspheres stored at 40°C (Figure 5.35) with microspheres of room temperature (21 ± 1°C) at a magnification of X450 depicts a granular surface for both micrographs. However, the micrograph for the microspheres stored at 40°C appears to possess a more compact, less porous surface relative to microspheres stored at room temperature (21 ± 1°C). Furthermore, there is a noticeable reduction in the presence of 'flakes' of cetostearyl alcohol. This observation is attributed to the coalescence of the cetostearyl alcohol 'flakes' at elevated temperatures.

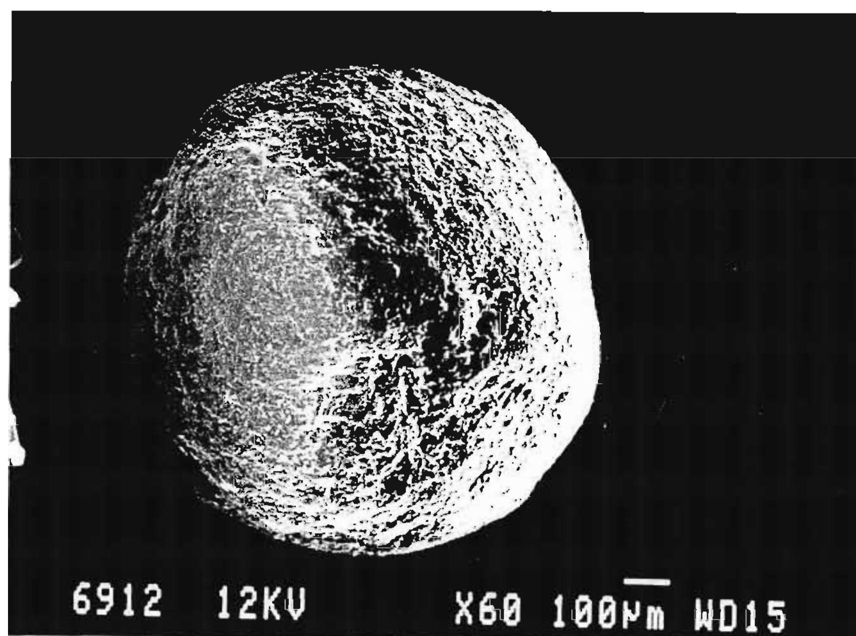


Figure 5.35 : Single Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after Storage at 37°C/80% Relative Humidity for 12 Weeks

5.5.2.1.3 *Microsphere Morphology During Dissolution*

Figure 5.36 and 5.37 show the whole microspheres (Batch NC81) after 1 hour and 8 hours of dissolution respectively. After drug release, morphological changes were evident. A greater degree of structural breakdown was observed after 8 hours dissolution testing. Larger pores and indentations are clearly evident on the surface of the microsphere subjected to 8 hours of dissolution. However, the overall shape of the microsphere is retained. Microspheres subjected to 1 hour dissolution testing show minimal structural change.

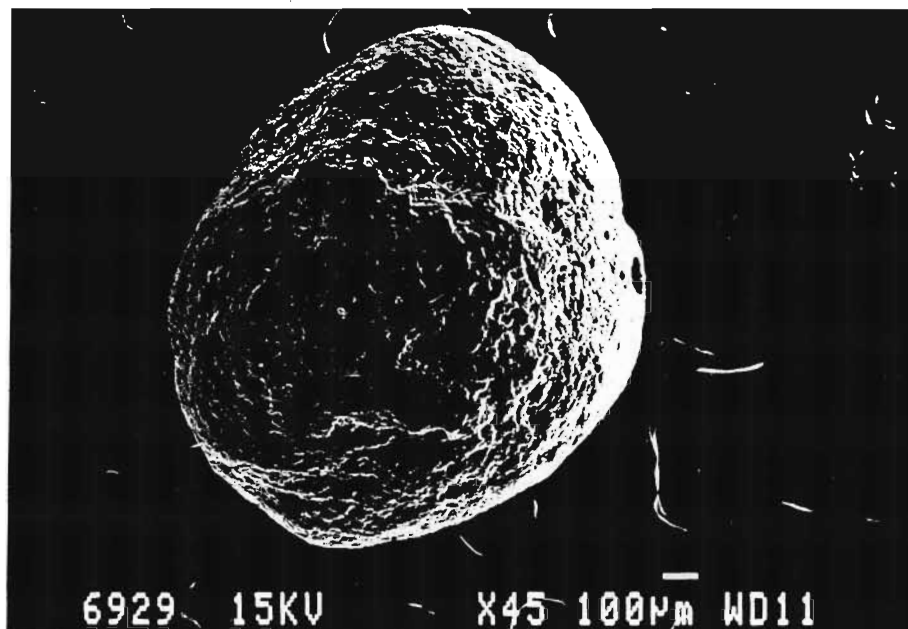


Figure 5.36 : Micrograph of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after 1 Hour of Dissolution Testing

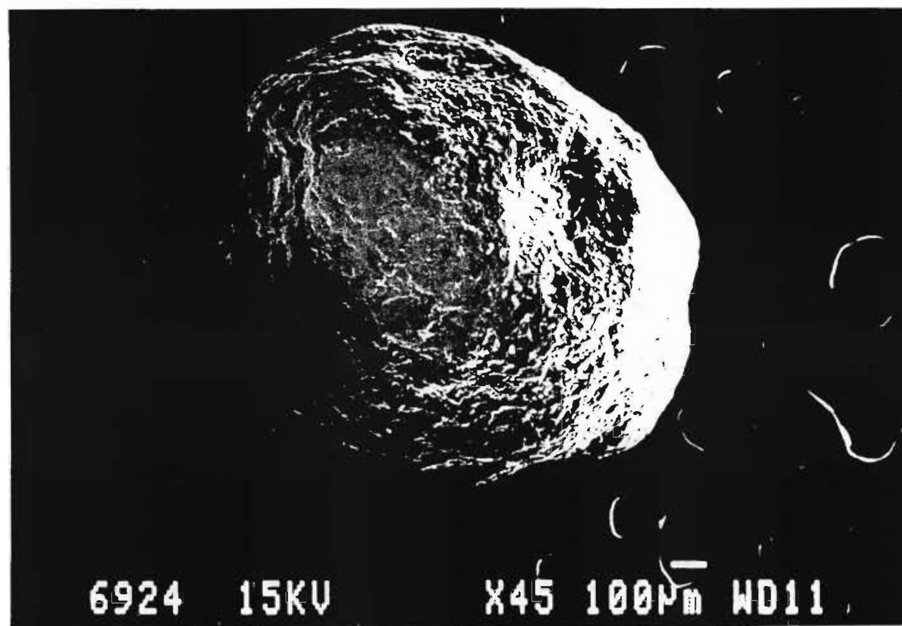


Figure 5.37 : Micrograph of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after 8 Hours of Dissolution Testing

A cross-section through microspheres subjected to 8 hours of dissolution reveals the presence of large pores created as a result of dissolution of drug (Figure 5.38). However, not all microspheres display similar structural breakup. Certain microspheres show the formation of channels originating from the surface of the microsphere (Figure 5.39). At higher magnifications (X270) small worm-like pits or indentations were observed, possibly due to dissolution of the drug. A few pores were also observed (Figure 5.40). Wong *et al.* (1992) reported similar observations after drug release from ibuprofen-cetostearyl alcohol microspheres.

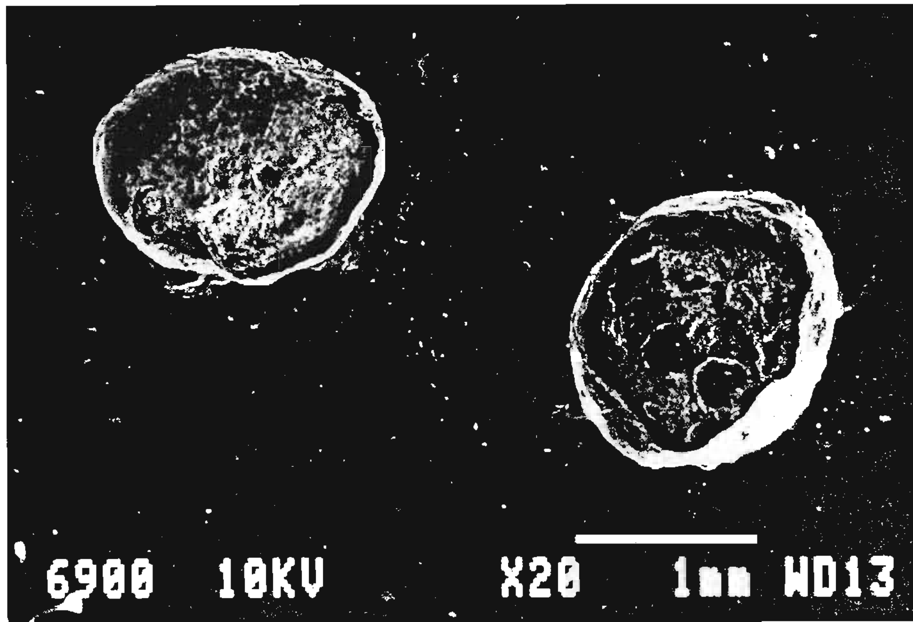


Figure 5.38 : Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 revealing the presence of large pores

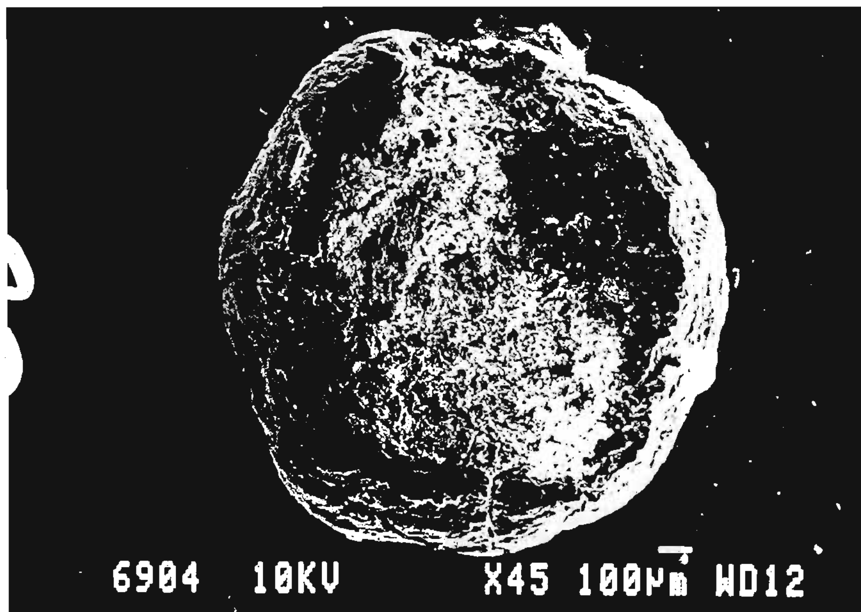


Figure 5.39 : Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 showing channel formation

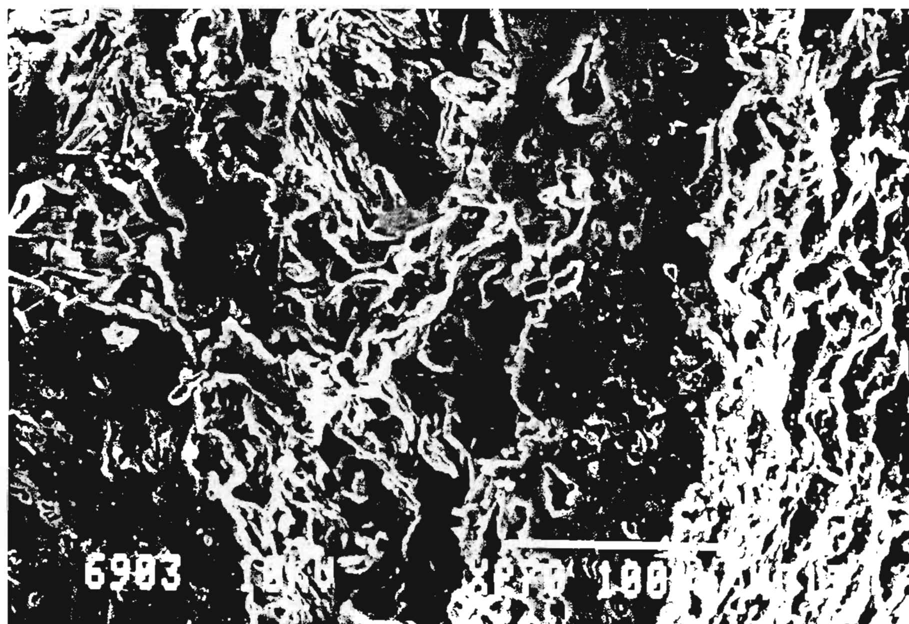
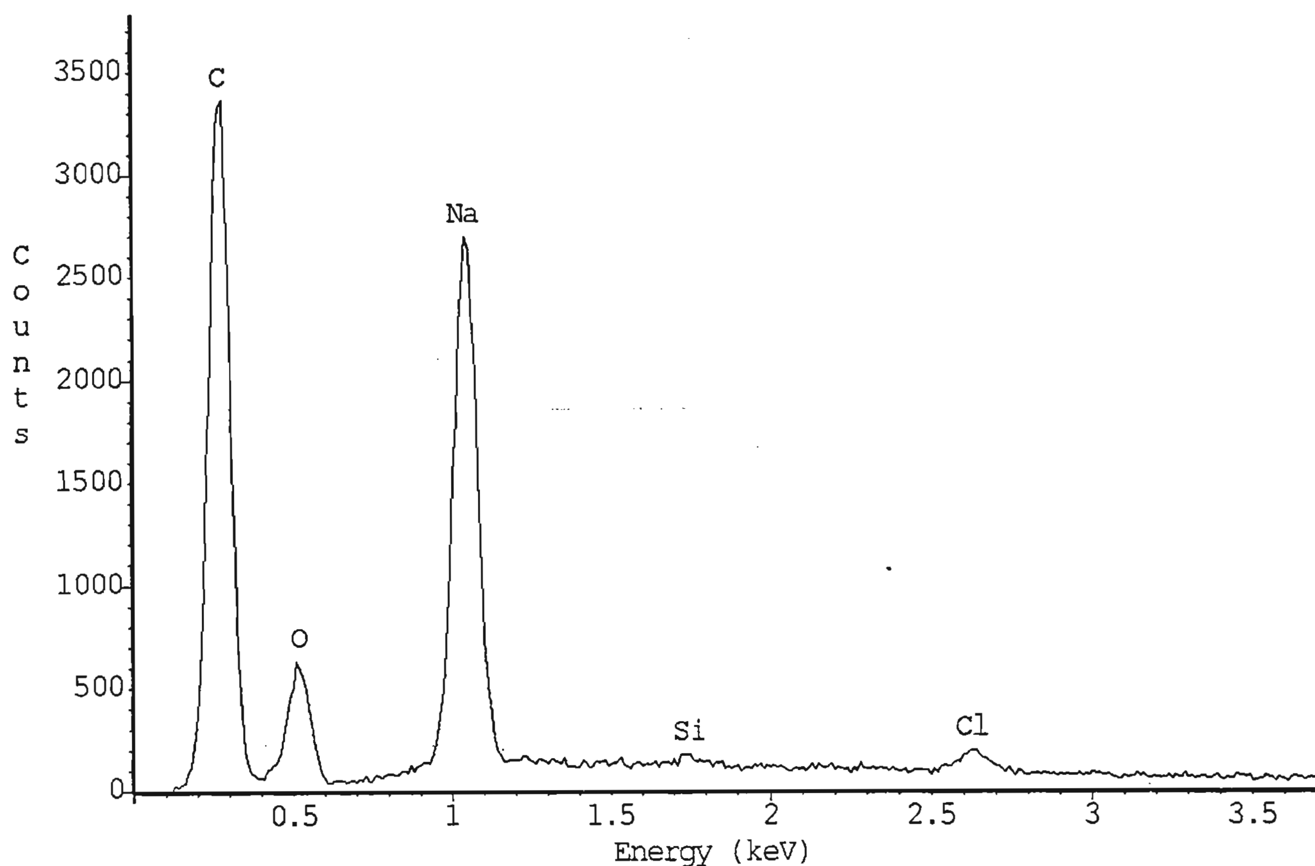


Figure 5.40 : Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere of Batch NC81 after 8 Hours of Dissolution Testing

5.5.2.2 Energy dispersive x-ray microprobe analysis (EDX)

The EDX spectrums of naproxen sodium, drug containing ethylcellulose microcapsules (Batch NE3) and drug-cetostearyl alcohol microspheres (Batch NC81) are presented in Figures 5.41, 5.42 and 5.43 respectively.

The quantitative data accompanying Figure 5.41 and 5. 43 exclude the skeleton elements, carbon and oxygen, when quantitating the elemental composition of these samples, while the data for Figure 5. 42 incorporates this skeleton. Consequently, it is more appropriate to interpret the results qualitatively.



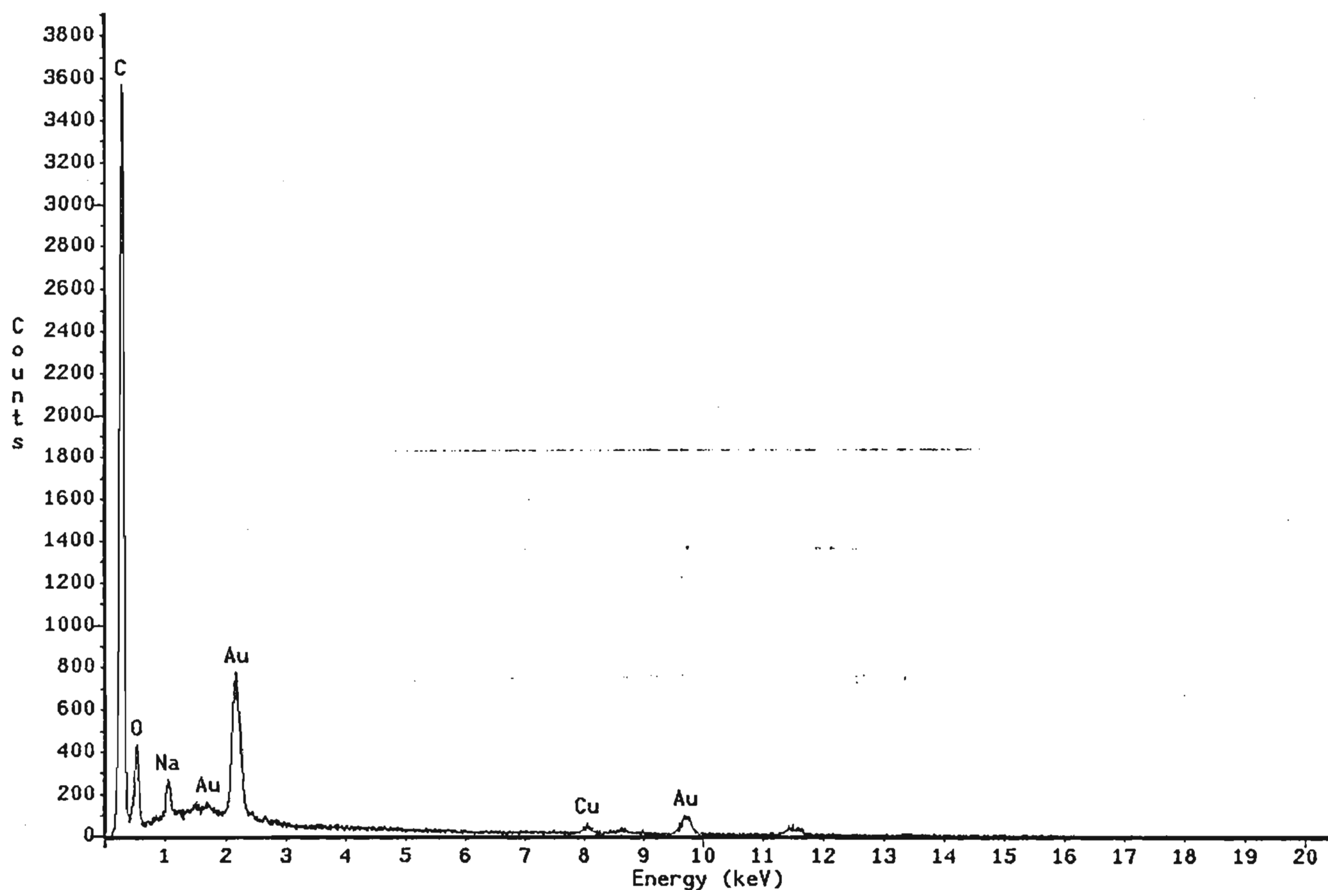
Chi-sqd = 2.50 Livetime = 60.0 Sec.PROZA Correction Acc.Volt.= 2

5 kV Take-off Angle=30.00 deg
Number of Iterations = 5

Element	k-ratio (calc.)	ZAF	Atom %	Element Wt %	Wt % Err. (1-Sigma)
Na-K	0.80280	1.128	93.26	90.58	+/- 0.78
Si-K	0.00827	3.107	2.16	2.57	+/- 0.80
Cl-K	0.04190	1.636	4.58	6.86	+/- 0.64
Total			100.00	100.00	

spectrum of naproxen sodium

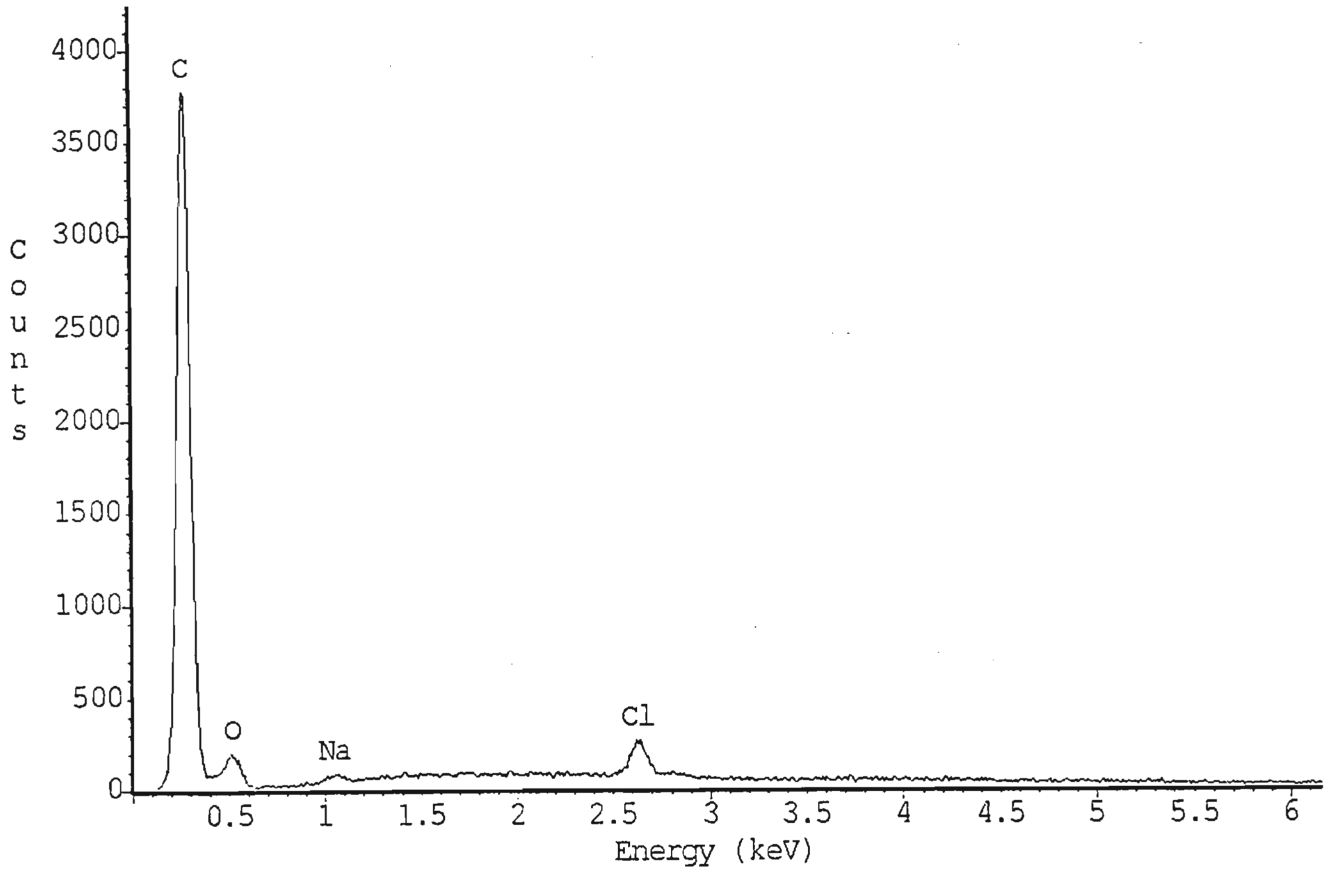
Figure 5.41 : EDX Spectrum of Naproxen Sodium



Elements Present:
C (6), O (8), Na(11), Au(79), Cu(29)

Energy	Intensity	Element
0.276	26330	C Ka
0.523	2725	O Ka
1.043	2138	Na Ka or Cu Lb3
1.694	409	Au Mz1
2.154	9205	Au Ma1
8.042	470	Cu Ka1
9.708	1227	Au La1

Figure 5.42 : EDX Spectrum of a Naproxen Sodium-Ethycellulose Microcapsule (Batch NE3)



Chi-sqd = 2.23 Livetime = 60.0 Sec.

Standardless Analysis

Element	k-ratio (calc.)	ZAF	Atom %	Element Wt %	Wt % Err. (1-Sigma)
Na-K	0.13256	2.060	36.56	27.30	+/- 4.21
Cl-K	0.63276	1.136	62.39	71.86	+/- 2.36
Mg-K	0.00313	2.665	1.06	0.83	+/- 2.50
Total			100.00	100.00	

Naproxen sodium pellet - carbon coated

Figure 5.43 : EDX Spectrum of a Naproxen Sodium-Cetostearyl Alcohol Microsphere (Batch NC81)

The EDX spectrums of naproxen sodium and the microspheres of Batch NC81 clearly reflect their elemental difference. The spectrum for naproxen sodium depicts a strong peak for sodium which is markedly suppressed in the spectrum of Batch NC81. A similar comparison is noted for the spectrum of Batch NE3 and that of naproxen sodium. Since the spectrum for naproxen sodium was obtained from a sample of pure drug therefore, a high concentration of drug was present at the point of analysis leading to an intense sodium peak. In comparison, the samples of Batch NC81 and NE3 contained relatively small amounts of drug in combination with cetostearyl alcohol and ethylcellulose respectively. Hence, the resultant sodium peak was markedly suppressed. Furthermore, Batch NE3 was formulated as an encapsulated preparation while Batch NC81 was a matrix-type preparation. Therefore, for Batch NE3 the drug is confined to a specific area within the microcapsule as compared to the drug being homogeneously distributed within the matrix of the microsphere of Batch NC81. Thus, it was anticipated that spot analysis by EDX would produce a more distinct peak for Batch NE3.

5.5.2.3 X-ray mapping and line scans

X-ray maps of cross-sections of Batches DE1, NE3 and NC81 detecting the presence of the sodium ion, are illustrated in Figures 5.44, 5.45 and 5.46 respectively. The line scan through a cross-section of a microsphere of Batch NC81 is depicted in Figure 5.47. Since all of the above batches contain a sodium salt of the drug and a retarding material which does not contain a sodium ion, it is possible to determine the distribution pattern of the drug within the formulation.

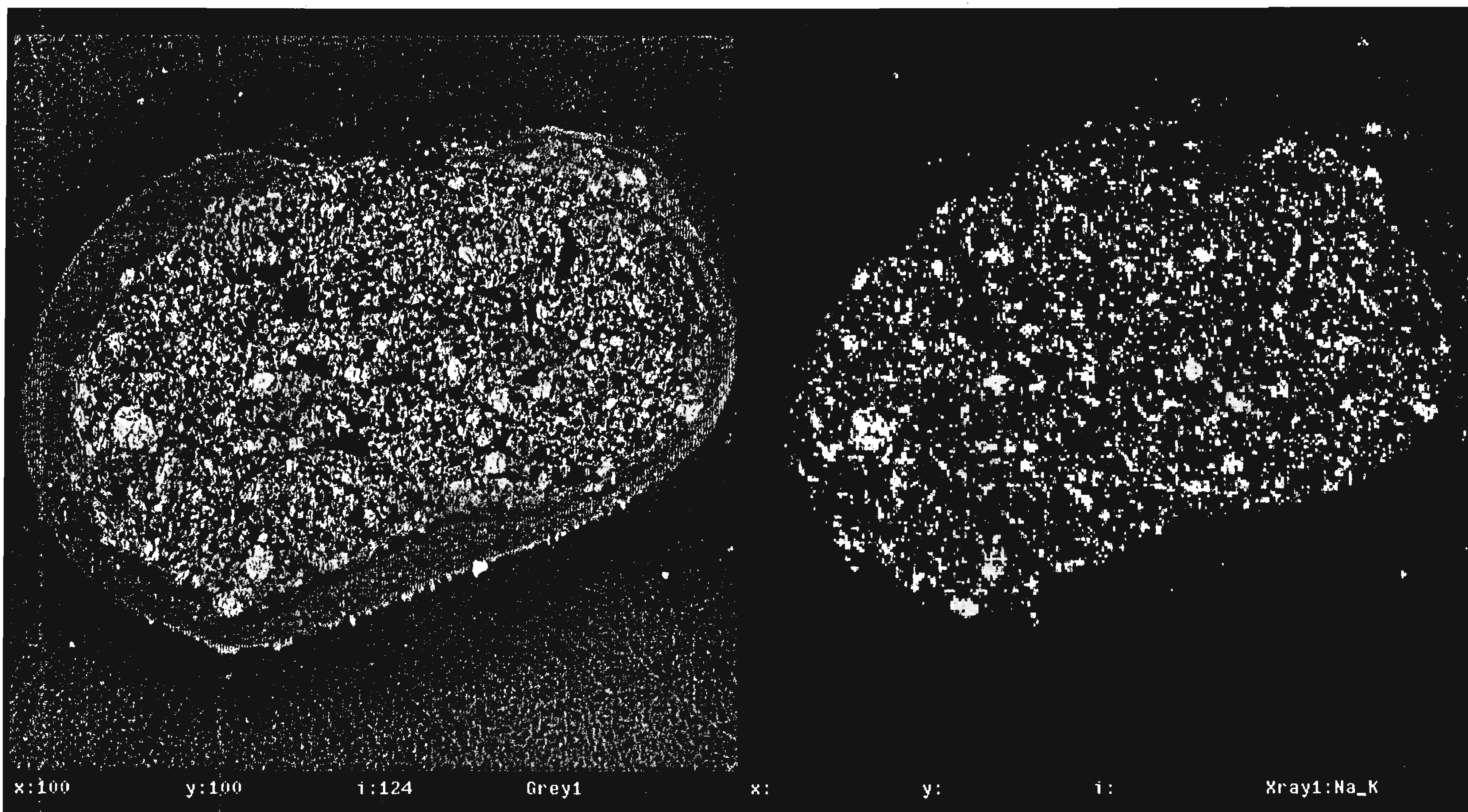


Figure 5.44 : X-ray Map of a Cross-section of a Diclofenac Sodium-Ethylcellulose Microcapsule (Batch DE1)

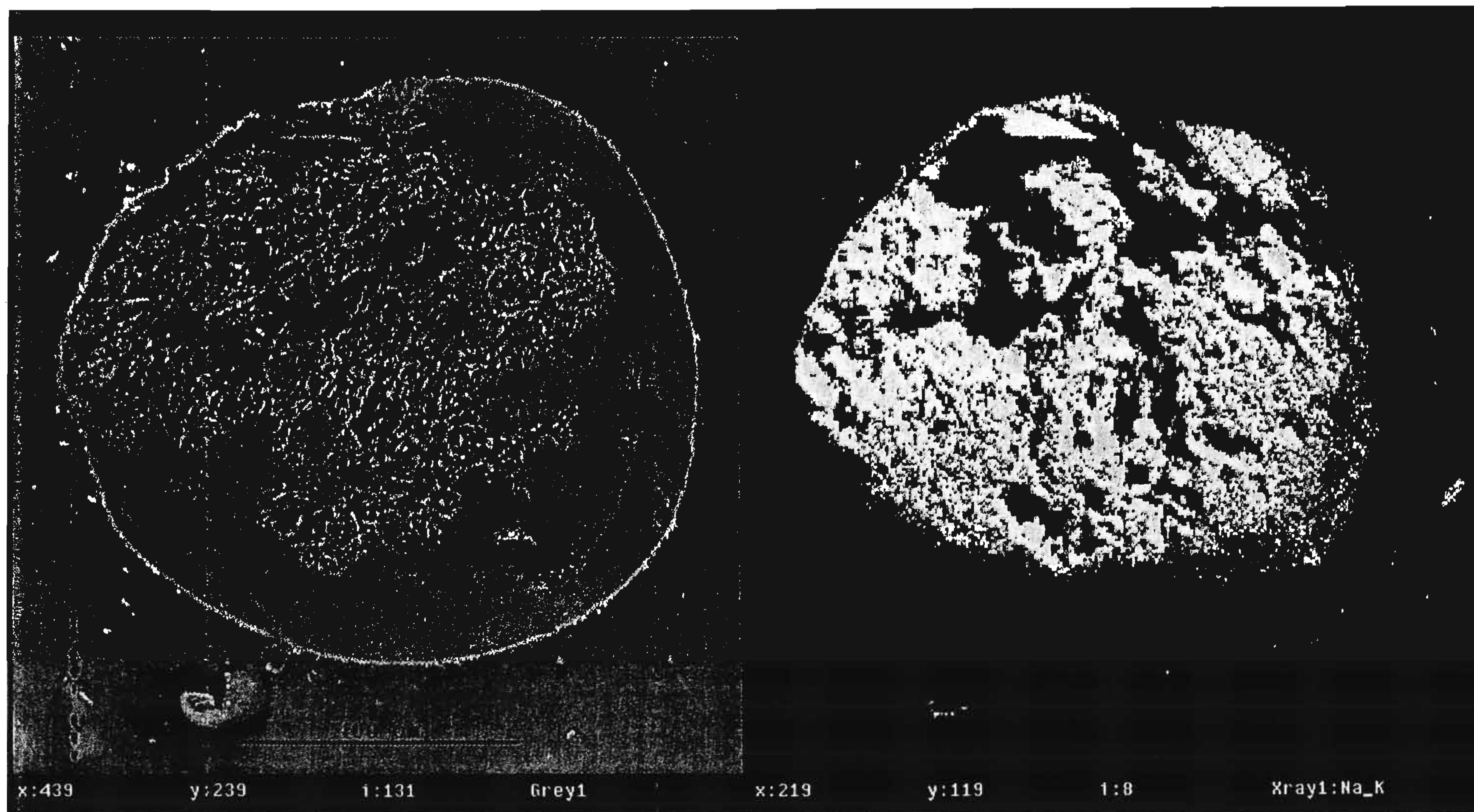


Figure 5.45 : X-ray Map of a Cross-section of a Naproxen Sodium-Ethylcellulose Microcapsule (Batch NE3)

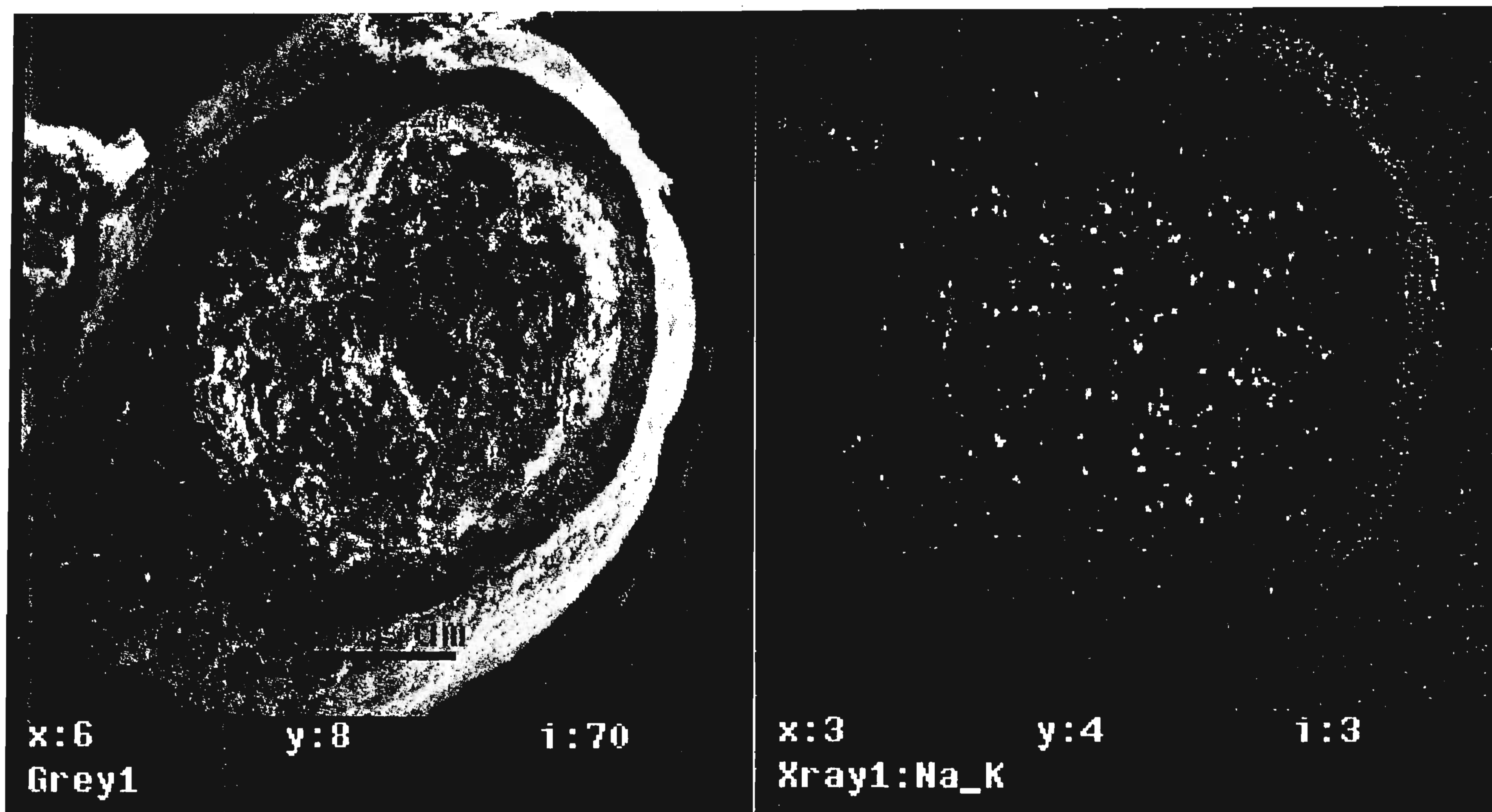


Figure 5.46 : X-ray Map of a Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere (Batch NC81)

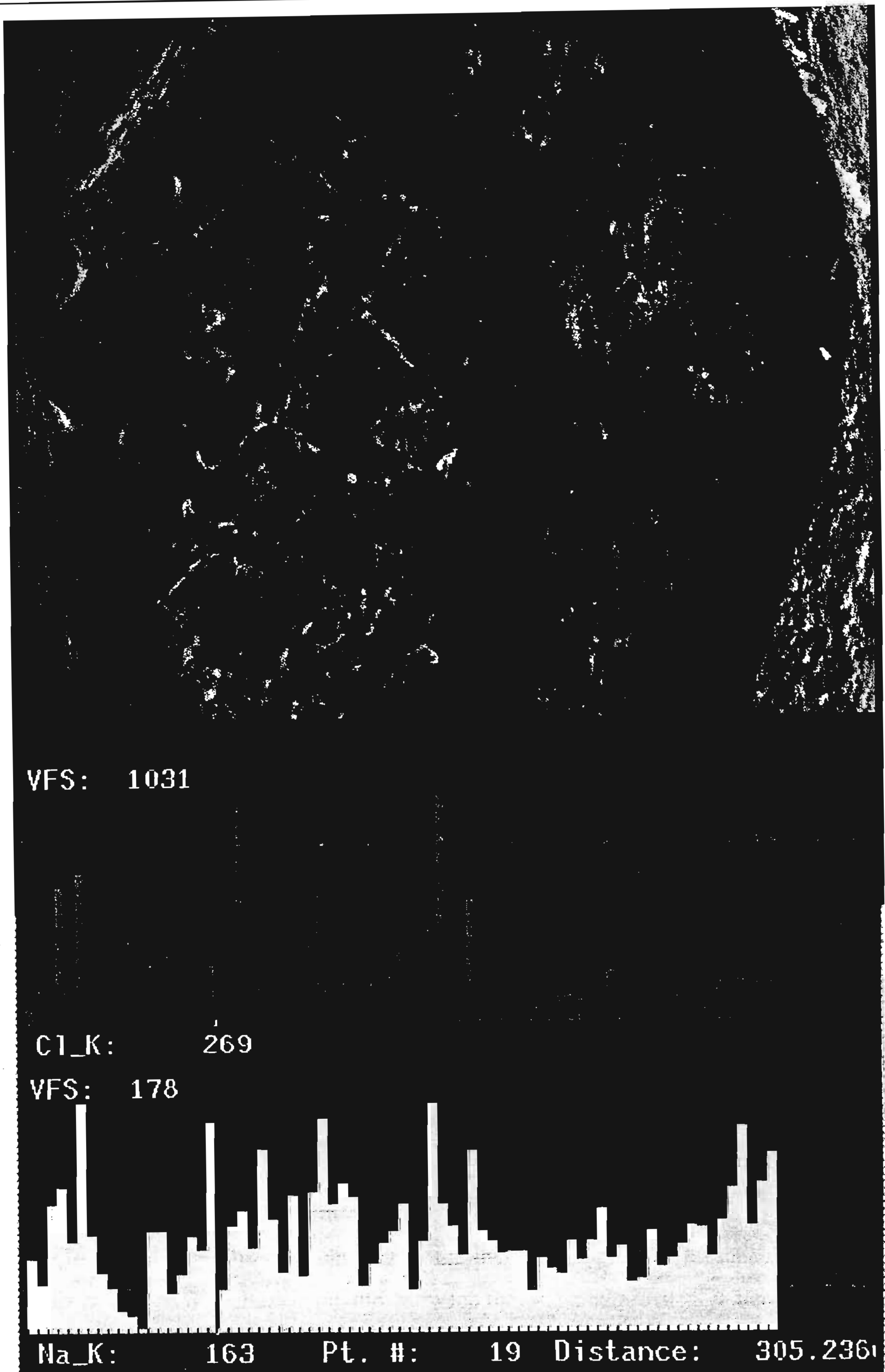


Figure 5.47 : Line Scan of a Cross-section of a Naproxen Sodium-Cetostearyl Alcohol Microsphere (Batch NC81)

The x-ray map of Batch NE3 reveals a high concentration of sodium located within a specific area. Figure 5.45 portrays the existence of a distinct dark region (ethylcellulose) enveloping a coloured region (naproxen sodium). A similar drug distribution pattern is observed for Batch DE1. However, the x-ray map of Batch DE1 differs slightly from Batch NE3 in that the central drug containing region does not depict a high concentration of drug within a specific site. Instead, drug appears to be confined within a granular matrix of polymer which in turn is encapsulated.

It is clearly evident that the drug distribution pattern of Batch NC81 differs from that obtained for Batches NE3 and DE1. As anticipated, the x-ray map of Batch NC81 depicts the drug to be homogeneously distributed within the cetostearyl alcohol matrix. The line scan through a cross-section of a microsphere of Batch NC81 also confirms the homogeneous distribution of the drug in the formulation. Furthermore, it is clearly evident from the sodium and chlorine peaks, that the sodium ion is bound to the drug since the sodium peaks do not correspond to the chlorine peaks. Therefore, the possibility of the sodium ion combining with the chlorine ion to form sodium chloride is excluded.

5.5.3 Differential Scanning Calorimetry (DSC)

DSC was employed to identify possible interaction between naproxen sodium and cetostearyl alcohol in the formulation and to compare it with that of the corresponding physical mixture to determine qualitative changes.

The DSC thermograms of pure naproxen sodium and cetostearyl alcohol is presented in Figures 5.48 and 5.49 respectively. Figure 5.50 depicts the DSC thermograms of microspheres formulated with drug:wax ratios of 1:2 (1), 1:1 (2) and 2:1 (3). Figure 5.51 graphically compares the selected formulation (1) with the naproxen sodium-cetostearyl alcohol 1:1 physical mix (2).

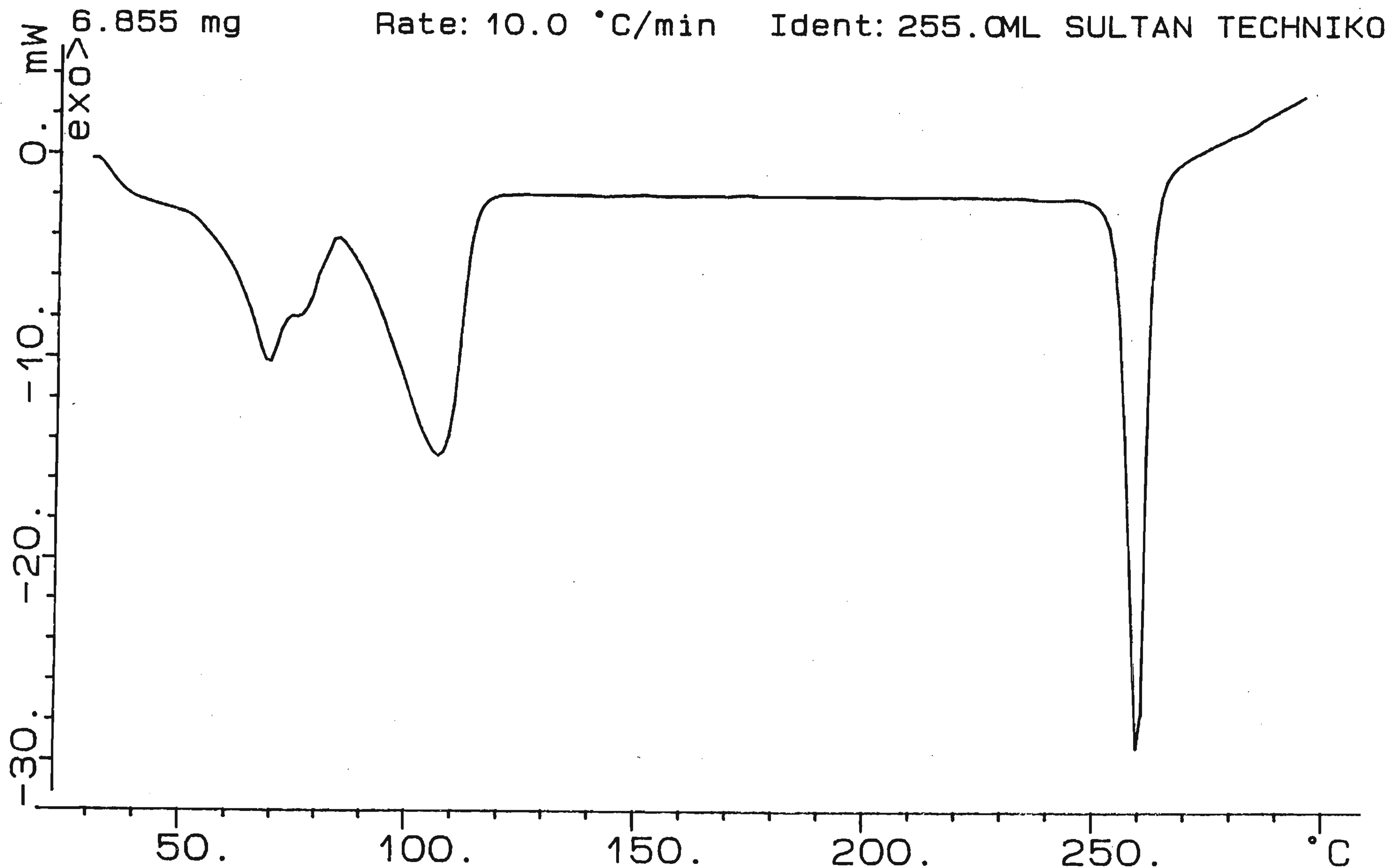


Figure 5.48 : DSC Thermogram of Naproxen Sodium Powder

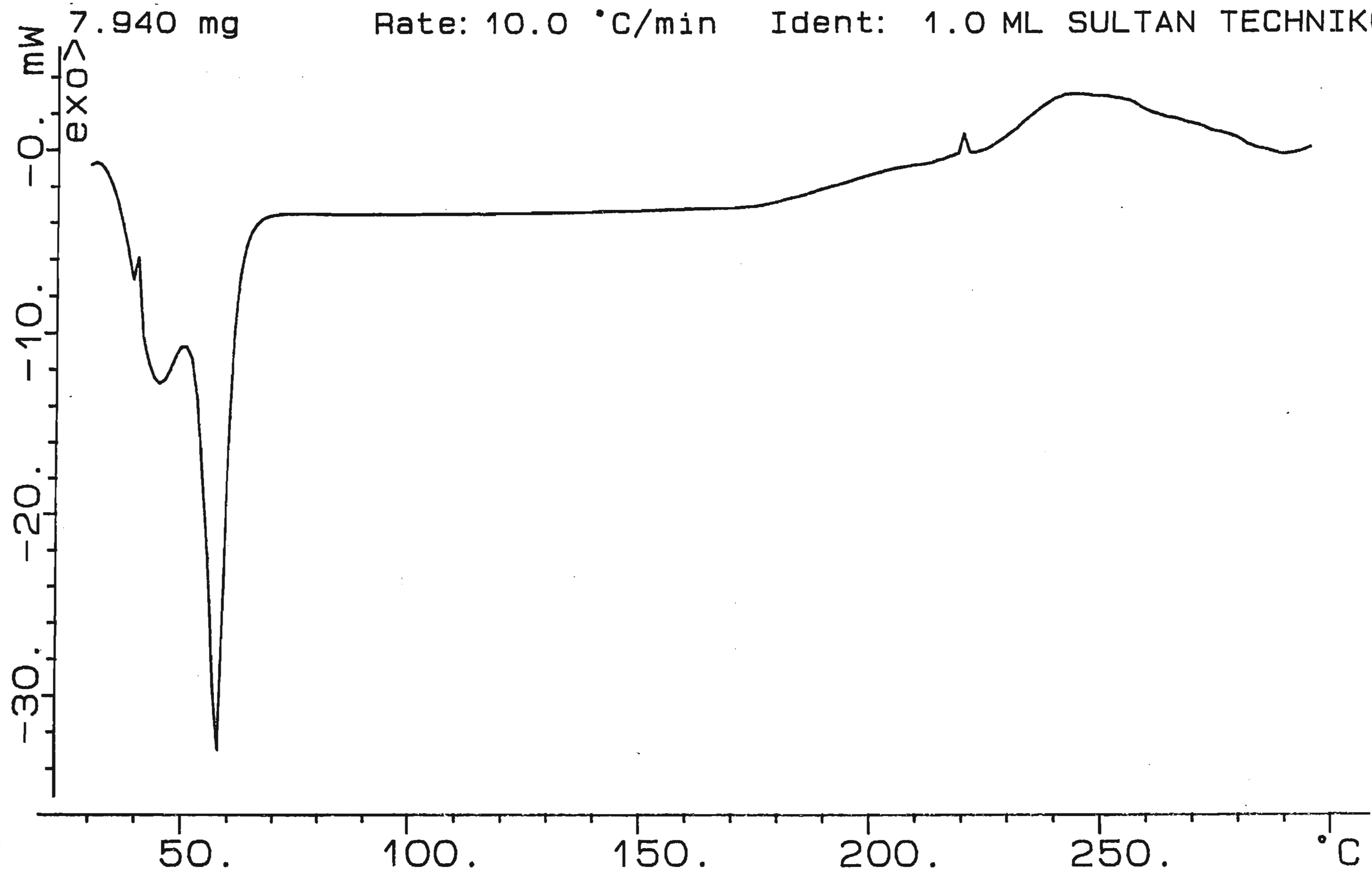


Figure 5.49 : DSC Thermogram of Cetostearyl Alcohol Wax

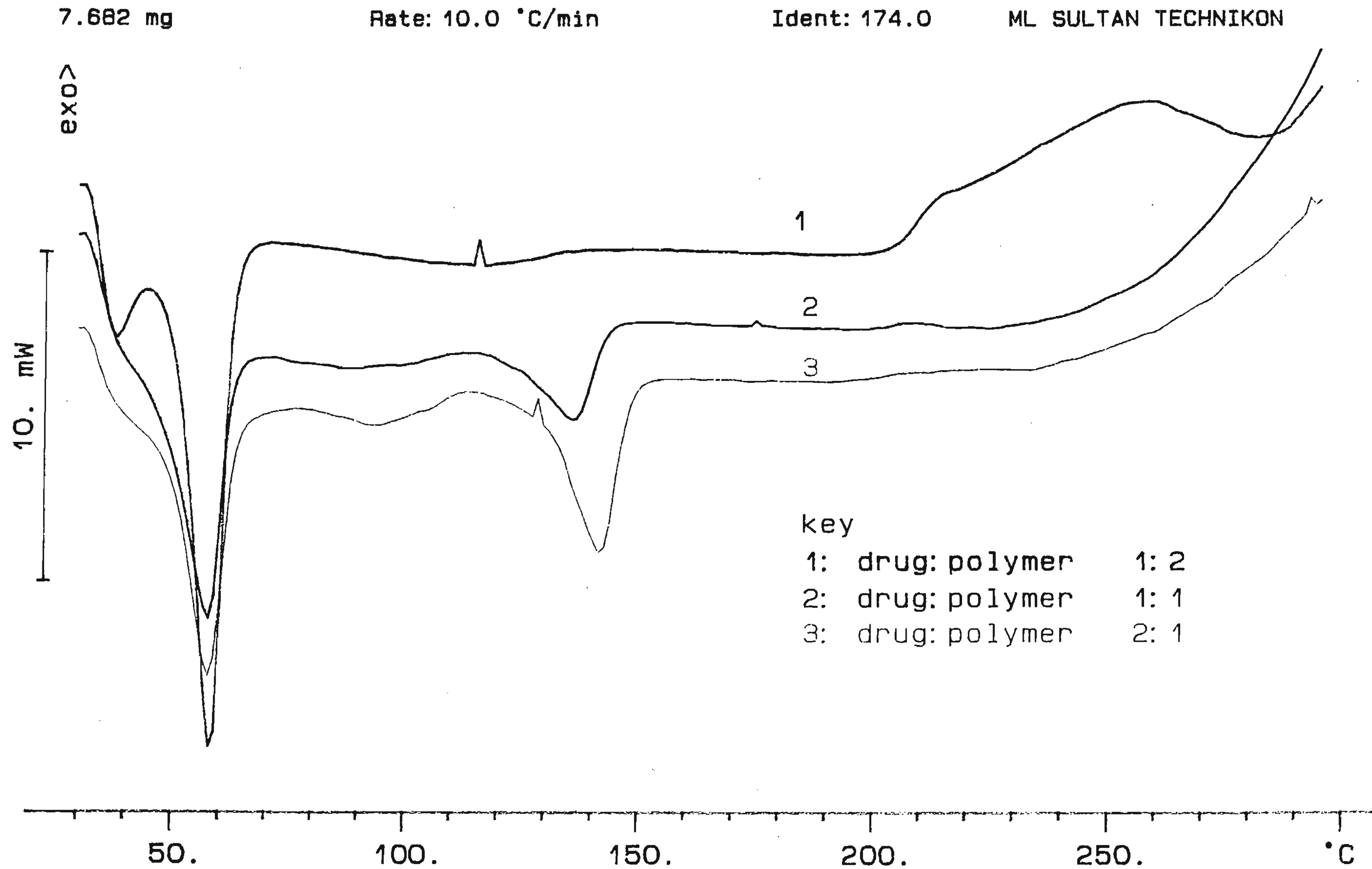


Figure 5.50 : DSC Thermograms of Naproxen Sodium-Cetostearyl Alcohol Microspheres Formulated with Different Drug:Wax Ratios

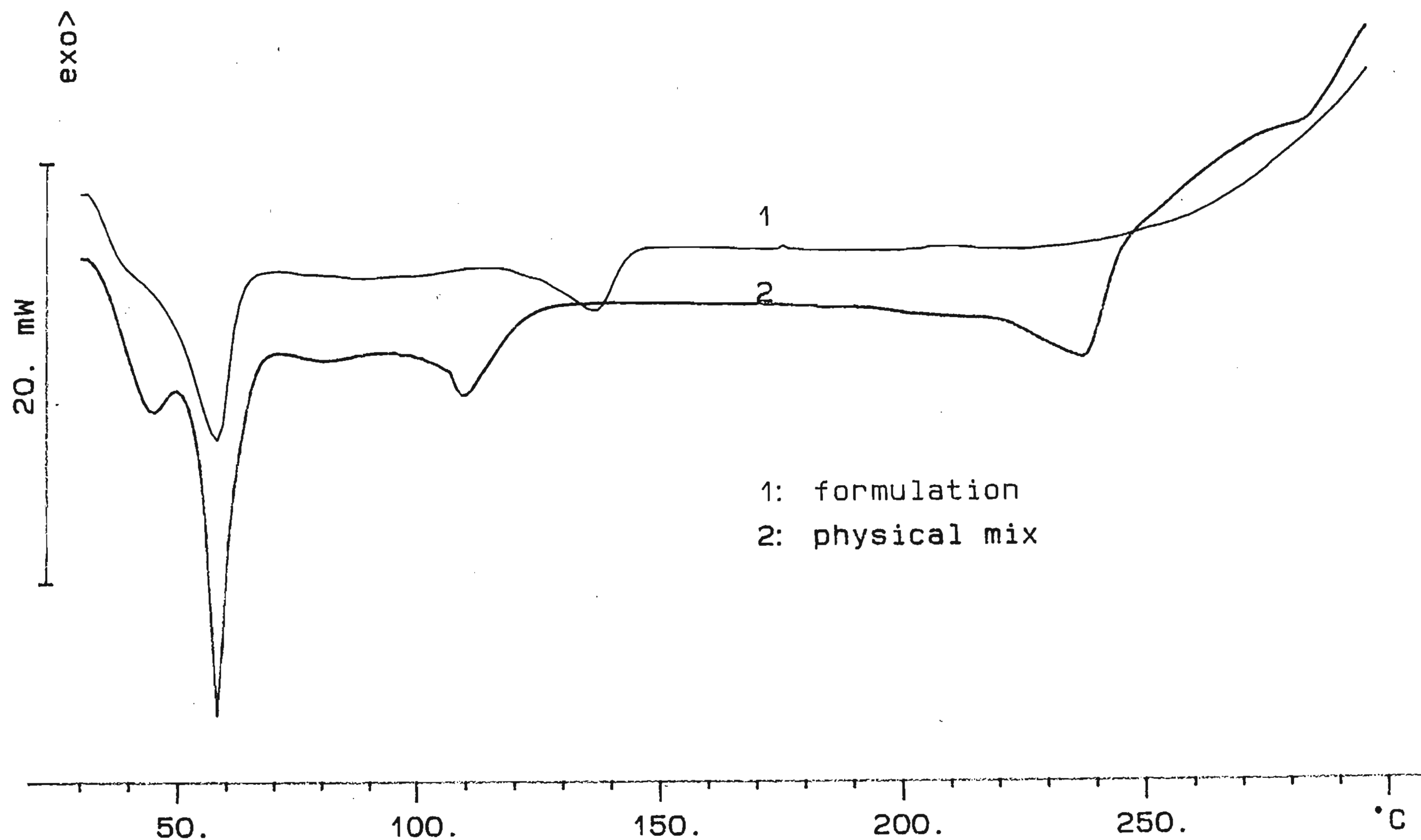


Figure 5.51 : DSC Thermograms of Naproxen Sodium-Cetostearyl Alcohol Microsphere (Batch NC81) and Naproxen Sodium-Cetostearyl Alcohol 1:1 Physical Mix

The endothermic peak, observed to occur at approximately 260°C (Figure 5.48) corresponds to the melting point of pure naproxen sodium. Two other endothermic peaks were also observed to occur at approximately 108°C and 70°C. The differential calorimetric scan for cetostearyl alcohol exhibits an endothermic peak at approximately 58°C which corresponds to the melting point of pure cetostearyl alcohol (Figure 5.49).

Figure 5.50 reveals the disappearance of the naproxen sodium endothermic peak at approximately 260°C. However, there is an emergence of a peak at approximately 142°C for the formulation with a 2:1 drug:wax ratio. A decrease in the endothermic peak is observed as the drug:wax ratio is increased (138°C for the formulation with a 1:1 drug:wax ratio). Microspheres formulated with a 1:2 drug:wax ratio exhibit an exothermic peak at approximately 115°C. In contrast, the physical mixture (Figure 5.51) displays an endothermic peak at approximately 240°C and a second endotherm at approximately 110°C which corresponds to the endothermic peaks of naproxen sodium. However, the intensity of these peaks are markedly suppressed.

For all formulations, as well as the physical mix, the endothermic peak for cetostearyl alcohol remained at approximately 58°C. However, there was an increase in the intensity of the endotherm with decreasing drug:wax ratios. Furthermore, a decrease in the intensity of the cetostearyl alcohol endotherm is observed for the selected formulation when compared to the physical mix. Therefore, it is concluded that there may exist an interaction between the drug and cetostearyl alcohol.

Gordon *et al.* (1984) and Wong *et al.* (1992) reported similar observations with regard to DSC thermograms of ibuprofen-stearyl alcohol mixtures and ibuprofen-cetostearyl alcohol microspheres respectively. Both studies attributed the observed changes in the thermograms to the formation of eutectic mixtures between the drug and the wax. Therefore, it is possible to deduce that observed changes in the thermograms of the present study may be due to the formation of a eutectic mixture between the drug and cetostearyl alcohol.

5.5.4 Stability Studies

The drug release profiles (4.9.3.1) of the drug-cetostearyl alcohol microspheres were obtained initially and after short-term storage under various conditions of temperature and humidity. The potency (4.9.3.2) and moisture content (4.9.3.3) were determined prior to and after 4, 8 and 12 weeks of storage under the various conditions.

5.5.4.1 Potency determination

Potency determinations (HPLC) for samples stored at 21 ± 1°C and 5 ± 1°C for 12 weeks revealed that the assay corresponded closely to the initial potency of the cetostearyl alcohol microspheres. However, the microspheres stored at 40°C and 37°C with 80% relative humidity showed a decrease in potency. After the 12 week storage period, microspheres stored at 40°C and 37°C with 80% relative humidity contained 94.52% and 93.75% of the initial potency respectively. The mean assay values are presented in Table 5.24 whilst Figure 5.52 depicts a typical chromatogram.

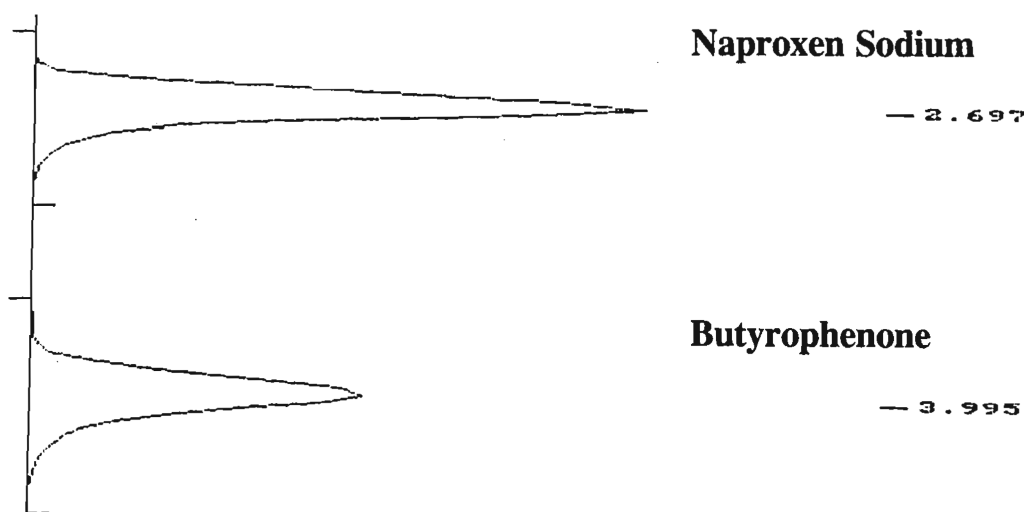


Figure 5.52 : HPLC Chromatogram of a Naproxen Sodium Sample

Table 5.24 : The Effect of Storage Conditions on the Potency of Microspheres from Batch NC81

STORAGE PERIOD (WEEKS)	*POTENCY AFTER STORAGE AT			
	(21 ± 1°C)	40°C	37°C/80% **RH	5 ± 1°C
0	277.51 ± 1.58	277.51 ± 1.58	277.51 ± 1.58	277.51 ± 1.58
4	275.73 ± 0.97	272.88 ± 1.37	272.57 ± 1.67	276.42 ± 1.15
8	273.99 ± 0.40	267.30 ± 2.59	267.83 ± 2.59	274.65 ± 1.37
12	271.30 ± 2.16	262.30 ± 3.71	260.17 ± 4.03	274.84 ± 1.74

* *Individual values for 3 replicate determinations are shown in Appendix 47 (Value corresponds to naproxen sodium content in 1.215 g of naproxen sodium-cetostearyl alcohol microspheres)*

** *Relative humidity*

By extrapolation, the shelf-life of the product was determined from an Arrhenius plot of the potency data. The data for the prediction of the shelf-life of the microspheres of Batch NC81 is presented in Tables 5.25 and 5.26 and Figures 5.53 and 5.54.

Table 5.25 : Log Potency of Microspheres Of Batch NC81 at Various Storage Conditions

STORAGE PERIOD (DAYS)	LOG POTENCY AFTER STORAGE AT			
	(21 ± 1°C)	40°C	37°C/80% *RH	5 ± 1°C
	294 ± 1°K	313°K	310°K	278 ± 1°K
0	2.443	2.443	2.443	2.443
30	2.440	2.436	2.435	2.442
60	2.438	2.427	2.428	2.439
90	2.433	2.419	2.415	2.439

* *Relative humidity*

Table 5.26 : Shelf-Life Prediction Data

TEMPERATURE (°K)	1/TEMPERATURE * 10^{-3} ($°K^{-1}$)	K * 10^{-4} ($days^{-1}$)	LOG K
294	3.40	2.30	-3.64
313	3.20	6.91	-3.16
310	3.23	6.91	-3.16
278	3.59	1.15	-3.94

The rate constants for the degradation of naproxen sodium at the various storage conditions were determined from the graph of log concentration versus time. By extrapolation of the log K versus the reciprocal of absolute temperature (1/°K), the value of the rate constant (K) at room temperature was determined. Subsequently, the shelf-life was calculated to be 1.07 years which may be deemed to be unacceptable for a pharmaceutical formulation. It is postulated that the low pH employed during the manufacturing process may have contributed significantly to the acceleration of the degradation of naproxen sodium. Furthermore, any interaction between the drug and the cetostearyl alcohol may also result in the instability of the preparation.

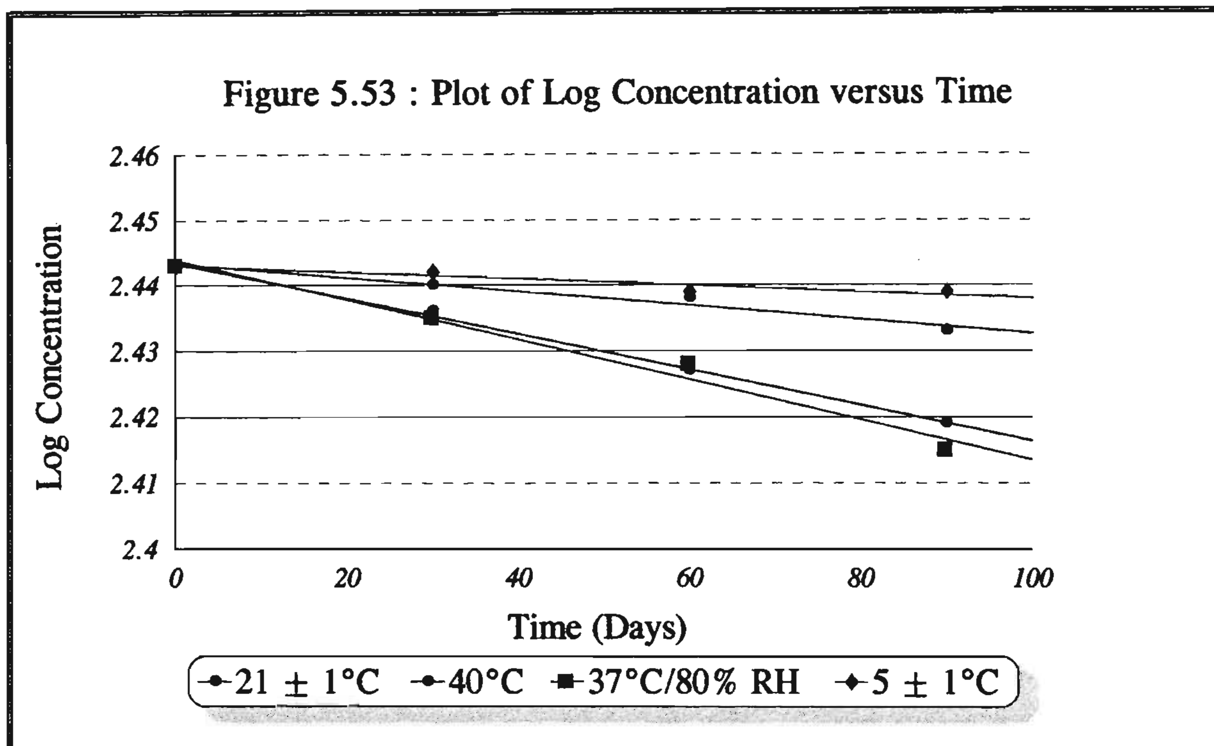


Figure 5.53 : Plot of Log Concentration versus Time
Log Concentration
2.46
2.45
2.44
2.43
2.42
2.41
2.4
0
20
40
60
80
100
Time (Days)
21 ± 1°C
40°C
37°C/80% RH
5 ± 1°C

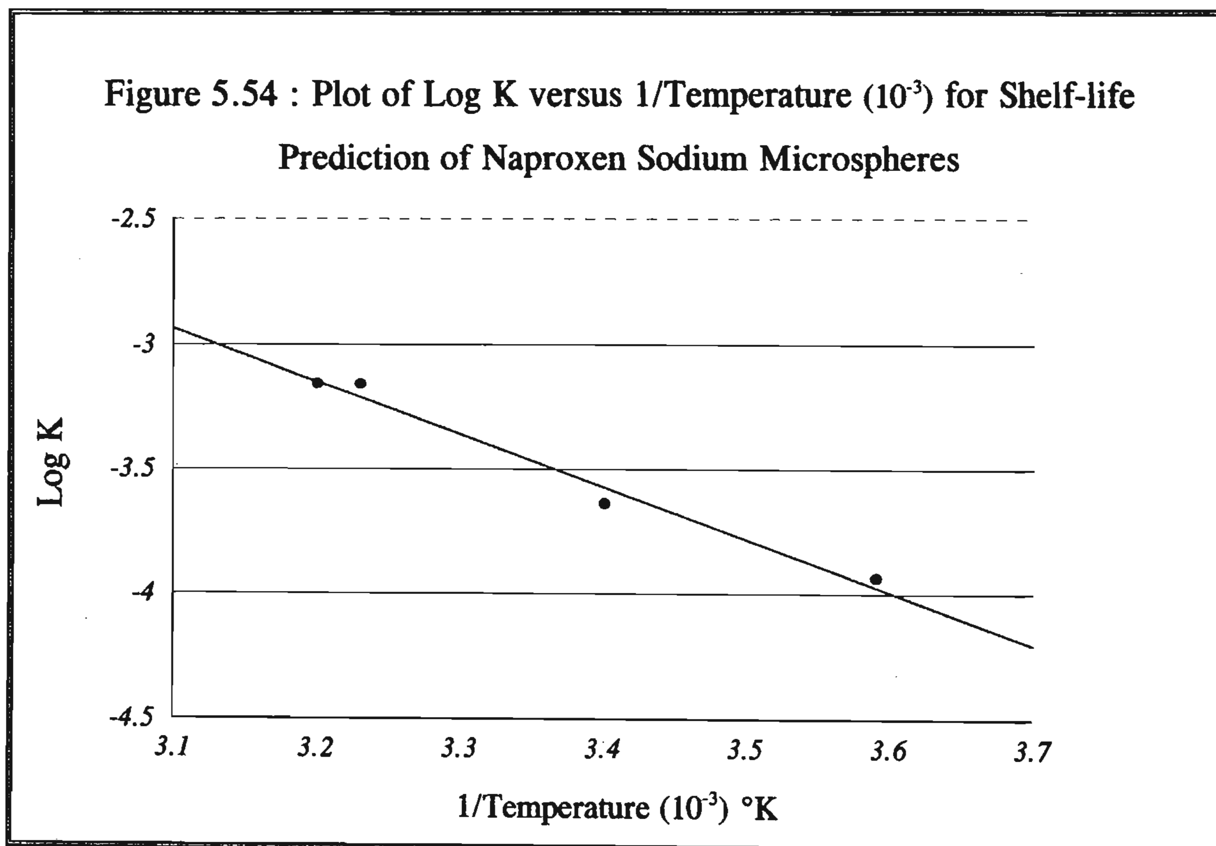


Figure 5.54 : Plot of Log K versus 1/Temperature (10⁻³) for Shelf-life Prediction of Naproxen Sodium Microspheres
Log K
-2.5
-3
-3.5
-4
-4.5
3.1
3.2
3.3
3.4
3.5
3.6
3.7
1/Temperature (10⁻³) °K

5.5.4.2 Moisture content determination

The moisture content of the microspheres was determined prior to and after 4, 8 and 12 weeks of storage. Table 5.27 depicts the moisture content of the microspheres as determined at the various storage intervals.

Table 5.27 : Moisture Content of Microspheres after Storage Under Different Storage Conditions

STORAGE CONDITION	MOISTURE CONTENT (%^{w}/w)			
	*INITIALLY	*4 WEEKS	*8 WEEKS	*12 WEEKS
21 ± 1°C	0.592 ± 0.096	0.381 ± 0.020	0.609 ± 0.043	0.541 ± 0.056
40°C	0.592 ± 0.096	0.642 ± 0.035	0.682 ± 0.135	0.489 ± 0.054
37°C/80% **RH	0.592 ± 0.096	1.304 ± 0.098	1.116 ± 0.080	1.538 ± 0.034
5 ± 1°C	0.592 ± 0.096	0.927 ± 0.132	1.076 ± 0.047	1.080 ± 0.175

* *Individual values for 3 replicate determinations are presented in Appendix 48*

** *relative humidity*

As indicated in Table 5.27, the microspheres that were stored at 21 ± 1°C and 40°C displayed negligible loss/gain of moisture. However, microspheres stored at 5 ± 1°C and 37°C with 80% relative humidity showed appreciable gain in moisture content of the microspheres. Therefore, it may be concluded that the drying process to which the microspheres have been subjected to after manufacture was adequate since the microspheres possess a low moisture content (0.592 ± 0.096%^{w}/w).

5.5.4.3 Drug release evaluation

5.5.4.3.1 *Storage at Room Temperature (21 ± 1°C)*

The mean drug release data and profiles obtained initially and after 2, 4, 8 and 12 weeks of storage at 21 ± 1°C are outlined in Table 5.28 and Figure 5.55 respectively.

Table 5.28 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Stored at Room Temperature (21 ± 1°C)

TIME	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD				
(HOURS)	0 WEEKS	2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	18.40 ± 0.42	18.97 ± 0.34	19.22 ± 0.58	17.87 ± 0.34	17.83 ± 0.69
1	27.18 ± 0.40	28.28 ± 0.25	28.32 ± 0.24	27.95 ± 0.41	24.92 ± 0.71
1.5	35.30 ± 0.50	36.21 ± 0.37	35.68 ± 0.76	36.33 ± 0.59	31.15 ± 0.69
2	41.88 ± 0.58	42.71 ± 0.70	42.71 ± 1.03	43.44 ± 0.40	37.67 ± 0.54
3	52.95 ± 0.71	54.60 ± 0.56	55.58 ± 0.78	54.77 ± 0.59	48.96 ± 0.65
4	62.08 ± 0.45	64.72 ± 0.73	64.32 ± 0.62	64.39 ± 0.49	60.31 ± 0.57
5	70.02 ± 0.40	72.60 ± 0.78	72.15 ± 0.43	72.63 ± 0.20	68.42 ± 0.65
6	76.09 ± 0.71	79.22 ± 0.74	79.75 ± 0.51	78.45 ± 0.35	76.27 ± 0.49
7	81.45 ± 0.62	83.78 ± 0.72	83.49 ± 0.29	83.46 ± 0.37	80.45 ± 0.42
8	85.86 ± 0.80	87.63 ± 0.58	87.26 ± 0.40	87.43 ± 0.35	87.72 ± 0.89

* *Individual values for 4 replicate determinations are depicted in Appendices 49 - 53 respectively*

According to the results presented in Table 5.28 and Figure 5.55, the microspheres stored at room temperature (21 ± 1°C) did not exhibit any appreciable change in the drug release characteristics for the duration of the stability study. Consequently, it was deduced that the formulation would be stable at room temperature with regard to the drug release characteristics of the microspheres.

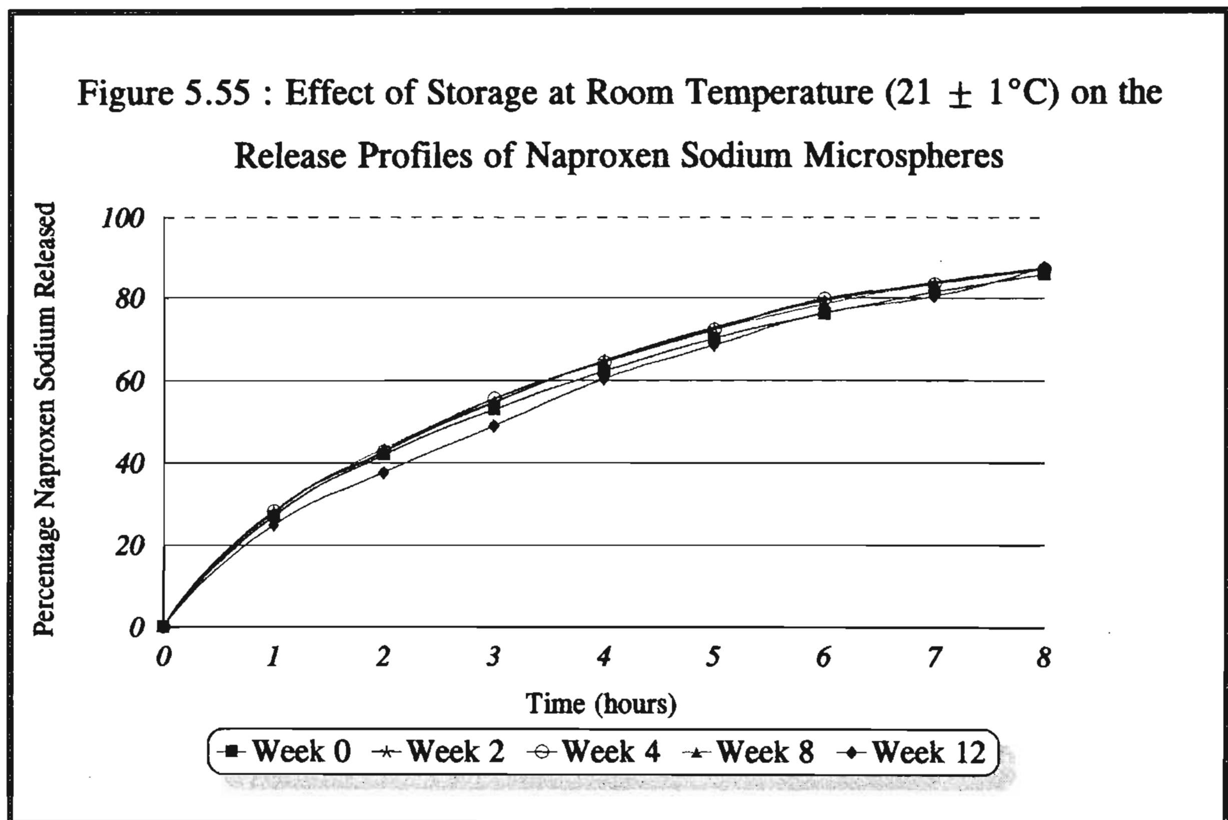


Figure 5.55 : Effect of Storage at Room Temperature (21 ± 1 °C) on the Release Profiles of Naproxen Sodium Microspheres

5.5.4.3.2 *Storage at 40°C*

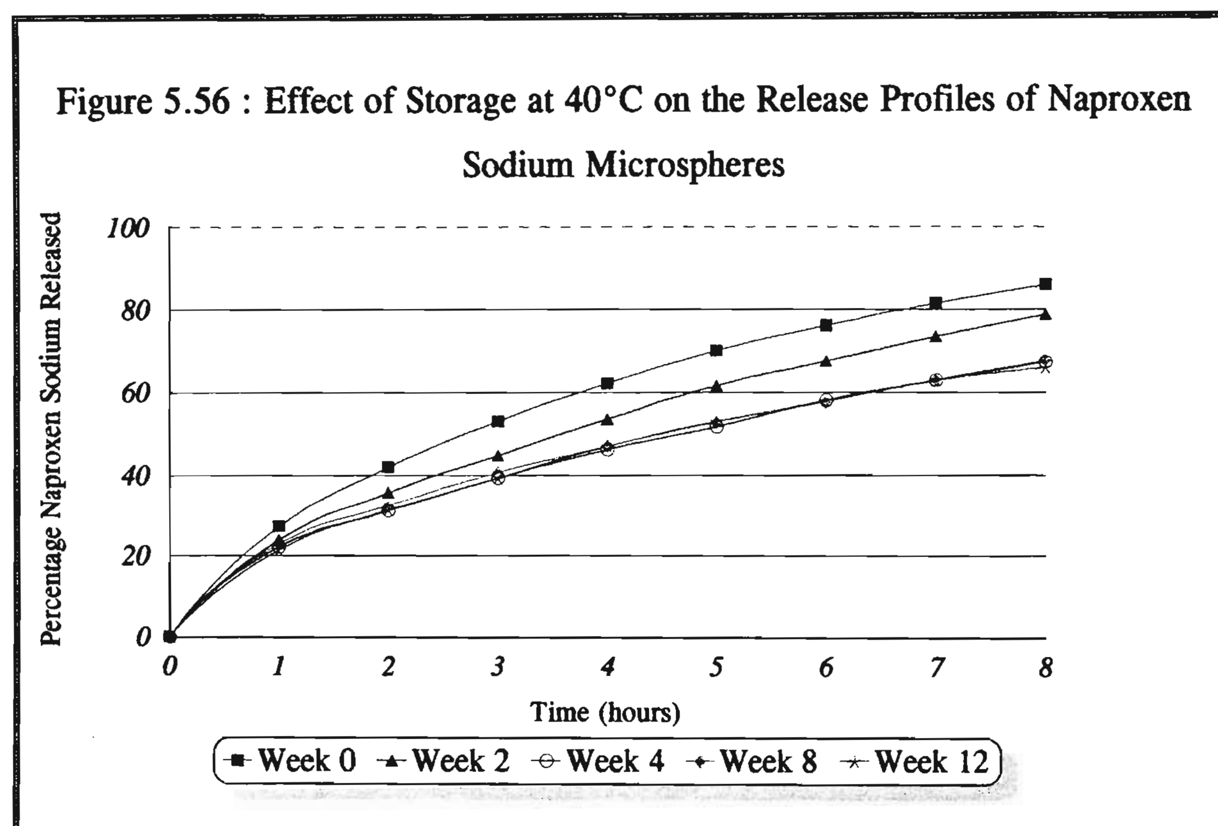
The mean cumulative percentage drug released and the corresponding drug release profiles for microspheres stored at 40°C initially and after 2, 4, 8 and 12 weeks of storage are depicted in Table 5.29 and Figure 5.56 respectively.

Table 5.29 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Stored at 40°C

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD				
	0 WEEKS	2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	18.40 ± 0.42	16.84 ± 0.16	15.53 ± 0.31	16.06 ± 0.21	14.91 ± 0.63
1	27.18 ± 0.40	23.80 ± 0.09	22.08 ± 0.19	22.90 ± 0.19	21.29 ± 0.49
1.5	35.30 ± 0.50	29.78 ± 0.36	27.24 ± 0.25	28.26 ± 0.23	26.69 ± 0.10
2	41.88 ± 0.58	35.76 ± 0.37	31.15 ± 0.21	32.55 ± 0.39	31.33 ± 0.49
3	52.95 ± 0.71	44.75 ± 0.16	39.26 ± 0.37	40.58 ± 0.34	39.24 ± 0.48
4	62.08 ± 0.45	53.46 ± 0.25	46.18 ± 0.36	46.94 ± 0.37	46.94 ± 0.90
5	70.02 ± 0.40	61.57 ± 0.27	51.67 ± 0.42	52.76 ± 0.37	52.88 ± 0.39
6	76.09 ± 0.71	67.51 ± 0.33	58.05 ± 0.44	57.67 ± 0.65	57.83 ± 0.48
7	81.45 ± 0.62	73.48 ± 0.31	62.82 ± 0.35	62.94 ± 0.35	62.77 ± 0.44
8	85.86 ± 0.80	78.79 ± 0.47	67.29 ± 0.24	67.75 ±0.28	65.97 ± 0.56

* *Individual values for 4 replicate determinations are depicted in Appendices 49 and 54 - 57 respectively*

Figure 5.56 : Effect of Storage at 40°C on the Release Profiles of Naproxen Sodium Microspheres



Clearly, as is evident from the drug release data, microspheres stored at 40°C failed to maintain the drug release characteristics of the formulation. Drug release from the microspheres displayed a 7.07% decrease at 8 hours after the 2 week storage period. A further decrease of 11.50% was noted after the 1 month storage period after which drug release remained almost similar for the remainder of the duration of stability testing. The difference in drug release at 8 hours between the initial profile and the profile obtained after 12 weeks of storage was 19.89%.

It is concluded that the suppression of the drug release profile observed with storage at 40°C may be attributed to a combination of two effects. Firstly, exposure of the microspheres to the elevated temperature resulted in gradual coalescence of the wax matrix. Secondly, the decrease in drug release may be correlated to the decrease in the potency of the microspheres that were stored at 40°C.

5.5.4.3.3 *Storage at 37°C with 80% Relative Humidity*

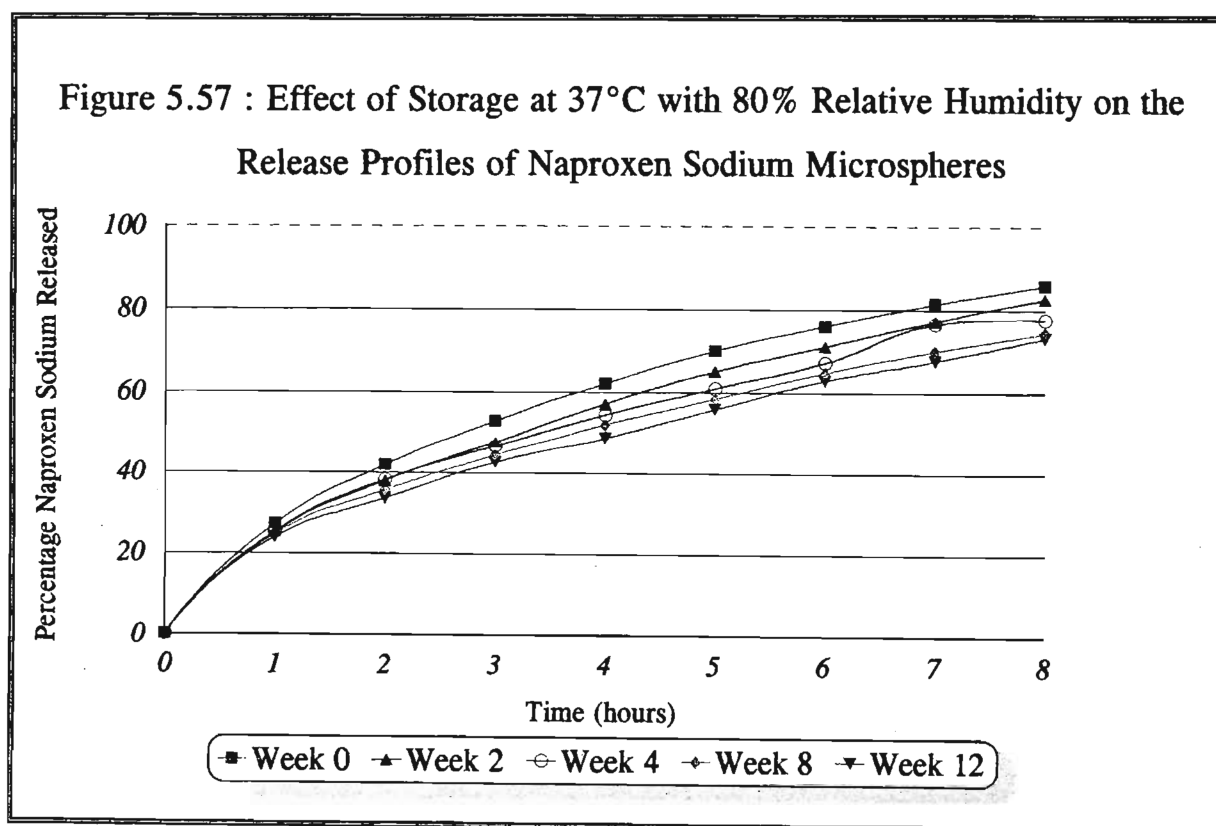
To determine the stability of the microspheres to elevated temperatures and humidity conditions, the drug release profiles of the microspheres stored at 37°C with 80% relative humidity were established over a period of 12 weeks. The mean drug release data and profiles for the above storage condition are presented in Table 5.30 and Figure 5.57 respectively.

Table 5.30 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Stored at 37°C with 80% Relative Humidity

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD				
	0 WEEKS	2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	18.40 ± 0.42	16.92 ± 0.23	17.46 ± 0.52	17.17 ± 0.39	16.72 ± 0.36
1	27.18 ± 0.40	25.08 ± 0.62	25.13 ± 0.99	24.63 ± 0.34	23.81 ± 0.62
1.5	35.30 ± 0.50	31.96 ± 0.50	32.10 ± 1.04	30.21 ± 0.39	28.40 ± 0.71
2	41.88 ± 0.58	37.91 ± 0.42	38.17 ± 1.16	35.57 ± 0.32	33.55 ± 0.88
3	52.95 ± 0.71	47.73 ± 0.42	46.68 ± 1.37	44.39 ± 0.42	42.57 ± 0.94
4	62.08 ± 0.45	57.11 ± 0.48	54.46 ± 1.73	52.04 ± 0.55	48.85 ± 0.87
5	70.02 ± 0.40	65.04 ± 0.37	60.90 ± 1.90	58.34 ± 0.35	55.91 ± 1.10
6	76.09 ± 0.71	71.12 ± 0.66	67.16 ± 1.99	64.71 ± 0.62	62.80 ± 1.12
7	81.45 ± 0.62	77.27 ± 0.50	76.61 ± 2.47	69.97 ± 0.36	67.64 ± 1.46
8	85.86 ± 0.80	82.72 ± 0.73	77.72 ± 2.24	74.52 ± 0.38	73.25 ± 1.46

* *Individual values for 4 replicate determinations are depicted in Appendices 49 and 58 - 61 respectively*

Figure 5.57 : Effect of Storage at 37°C with 80% Relative Humidity on the Release Profiles of Naproxen Sodium Microspheres



It is evident from the drug release profiles that storage at 37°C with 80% relative humidity affects the drug release characteristics of the microspheres. The drug release data depicts an overall decrease, at the 8 hour dissolution sampling interval, of 12.61% at the 12 week storage period when compared to the initial drug release profile. This effect is similar to the effect observed for microspheres stored at 40°C. Therefore, the depression in the drug release profile observed at the 37°C with 80% relative humidity storage condition is also be attributed to coalescence of the wax matrix (Figure 5.34) and the decreased potency of the microspheres.

Consequently, it is argued that, in order for the newly formulated microspheres to maintain their potency and initial drug release characteristics, it is necessary to store the microspheres at temperatures below 37°C. Furthermore, the data suggests that storage at a temperature of approximately 21°C (room temperature) would be preferable.

5.5.4.3.4 *Storage at Low Temperature (5 ± 1 °C)*

The mean cumulative percentage of drug released from microspheres stored at 5 ± 1°C after 2, 4, 8 and 12 weeks and their respective profiles are shown in Table 5.31 and Figure 5.58 respectively.

Table 5.31 : Mean Cumulative Percentages of Naproxen Sodium Released from Microspheres Stored at 5 ± 1°C

TIME (HOURS)	*MEAN CUMULATIVE PERCENTAGE RELEASED ± SD				
	0 WEEKS	2 WEEKS	4 WEEKS	8 WEEKS	12 WEEKS
0.5	18.40 ± 0.42	18.04 ± 0.24	17.62 ± 0.72	20.99 ± 1.12	20.91 ± 0.36
1	27.18 ± 0.40	26.85 ± 0.19	24.92 ± 0.25	30.80 ± 1.80	31.29 ± 0.40
1.5	35.30 ± 0.50	34.12 ± 0.17	31.68 ± 0.70	38.94 ± 1.62	39.97 ± 0.41
2	41.88 ± 0.58	42.73 ±0.33	37.99 ± 0.24	46.24 ± 2.30	47.02 ± 0.34
3	52.95 ± 0.71	50.82 ± 0.24	45.36 ± 0.23	57.45 ± 2.74	59.15 ± 0.57
4	62.08 ± 0.45	59.85 ± 0.10	51.34 ± 0.27	67.42 ± 3.24	69.21 ± 0.55
5	70.02 ± 0.40	67.46 ± 0.24	61.80 ± 0.25	73.84 ± 3.19	77.60 ± 0.57
6	76.09 ± 0.71	72.93 ± 0.35	70.36 ± 0.44	81.73 ± 4.11	84.08 ± 0.57
7	81.45 ± 0.62	78.12 ± 0.40	79.30 ± 0.34	87.90 ± 3.91	89.69 ±0.46
8	85.86 ± 0.80	83.74 ± 0.37	84.72 ± 0.39	91.28 ± 5.39	93.86 ± 0.97

* *Individual values for 4 replicate determinations are depicted in Appendices 49 and 62 - 65 respectively*

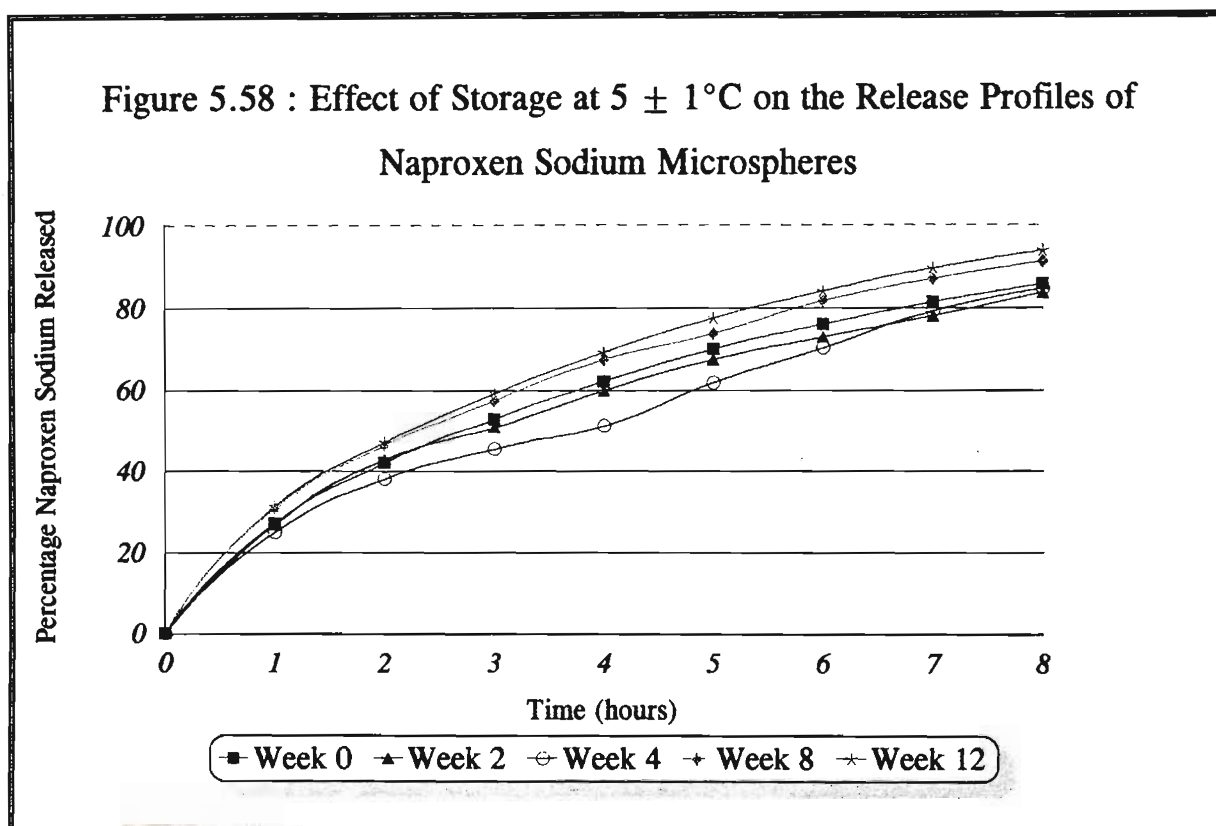


Figure 5.58 : Effect of Storage at 5 ± 1°C on the Release Profiles of Naproxen Sodium Microspheres

The dissolution characteristics of the microspheres stored at 5 ± 1°C did not change significantly after the 12 week storage period. Figure 5.58 depicts the drug release profile initially and after 12 weeks to be with the acceptable limits. Therefore, it was concluded that the microspheres were considered to be stable for the period of the study (12 weeks) when stored at 5 ± 1°C.

5.5.5 Characterization of Drug Release from Cetostearyl alcohol Microspheres

The dissolution data obtained from cetostearyl alcohol microspheres (Batch NC81) in phosphate buffer pH 7.4 were employed to elucidate the mechanism/s of drug release. The drug release kinetics were determined by fitting the dissolution data to each of the following models :-

1) Zero-order kinetics
2) First order kinetics
3) Square root of time model (Higuchi Equation)
4) Power Law Expression
5) Cube Root Law

Linear regression was performed to obtain the equations and correlation coefficients (r^2) values describing the respective curves.

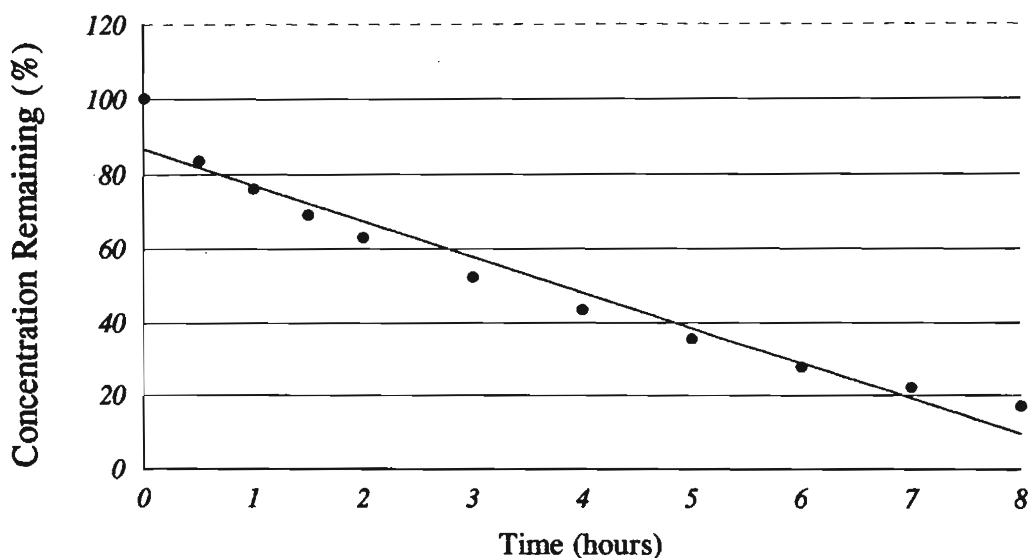
5.5.5.1 Zero- and First order kinetics

In accordance with Martin *et al.* (1993), the dissolution data of Batch NC81 were tabulated (Table 5.32) and graphically illustrated in Figures 5.59 and 5.60.

Table 5.32 : Determination of the Order of Drug Release from Batch NC81

TIME (HOURS)	*C (%)	LOG C
0	100	2.00
0.5	83.32	1.92
1	75.95	1.88
1.5	68.90	1.84
2	62.80	1.80
3	52.16	1.72
4	43.31	1.64
5	35.55	1.55
6	27.59	1.44
7	21.96	1.34
8	16.79	1.23

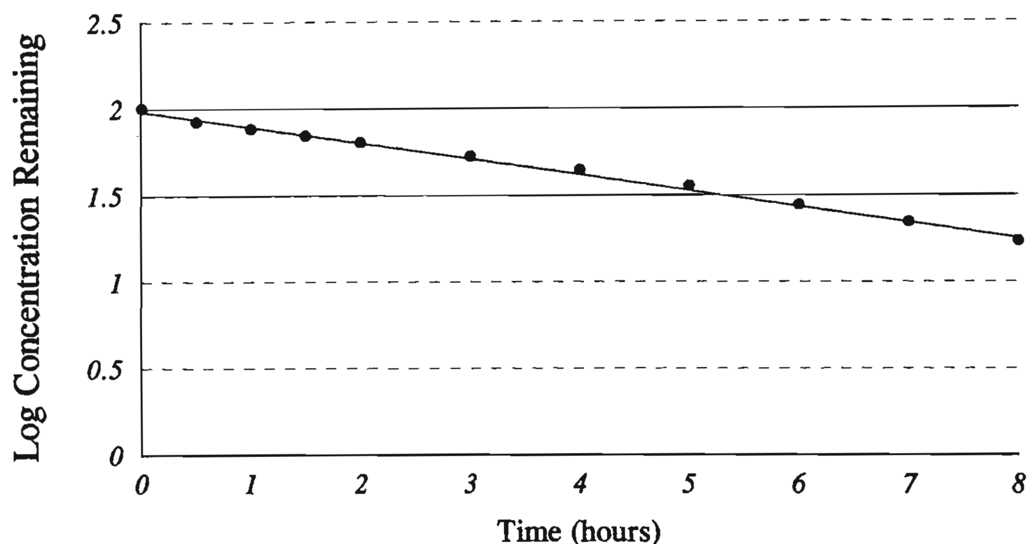
Figure 5.59 : Determination of the Order of Drug Release (Batch NC81): Zero-Order Model



R-squared = 0.954

y = -9.63x + 86.76

Figure 5.60 : Determination of the Order of Drug Release (Batch NC81): First Order Model



R-squared = 0.996

y = -0.09x + 1.99

The zero-order rate constant (-slope) was found to be 9.63 %/hour (r^2 = 0.954) and the first order rate constant was found to be 0.21 $hour^{-1}$ (r^2 = 0.996) respectively. The results of linear regression indicate that the cetostearyl microspheres exhibited mixed first and zero-order drug release characteristics. However, it is clearly evident that there is a tendency towards first order drug release, based on the higher r^2 value obtained for the first order fit.

5.5.5.2 The square root of time model

The Higuchi Equation (equation 2.6) shows that the liberation of drug is a linear function of the square root of time. Although Higuchi's square root of time model relates to planar systems, it has been used frequently as a general empirical model for describing drug

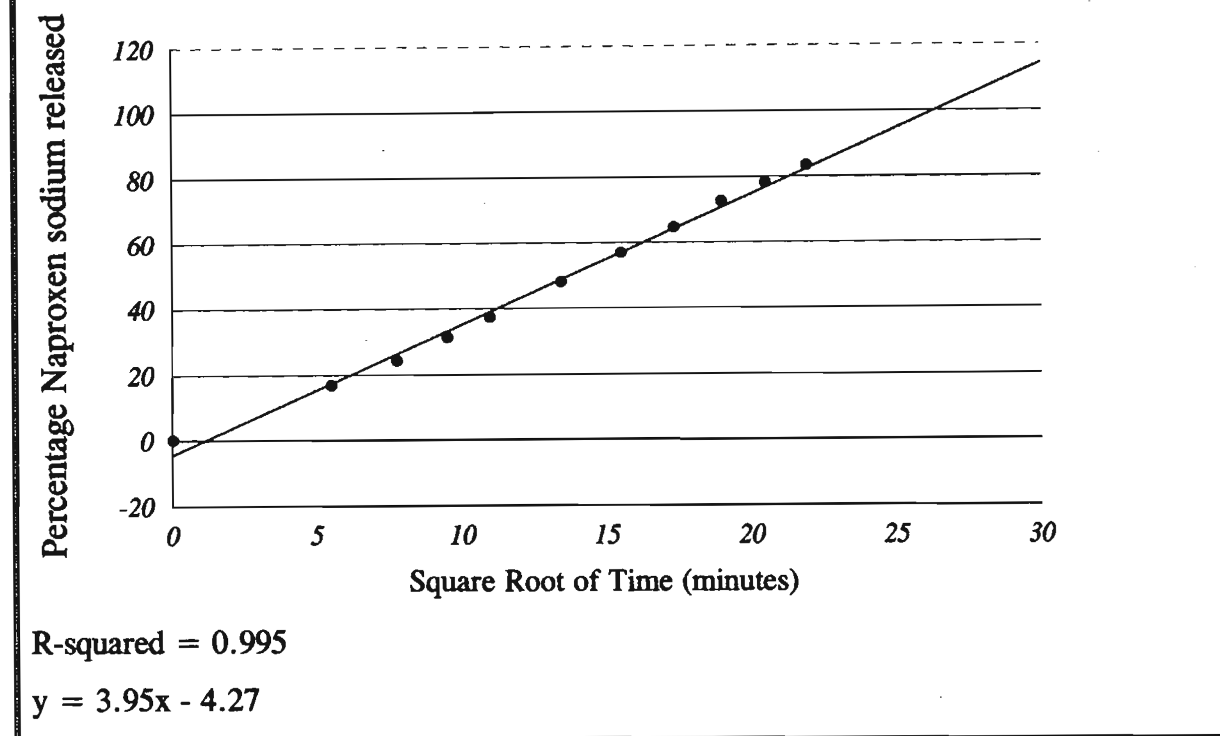
release from suspension matrix systems irrespective of their geometrical shape (Wong *et al.*, 1992). The drug release data and profiles for the application of dissolution data to the square root of time model are presented in Table 5.33 and Figure 5.61.

Table 5.33 : Drug Release Data in Accordance with the Higuchi Equation

SQUARE ROOT OF TIME (MINUTES$^{0.5}$)	MEAN CUMULATIVE PERCENTAGE DRUG RELEASED ± SD
0	0
5.48	16.68
7.75	24.05
9.49	31.10
10.95	37.20
13.42	47.84
15.49	56.69
17.32	64.45
18.97	72.41
20.49	78.04
21.91	83.21

A good fit and a high correlation coefficient was obtained for the square root of time model (r^2 = 0.995). It appears therefore that the microspheres behave as contracting spheres with the drug-depleted zones providing little diffusive barrier to the diffusion of drug from the microspheres.

Figure 5.61 : Release Profile of Naproxen Sodium from Batch NC81 as a Function of the Square Root of Time Model



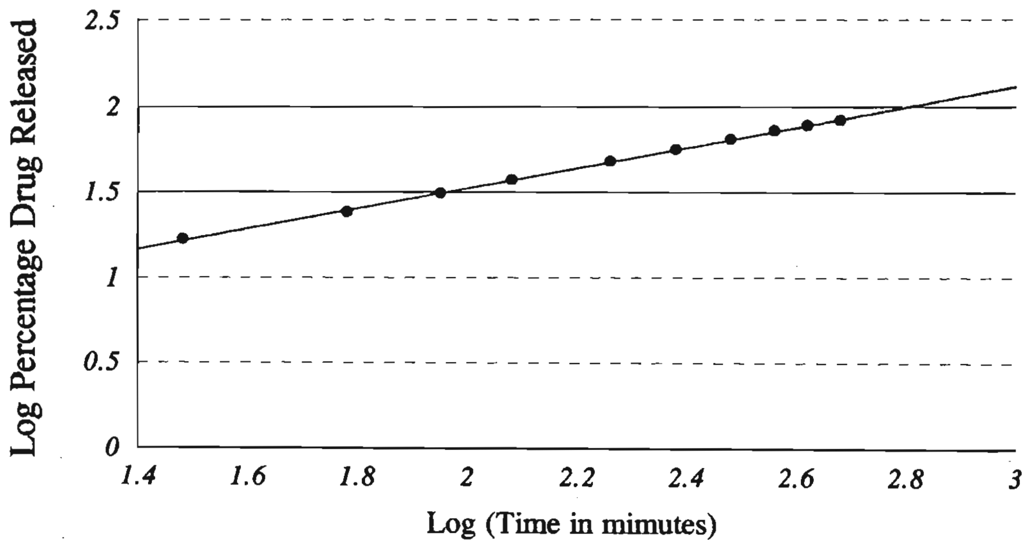
5.5.5.3 The power law expression

Table 5.34 represents the drug release data in terms of the Power Law Expression (equation 2.14) and Figure 5.62 graphically illustrates the application of the Power Law on the drug release data from cetostearyl alcohol microspheres. The value of the kinetic exponent (n) was found to be 0.59 which is indicative of non-fickian diffusion since 0.59 falls within the range of $0.5 < n < 1.0$. The trend towards first order drug release was evident from the r^2 values obtained by linear regression (0.996 - first order; 0.954 - zero-order). The Power Law Expression generated a (n) value of 0.59 which is closer to 0.5 than to 1.0, and further emphasizes the tendency towards first order drug release.

Table 5.34 : Drug Release Data in Accordance with the Power Law Expression

LOG TIME	LOG PERCENTAGE DRUG RELEASED
0	0
1.48	1.22
1.78	1.38
1.95	1.49
2.08	1.57
2.26	1.68
2.38	1.75
2.48	1.81
2.56	1.86
2.62	1.89
2.68	1.92

Figure 5.62 : Application of the Power Law Expression on the Drug Release Data of Batch NC81



R-squared = 0.999

y = 0.59x + 0.34

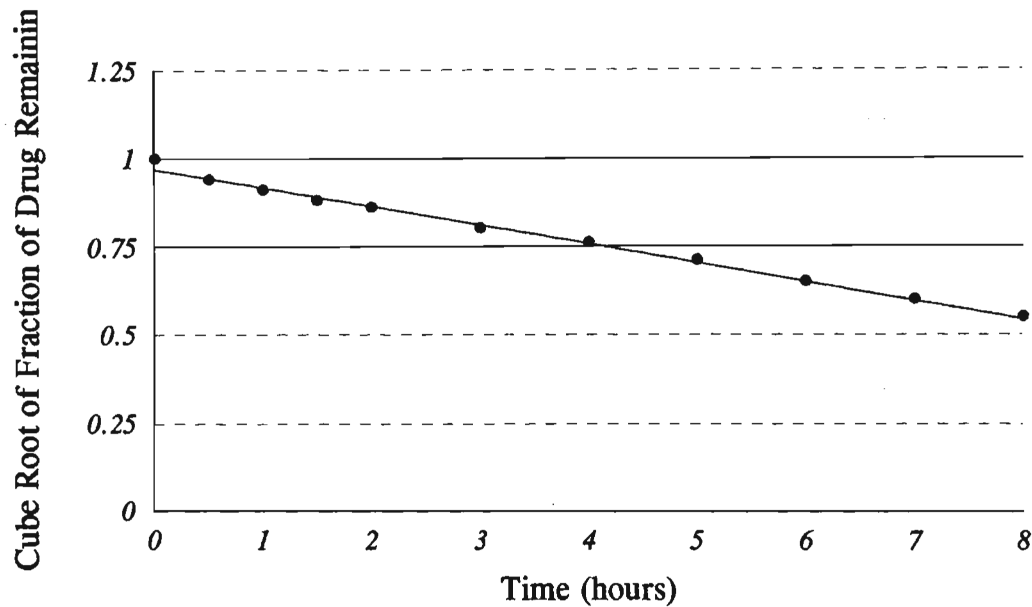
5.5.5.4 The cube root equation

The cube root equation is employed to check for dissolution rate limitation if the pellets are of a cubic shape and do not change shape during drug release. The application of the cube root law (equation 2.13) is presented in Table 5.35 and Figure 5.63.

Table 5.35 : Drug Release Data as a Function of the Cube Root Law

TIME (HOURS)	CUBE ROOT OF FRACTION OF DRUG REMAINING
0	1.00
0.5	0.94
1	0.91
1.5	0.88
2	0.86
3	0.80
4	0.76
5	0.71
6	0.65
7	0.60
8	0.55

Figure 5.63 : Release Profile of Naproxen Sodium from Batch NC81 as a Function of the Cube Root Law



R-squared = 0.995

y = 0.05x + 0.97

Linear regression analysis performed on the above data depicted a high correlation coefficient (r^2 = 0.995) which was virtually identical to the correlation coefficient obtained for the first order model. The high correlation coefficient observed for the cube root plot serves to confirm that drug release occurs as a result of diffusion of drug rather than by dissolution of the wax matrix.

Chapter Six

Conclusions and Recommendations

6.1 CONCLUSIONS

6.1.1 Formulation of Ethylcellulose-walled Microcapsules

(i) The coacervation phase-separation technique proved successful in the formulation of diclofenac sodium microcapsules. A 1:1 polymer:drug ratio produced microcapsules displaying suitable drug release characteristics.

(ii) The coacervation-inducing agent, polyisobutylene, produced smaller microcapsules than the formulation that did not contain polyisobutylene of diclofenac sodium with a faster drug release profile.

(iii) Employing the coacervation phase-separation technique, the present study was unable to formulate a modified release preparation of naproxen sodium displaying suitable drug release characteristics.

6.1.2 Formulation of Naproxen Sodium Cetostearyl Alcohol Microspheres

6.1.2.1 Development of the formulation

(i) A suitable encapsulation efficiency was achieved at pH 0.8 since a further decrease in the pH of the liquid manufacturing vehicle did not result in any significant changes in the encapsulation efficiency of the microspheres. However, the optimum pH of the liquid manufacturing vehicle was 0.6 since this pH provided a suitable drug release profile.

(ii) A 1:1 naproxen sodium:cetostearyl alcohol ratio was suitable since it facilitated ease of manufacture and allowed for the incorporation of the high dose of drug required.

(iii) Incorporation of magnesium stearate prevented aggregation and clumping of the dispersed drug-wax melt. The optimum magnesium stearate concentration was 2% $^{m}/_{m}$.

(iv) The inclusion of 1% $^{m}/_{m}$ Span 20 to the wax melt and 2% $^{m}/_{m}$ Tween 60 to the dispersion medium improved the sphericity of the formulation.

6.1.2.2 Effect of formulation variables

6.1.2.2.1 *Influence of Naproxen Sodium:Cetostearyl Alcohol Ratios*

A significant decrease in drug release results from a decrease in the naproxen sodium:cetostearyl alcohol ratio. A 1:1 naproxen sodium:cetostearyl alcohol ratio resulted in microspheres with desirable drug release characteristics. The density of the naproxen sodium-cetostearyl alcohol microspheres increased with increasing drug:wax ratios.

6.1.2.2.2 *Influence of pH of the Liquid Manufacturing Vehicle*

(i) A decrease in the pH of the liquid manufacturing vehicle, over the range 3 to 0.4, produces an increase in the encapsulation efficiency of the cetostearyl alcohol microspheres. Furthermore, a decrease in the pH of the liquid manufacturing vehicle decreases the release of naproxen sodium from the microspheres.

(ii) A decrease in the pH of the liquid manufacturing vehicle produces microspheres with an increased median particle size which further contributed to the decrease in the drug release profile.

6.1.2.2.3 *Influence of Magnesium Stearate*

Altering the concentration of magnesium stearate included in the formulation did not reflect a pharmaceutically significant difference in the drug release profiles. However, there was a trend towards a decrease in drug release at lower magnesium stearate concentrations. EDX reveals that a minute amount of magnesium is present in the formulation (0.83%). The median particle size also decreased as the magnesium stearate concentration increased.

6.1.3 Reproducibility Study

Using similar manufacturing conditions, the drug release characteristics of Batch NC81a and Batch NC81b were found to be virtually identical to the optimized formulation, Batch NC81. Therefore, the meltable aqueous dispersion technique provides a reproducible option for the formulation of drug-containing cetostearyl alcohol microspheres in order to achieve modified release drug delivery.

6.1.4 Effect of Dissolution Methods, Agitation Intensities and Dissolution Media

6.1.4.1 Dissolution methods

Significant differences in drug release were observed for microspheres subjected to the rotating paddle, rotating basket and rotating bottle methods. The greatest differences were noted in the rotating basket and rotating bottle methods. It is therefore concluded that in order to optimize the formulation, drug release characteristics must be compared within the same dissolution methods since different dissolution methods affect drug release drastically.

6.1.4.2 Agitation intensities

The drug release from cetostearyl alcohol microspheres were found to be virtually independent of agitation intensities when employing the rotating paddle method. However, drug release is significantly affected by the agitation intensity when employing the rotating basket method.

6.1.4.3 Dissolution media

The release of naproxen sodium from cetostearyl alcohol microspheres is dependent on the pH of the dissolution media. Dissolution testing in different media revealed a slower release of drug in acidic (pH 1.5 and 4.5) media as compared to basic (pH 6.9, 7.4 and 8.0) media. Since the cetostearyl alcohol microspheres maintain their integrity during dissolution testing, it was concluded that the pH-dependent drug release characteristics was due to the pH-dependent solubility of naproxen sodium.

Dissolution testing employing dissolution media that simulated the gastrointestinal milieu following oral administration produced an acceptable modified release profile of naproxen sodium.

6.1.5 Electron Microscopy

6.1.5.1 Scanning electron microscopy

(i) Scanning electron microscopy revealed the spherical nature of the formulation. The microspheres displayed a 'rough' and uneven surface appearance.

(ii) Microscopic evaluation of naproxen sodium-cetostearyl alcohol microspheres subjected to dissolution testing revealed the presence of worm-like indentations and pore formation. Furthermore, the microspheres maintained their overall shape. It was therefore concluded that drug release occurs by diffusion of drug from the matrix rather than by dissolution of the cetostearyl alcohol matrix.

(iii) Scanning electron microscopy performed on microspheres stored at elevated temperatures revealed a more uniform, less porous surface which may be attributed to the coalescence of cetostearyl alcohol.

6.1.5.2 Energy dispersive x-ray microprobe analysis (EDX)

EDX adequately reflected that the elemental composition of naproxen sodium-ethylcellulose microcapsules and naproxen sodium-cetostearyl alcohol microspheres was a composite of the pure ingredients.

6.1.5.3 X-ray mapping and line scan

(i) X-ray mapping confirms that Batches DE1 and NE3 are encapsulated formulations whilst Batch NC81 is a matrix-type preparation with a homogenous distribution of drug within the matrix.

(ii) The line scan through a cross-section of a microsphere of Batch NC81 further serves to emphasize the homogenous drug distribution of the formulation. Furthermore, the line scan confirms that the sodium ion is bound to the drug and has not combined with the hydrochloric acid to form sodium chloride.

6.1.6 Differential Scanning Calorimetry

A comparison of the endothermic peaks for the pure ingredients and the selected formulation reveals a difference in the thermograms. Furthermore, a comparison of the 1:1 physical mix and the selected formulation reveals a change in the thermograms. A possible interaction between the drug and cetostearyl alcohol may have occurred which is potentiated during the formulation process.

6.1.7 Stability Studies

(i) HPLC studies performed on the selected formulation subjected to various storage conditions depict significant changes in the potencies of the formulation stored at 40°C and 37°C/80% relative humidity.

(ii) The moisture content of the microspheres prior to and after 4, 8 and 12 weeks remained relatively constant for the 21 ± 1°C and 40°C storage condition but increased for the 37°C/80% relative humidity and 5 ± 1°C storage conditions.

(iii) No pharmaceutically significant differences were noted in the drug release profiles relative to the initial drug release when stored at room temperature (21 ± 1°C) for the duration of the stability study. In contrast, microspheres stored at 37°C/80% relative humidity and 40°C depicted a decrease in the drug release profiles whilst microspheres stored at 5 ± 1°C showed an increase in the drug release profiles.

(iv) By extrapolation of the stability data from an Arrhenius plot, the shelf-life was calculated to be 1.07 years.

(v) It can therefore be concluded that naproxen sodium is unstable on incorporation into the cetostearyl alcohol matrix. It is further concluded that the observed instability may be due to one of the following reasons:
   a) the low pH employed during formulation
   b) an interaction between naproxen sodium and cetostearyl alcohol
   c) a combination of these two factors.

6.1.8 Characterization of the Drug Release from Naproxen Sodium-Cetostearyl Alcohol Microspheres

A mixed fit of the dissolution data of naproxen sodium-cetostearyl alcohol microspheres, to both first-order and the cube-root models, was established. A good fit of the dissolution data was also obtained for the square-root of time model. The Power law yielded a kinetic exponent of 0.59 which suggest that drug release occurs by non-fickian diffusion.

In consideration of the above mentioned conclusions, it is clearly evident that a multiple-unit modified release preparation containing 550 mg of naproxen sodium displaying predictable and reproducible drug release characteristics can be formulated employing the meltable aqueous dispersion technique. Furthermore, the relative simplicity of the technique makes it a pharmaceutically and commercially viable option in the formulation of modified release

drug delivery systems. However, the limited shelf-life of the formulation warrants further investigation into the formulation of a more stable preparation.

6.2 RECOMMENDATIONS

The following recommendations may be considered for further studies employing modified release drug delivery technology:-

1) Due to the adverse effects of the pH of the liquid manufacturing vehicle on the stability of the formulation it is suggested that the possibility of employing a different liquid manufacturing vehicle could be explored. One possible option may be the use of silicone oil instead of an aqueous medium especially if highly water soluble drugs are employed.

2) The use of different wax materials could be examined. Carnuba wax may prove to be a viable alternative to cetostearyl alcohol.

3) To investigate and validate the meltable aqueous dispersion technique fully, the effect of various cooling protocols and the effect of different stirring rates during the formulation process is warranted.

4) An investigation into the effect of varying concentrations of the two surfactants employed (Span 20 and Tween 60) on the drug release profile could be examined. Furthermore, the incorporation of various surfactants or combination of surfactants could also be explored.

5) To adequately identify any possible interaction between naproxen sodium and cetostearyl alcohol, additional thermal analytical techniques such as thermogravimetric analysis (TGA) and thermomechanical analysis (TMA) could be performed. A more in-depth differential scanning calorimetric (DSC) study could

also be performed in order to construct a phase diagram so that possible eutectic formation could be investigated and properly defined.

6) The present study has revealed that particle size of the microspheres affects drug release behaviour significantly. Consequently, the use of a combination of microspheres of different particle size range could be explored in an attempt to produce an improved drug release profile.

7) Since microspheres subjected to storage at high temperatures have displayed a smoother surface and retarded drug release profiles, curing studies at elevated temperatures could be examined.

8) To verify the *in vitro* dissolution characteristics from the naproxen sodium-cetostearyl alcohol microspheres, an appropriate *in vitro-in vivo* correlation could be developed.

9) As an alternative to employing gelatin capsules to administer the microspheres, other dosage forms such as rapidly disintegrating tablets or modified release suspension could be considered.

10) An investigation of the effect of a scale-up process is warranted to determine the feasibility of the meltable aqueous dispersion technique for pharmaceutical industrial application.

Appendices

1) THE DIFFERENT MATERIALS EMPLOYED DURING THE STUDY AND THEIR SUPPLIERS

MATERIAL	SUPPLIER
Naproxen sodium	Natco Laboratories (Pty) Ltd
Naproxen sodium USP Reference Standard	United States Pharmacopoeial Convention
Diclofenac sodium	Lennon Ltd
Ethylcellulose	BDH Chemicals
Cetostearyl alcohol	BDH Chemicals
Magnesium stearate	Hopkin and Williams
Span 20	Crodesta
Tween 60	Crodesta
Polyisobutylene	Jansen Chemica
Synflex® tablets	Syntex Pharmaceuticals
Hydrochloric acid (1N)	BDH Chemicals
Sodium hydrochloric	BDH Chemicals
di-Sodium hydrogen orthophosphate	SAAR Chem
Sodium di-hydrogen orthophosphate	SAAR Chem
Methanol	Romil
Karl Fischer solution	SAAR Chem
Empty gelatin capsules	Capsugel AG
Acetonitrile	Romil
Glacial acetic acid	BDH Chemicals

2) MONOGRAPH OF NAPROXEN SODIUM POWDER (USP XXIII, 1995)

Naproxen Sodium

$C_{14}H_{13}NaO_3$ 252.25
2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (−)-.
(−)-Sodium 6-methoxy-α-methyl-2-naphthaleneacetate
[*26159-34-2*].

» Naproxen Sodium contains not less than 98.0 percent and not more than 102.0 percent of $C_{14}H_{13}NaO_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Naproxen Sodium RS.*

Identification—
A: *Infrared Absorption* ⟨197K⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 1 in 40,000.
Medium: methanol. Absorptivities at 272 nm, calculated on the dried basis, do not differ by more than 3%.

Specific rotation ⟨781S⟩: between −15.3° and −17.0°.
Test solution: 50 mg per mL, in 0.1 *N* sodium hydroxide.

Loss on drying ⟨731⟩—Dry it in vacuum at 105° for 3 hours: it loses not more than 1.0% of its weight.

Heavy metals, *Method I* ⟨231⟩—Dissolve 1.0 g in 20 mL of water in a separator, add 5 mL of 1 *N* hydrochloric acid, and extract with successive 20-mL, 20-mL, and 10-mL portions of methylene chloride. Discard the methylene chloride extracts, and use the aqueous layer for the test: the limit is 0.002%.

Free naproxen—Dissolve about 5.0 g in 25 mL of water in a separator, and extract the solution with three 15-mL portions of chloroform. Evaporate the combined extracts on a steam bath to dryness. Dissolve the residue in 10 mL of a mixture of methanol and water (3:1) previously neutralized with 0.1 *N* sodium hydroxide to the phenolphthalein endpoint. Add phenolphthalein TS, and titrate with 0.10 *N* sodium hydroxide: not more than 2.2 mL is consumed (1.0%).

Chromatographic purity—Dissolve 100 mg in 5 mL of methanol. Dissolve a suitable quantity of USP Naproxen Sodium RS in methanol to obtain a *Standard solution* having a known concentration of about 20 mg per mL. Dilute a portion of this solution quantitatively with methanol to obtain three *Comparison solutions* having concentrations of 20, 60, and 100 µg per mL (0.1%, 0.3%, and 0.5% of the *Standard solution*), respectively. Apply separate 10-µL portions of the five solutions on the starting line to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of toluene, tetrahydrofuran, and glacial acetic acid (30:3:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, air-dry, and view under short-wavelength ultraviolet light: the R_f value of the principal spot in the chromatogram of the solution under test corresponds to that of the *Standard solution*, the intensity of any individual secondary spot does not exceed that of the 100-µg-per-mL *Comparison solution* (0.5%), and the sum of the intensities of any secondary spots, similarly compared, does not exceed 2.0%.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—Dissolve about 200 mg of Naproxen Sodium, accurately weighed, in 50 mL of glacial acetic acid containing 2 drops of 1-naphtholbenzein previously neutralized with 0.1 *N* perchloric acid if necessary. Titrate with 0.1 *N* perchloric acid VS. Each mL of 0.1 *N* perchloric acid is equivalent to 25.22 mg of $C_{14}H_{13}NaO_3$.

3) MONOGRAPH OF NAPROXEN SODIUM TABLETS (USP XXIII, 1995)

Naproxen Sodium Tablets

» Naproxen Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{13}NaO_3$.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Naproxen Sodium RS.*

Identification —

A: Transfer a quantity of finely powdered Tablets, equivalent to about 250 mg of naproxen sodium, to a centrifuge tube, and add 12 mL of water and 1 mL of hydrochloric acid: a dense white precipitate is formed. Centrifuge the mixture: the clear, supernatant solution responds to the identification test for *Sodium* ⟨191⟩.

B: Prepare a mixture of the *Standard preparation* and the *Assay preparation* (1 : 1), prepared as directed in the *Assay*, and chromatograph as directed in the *Assay*: the chromatogram thus obtained exhibits two main peaks, corresponding to naproxen and the internal standard.

Dissolution ⟨711⟩—

Medium: 0.1 *M* phosphate buffer (pH 7.4), prepared by dissolving 2.62 g of monobasic sodium phosphate and 11.50 g of anhydrous dibasic sodium phosphate in water to make 1000 mL; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Standard preparation—Dissolve an accurately weighed portion of USP Naproxen Sodium RS in *Dissolution Medium* to obtain a solution having a known concentration of about 50 µg per mL.

Procedure—Dilute a filtered portion of the solution under test quantitatively with *Dissolution Medium* as necessary to obtain a solution having a concentration of about 50 µg per mL of $C_{14}H_{13}NaO_3$. Determine the amount of $C_{14}H_{13}NaO_3$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 332 nm of this solution in comparison with the *Standard preparation.*

Tolerances—Not less than 70% (*Q*) of the labeled amount of $C_{14}H_{13}NaO_3$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Mobile phase, Solvent mixture, Internal standard solution, and *Chromatographic system*—Prepare as directed in the *Assay* under *Naproxen Tablets.*

Standard preparation—Dissolve an accurately weighed quantity of USP Naproxen Sodium RS in *Solvent mixture* to obtain a solution having a known concentration of about 2.75 mg per mL. Transfer 1.0 mL of the resulting solution and 2.0 mL of *Internal standard solution* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 27.5 µg of USP Naproxen Sodium RS per mL.

Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 275 mg of naproxen sodium, to a 100-mL volumetric flask. Add 10 mL of water, and shake until the material is completely dispersed. Dilute with acetonitrile to volume, and mix. Allow any insoluble matter to settle, then transfer 1.0 mL of the clear supernatant solution to a 100-mL volumetric flask, add 2.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Naproxen Tablets.* Calculate the quantity, in mg, of $C_{14}H_{13}NaO_3$ in the portion of Tablets taken by the formula:

$$10C(R_U/R_S),$$

in which *C* is the concentration, in µg per mL, of USP Naproxen Sodium RS in the *Standard preparation*, and R_U and R_S are the ratios of the response of the naproxen peak to the response of the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

4) PREPARATION OF BUFFER SOLUTIONS

BUFFER SOLUTIONS

The successful completion of many Pharmacopeial tests and assays requires adjustment to or maintenance of a specified pH by the addition of buffer solutions. In pH measurements, standard buffer solutions are required for reference purposes. For convenience, the preparation of these solutions is in some instances described in the sections in which their use is specified; i.e., five separate phosphate buffers are described under *Antibiotics—Microbial Assays* ⟨81⟩, and several miscellaneous single-purpose solutions are described in the individual monographs.

A solution is said to be buffered if it resists changes in the activity of an ion on the addition of substances that are expected to change the activity of that ion. Buffers are substances or combinations of substances that impart this resistance to a solution. Buffered solutions are systems in which the ion is in equilibrium with substances capable of removing or releasing the ion.

Buffer capacity refers to the amount of material that may be added to a solution without causing a significant change in ion activity. It is defined as the ratio of acid or base added (in gram-equivalents per liter) to the change in pH (in pH units). The capacity of a buffered solution is adjusted to the conditions of use, usually by adjustment of the concentrations of buffer substances.

Buffers are used to establish and maintain an ion activity within narrow limits. The most common systems are used (a) to establish hydrogen-ion activity for the calibration of pH meters, (b) in the preparation of dosage forms that approach isotonicity, (c) in analytical procedures, and (d) to maintain stability of various dosage forms. Buffers used in physiological systems are carefully chosen so as not to interfere with pharmacological activity of the medicament or normal function of the organism. It is essential that buffers used in chemical analysis be compatible with the substance determined and the reagents used.

Standard Buffer Solutions—Standard solutions of definite pH are readily available in buffer solutions prepared from the appropriate reagents. In addition, buffer solutions, buffer tablets, and buffer solids may be obtained from commercial sources in convenient prepackaged form. Such preparations are available for the entire working range in pharmaceutical analysis, but are not recommended for pH meter standardization (see *pH* ⟨791⟩).

The required reagents are described in the section, *Reagents*. Previously dry the crystalline reagents, except the boric acid, at 110° to 120° for 1 hour.

NOTE—Where water is specified for solution or dilution of test substances in pH determinations, use carbon dioxide-free water.

Store the prepared solutions in chemically resistant, tight containers such as Type I glass bottles. Use the solutions within 3 months.

Standard buffer solutions for various ranges between pH 1.2 and 10.0 may be prepared by appropriate combinations of 0.2 *M* solutions described herein, used in the proportions shown in the accompanying table. The volumes shown in the table are for 200 mL of buffer solution.

1. *Hydrochloric Acid, 0.2 M,* and *Sodium Hydroxide, 0.2 M*—Prepare and standardize as directed under *Volumetric Solutions.*
2. *Potassium Biphthalate, 0.2 M*—Dissolve 40.85 g of potassium biphthalate $[KHC_6H_4(COO)_2]$ in water, and dilute with water to 1000 mL.
3. *Potassium Phosphate, Monobasic 0.2 M*—Dissolve 27.22 g of monobasic potassium phosphate (KH_2PO_4) in water, and dilute with water to 1000 mL.
4. *Boric Acid and Potassium Chloride, 0.2 M*—Dissolve 12.37 g of boric acid (H_3BO_3) and 14.91 g of potassium chloride (KCl) in water, and dilute with water to 1000 mL.
5. *Potassium Chloride, 0.2 M*—Dissolve 14.91 g of potassium chloride (KCl) in water, and dilute with water to 1000 mL.

Composition of Standard Buffer Solutions

Hydrochloric Acid Buffer

Place 50 mL of the potassium chloride solution in a 200-mL volumetric flask, add the specified volume of the hydrochloric acid solution, then add water to volume.

pH	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
HCl, mL	85.0	67.2	53.2	41.4	32.4	26.0	20.4	16.2	13.0	10.2	7.8

Acid Phthalate Buffer

Place 50 mL of the potassium biphthalate solution in a 200-mL volumetric flask, add the specified volume of the hydrochloric acid solution, then add water to volume.

pH	2.2	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0
HCl, mL	49.5	42.2	35.4	28.9	22.3	15.7	10.4	6.3	2.9	0.1

Neutralized Phthalate Buffer

Place 50 mL of the potassium biphthalate solution in a 200-mL volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8
NaOH, mL	3.0	6.6	11.1	16.5	22.6	28.8	34.1	38.8	42.3

Phosphate Buffer

Place 50 mL of the monobasic potassium phosphate solution in a 200-mL volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	5.8	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0
NaOH, mL	3.6	5.6	8.1	11.6	16.4	22.4	29.1	34.7	39.1	42.4	44.5	46.1

Alkaline Borate Buffer

Place 50 mL of the boric acid and potassium chloride solution in a 200-mL volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	8.0	8.2	8.4	8.6	8.8	9.0	9.2	9.4	9.6	9.8	10.0
NaOH, mL	3.9	6.0	8.6	11.8	15.8	20.8	26.4	32.1	36.9	40.6	43.7

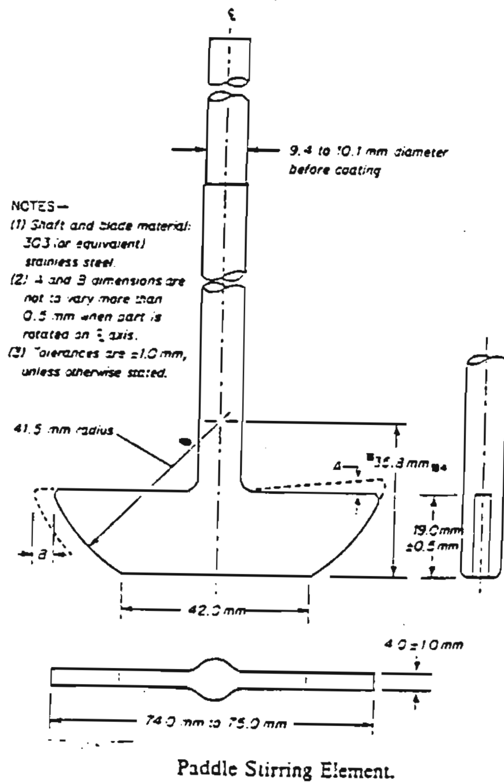
(USP XXIII, 1995)

Phosphate Buffer pH 4.5, Acid Dissolve 13.61 g of *potassium dihydrogen orthophosphate* in 750 ml of *water*, adjust the solution to pH 4.5 with 0.1M *hydrochloric acid* and dilute to 1000 ml with *water*.

(BP 1993)

5) SPECIFICATIONS FOR THE ROTATING PADDLE APPARATUS (USP XXIII, 1995)

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel, and rotates smoothly without significant wobble. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.



Paddle Stirring Element.

6) SPECIFICATIONS FOR THE ROTATING BASKET APPARATUS (USP XXIII, 1995)

⟨711⟩ DISSOLUTION

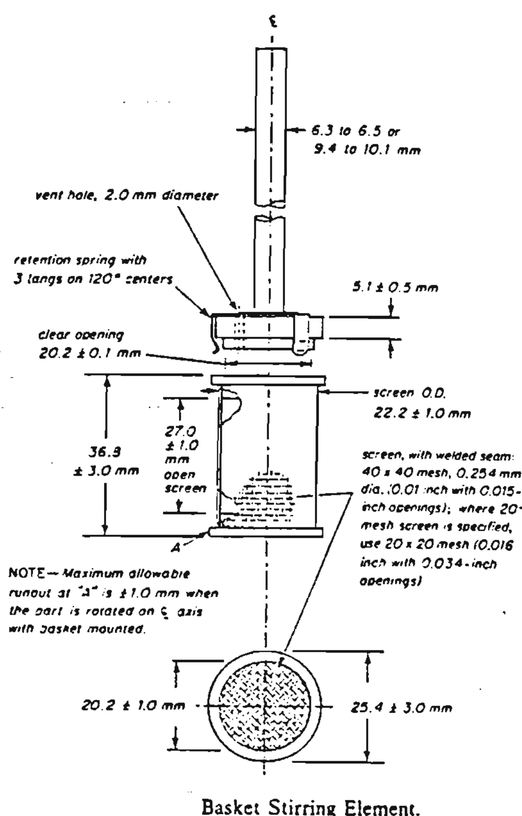
This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed. Requirements for *Dissolution* do not apply to soft gelatin capsules unless specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 mm to 175 mm high, its inside diameter is 98 mm to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 µm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.



Basket Stirring Element.

7) EXAMPLE OF QUATTRO PRO CELL FORMULAE USED TO COMPUTE DISSOLUTION DATA

TIME (HOURS)	ABS*	mg/900 ml	CORRECTION FACTOR	CORRECTED AMOUNT	% RELEASED	MEAN % RELEASED	STANDARD DEVIATION
15 min		@SUM(B10*900)	0.000	@SUM(C10+D10)	@SUM(E10/550*100)	@SUM((F10+F11+F12+F13+F14)/4)	@STDS(F10..F14)
		@SUM(B11*900)	0.000	@SUM(C11+D11)	@SUM(E11/550*100)		
		@SUM(B12*900)	0.000	@SUM(C12+D12)	@SUM(E12/550*100)		
		@SUM(B13*900)	0.000	@SUM(C13+D13)	@SUM(E13/550*100)		
30 min		@SUM(B20*900)	@SUM(B10*5)	@SUM(C20+D20)	@SUM(E20/550*100)	@SUM((F20+F21+F22+F23+F24)/4)	@STDS(F20..F24)
		@SUM(B21*900)	@SUM(B11*5)	@SUM(C21+D21)	@SUM(E21/550*100)		
		@SUM(B22*900)	@SUM(B12*5)	@SUM(C22+D22)	@SUM(E22/550*100)		
		@SUM(B23*900)	@SUM(B13*5)	@SUM(C23+D23)	@SUM(E23/550*100)		
1 hour		@SUM(B30*900)	@SUM((B20*5)+D20)	@SUM(C30+D30)	@SUM(E30/550*100)	@SUM((F30+F31+F32+F33+F34)/4)	@STDS(F30..F34)
		@SUM(B31*900)	@SUM((B21*5)+D21)	@SUM(C31+D31)	@SUM(E31/550*100)		
		@SUM(B32*900)	@SUM((B22*5)+D22)	@SUM(C32+D32)	@SUM(E32/550*100)		
		@SUM(B33*900)	@SUM((B23*5)+D23)	@SUM(C33+D33)	@SUM(E33/550*100)		
1 1/2 hours		@SUM(B40*900)	@SUM((B30*5)+D30)	@SUM(C40+D40)	@SUM(E40/550*100)	@SUM((F40+F41+F42+F43+F44)/4)	@STDS(F40..F44)
		@SUM(B41*900)	@SUM((B31*5)+D31)	@SUM(C41+D41)	@SUM(E41/550*100)		
		@SUM(B42*900)	@SUM((B32*5)+D32)	@SUM(C42+D42)	@SUM(E42/550*100)		
		@SUM(B43*900)	@SUM((B33*5)+D33)	@SUM(C43+D43)	@SUM(E43/550*100)		

2 hours		@SUM(B50*900)	@SUM((B40*5)+D40)	@SUM(C50+D50)	@SUM(E50/550*100)	@SUM((F50+F51+F52+F53+F54)/4)	@STDS(F50..F54)
		@SUM(B51*900)	@SUM((B41*5)+D41)	@SUM(C51+D51)	@SUM(E51/550*100)		
		@SUM(B52*900)	@SUM((B42*5)+D42)	@SUM(C52+D52)	@SUM(E52/550*100)		
		@SUM(B53*900)	@SUM((B43*5)+D43)	@SUM(C53+D53)	@SUM(E53/550*100)		
3 hours		@SUM(B60*900)	@SUM((B50*5)+D50)	@SUM(C60+D60)	@SUM(E60/550*100)	@SUM((F60+F61+F62+F63+F64)/4)	@STDS(F60..F64)
		@SUM(B61*900)	@SUM((B51*5)+D51)	@SUM(C61+D61)	@SUM(E61/550*100)		
		@SUM(B62*900)	@SUM((B52*5)+D52)	@SUM(C62+D62)	@SUM(E62/550*100)		
		@SUM(B63*900)	@SUM((B53*5)+D53)	@SUM(C63+D63)	@SUM(E63/550*100)		
4 hours		@SUM(B70*900)	@SUM((B60*5)+D60)	@SUM(C70+D70)	@SUM(E70/550*100)	@SUM((F70+F71+F72+F73+F74)/4)	@STDS(F70..F74)
		@SUM(B71*900)	@SUM((B61*5)+D61)	@SUM(C71+D71)	@SUM(E71/550*100)		
		@SUM(B72*900)	@SUM((B62*5)+D62)	@SUM(C72+D72)	@SUM(E72/550*100)		
		@SUM(B73*900)	@SUM((B63*5)+D63)	@SUM(C73+D73)	@SUM(E73/550*100)		
5 hours		@SUM(B80*900)	@SUM((B70*5)+D70)	@SUM(C80+D80)	@SUM(E80/550*100)	@SUM((F80+F81+F82+F83+F84)/4)	@STDS(F80..F84)
		@SUM(B81*900)	@SUM((B71*5)+D71)	@SUM(C81+D81)	@SUM(E81/550*100)		
		@SUM(B82*900)	@SUM((B72*5)+D72)	@SUM(C82+D82)	@SUM(E82/550*100)		
		@SUM(B83*900)	@SUM((B73*5)+D73)	@SUM(C83+D83)	@SUM(E83/550*100)		
6 hours		@SUM(B90*900)	@SUM((B80*5)+D80)	@SUM(C90+D90)	@SUM(E90/550*100)	@SUM((F90+F91+F92+F93+F94)/4)	@STDS(F90..F94)
		@SUM(B91*900)	@SUM((B81*5)+D81)	@SUM(C91+D91)	@SUM(E91/550*100)		
		@SUM(B92*900)	@SUM((B82*5)+D82)	@SUM(C92+D92)	@SUM(E92/550*100)		
		@SUM(B93*900)	@SUM((B83*5)+D83)	@SUM(C93+D93)	@SUM(E93/550*100)		

7 hours		@SUM(B100*900)	@SUM((B90*5)+D90)	@SUM(C100+D100)	@SUM(E100/550*100)	@SUM((F100+F101+F102+F103+F104)/4)	@STDS(F100..F104)
		@SUM(B101*900)	@SUM((B91*5)+D91)	@SUM(C101+D101)	@SUM(E101/550*100)		
		@SUM(B102*900)	@SUM((B92*5)+D92)	@SUM(C102+D102)	@SUM(E102/550*100)		
		@SUM(B103*900)	@SUM((B93*5)+D93)	@SUM(C103+D103)	@SUM(E103/550*100)		
8 hours		@SUM(B110*900)	@SUM((B100*5)+D100)	@SUM(C110+D110)	@SUM(E110/550*100)	@SUM((F110+F111+F112+F113+F114)/4)	@STDS(F110..F114)
		@SUM(B111*900)	@SUM((B101*5)+D101)	@SUM(C111+D111)	@SUM(E111/550*100)		
		@SUM(B112*900)	@SUM((B102*5)+D102)	@SUM(C112+D112)	@SUM(E112/550*100)		
		@SUM(B113*900)	@SUM((B103*5)+D103)	@SUM(C113+D113)	@SUM(E113/550*100)		

**Manual data input*

Note : Cell B10 = B1. The same sequence also applies to other cells

8) INFRARED SPECTRUM OF NAPROXEN SODIUM USP REFERENCE STANDARD OBTAINED IN THE PRESENT STUDY

SPECTRUM / MEASURE BKG 40 / 40 SAMPLE 40 / 40 DISPLAY 40

%T 80.00 60.00 40.00 20.00 0.00 -10.00

2000.0 1500.0 1000.0

INFRARED SPECTRUM OF NAPROXEN SODIUM OBTAINED IN THE PRESENT STUDY

SPECTRUM / MEASURE BKG 40 / 40 SAMPLE 40 / 40

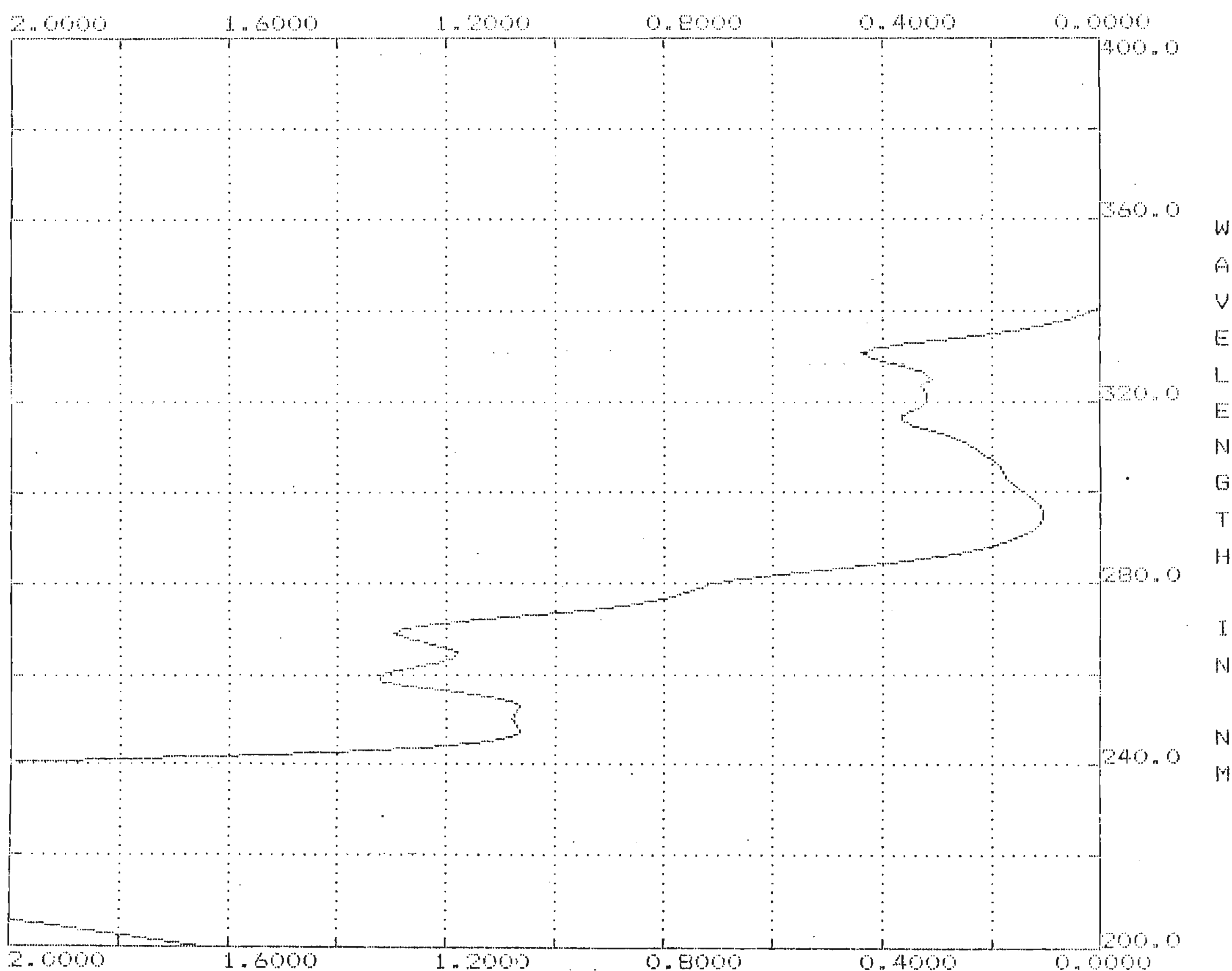
%T 80.00 60.00 40.00 20.00 0.00

2000.0 1500.0

RESOLUTION: 4.0 cm-1 AMP. GAIN: AUTO (X4)

MIRROR SPEED 1: 2.8 mm/s APODIZATION: HAPP-GENZEL

9) ULTRAVIOLET WAVELENGTH SCAN OF NAPROXEN SODIUM IN A 1 IN 40 000 SOLUTION IN METHANOL



10) Cumulative Percentages of Naproxen Sodium Released from Synflex®

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	66.76	82.96	77.40	72.49	74.90 ± 6.91
0.5	90.21	95.21	90.76	87.95	91.03 ± 3.04
1	94.47	96.71	93.71	93.18	94.52 ± 1.56
1.5	96.14	97.90	95.05	96.15	96.31 ± 1.18
2	96.83	99.25	95.57	97.66	97.33 ± 1.55
3	98.99	98.32	96.41	98.84	98.14 ± 1.19
4	99.03	98.04	96.61	99.87	98.39 ± 1.40
5	97.93	98.56	96.64	99.59	98.18 ± 1.23
6	97.31	98.60	96.83	99.96	98.17 ± 1.40
7	97.83	98.80	96.85	100.16	98.41 ± 1.41
8	98.35	98.83	96.71	99.88	98.44 ± 1.32

11) Cumulative Percentages of Naproxen Sodium Released from Batch DE1

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	2.89	2.60	2.31	2.02	2.46 ± 0.37
0.5	2.33	2.62	2.62	2.32	2.47 ± 0.17
1	4.96	4.67	4.96	4.66	4.81 ± 0.17
1.5	6.74	6.74	6.74	6.44	6.67 ± 0.15
2	8.82	9.11	8.82	8.81	8.89 ± 0.15
3	12.38	12.96	12.67	12.66	12.67 ± 0.24
4	15.67	16.26	15.96	15.37	15.82 ± 0.38
5	18.96	19.87	19.28	19.28	19.28 ± 0.48
6	22.62	24/10	22.62	22.62	22.99 ± 0.74
7	25.98	27.48	26.27	25.98	26.43 ± 0.71
8	29.67	31.18	29.68	29.38	29.98 ± 0.81

12) Cumulative Percentages of Naproxen Sodium Released from Batch DE2

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	9.30	8.42	8.42	9.01	8.79 ± 0.44
0.5	16.08	15.20	13.44	14.91	14.91 ± 1.10
1	25.56	23.50	22.31	23.21	23.65 ± 1.37
1.5	31.61	29.23	28.62	28.94	29.60 ± 1.36
2	40.96	38.26	36.17	37.96	38.34 ± 1.98
3	53.08	51.53	49.11	50.05	50.94 ± 1.74
4	59.96	59.89	58.04	58.09	59.00 ± 1.07
5	66.90	66.23	65.27	65.62	65.98 ± 0.68
6	73.59	70.53	71.05	70.80	71.49 ± 1.41
7	79.15	78.77	77.78	78.44	78.54 ± 0.58
8	82.33	84.05	82.76	81.92	82.77 ± 0.92

13) Cumulative Percentages of Naproxen Sodium Released from Batch DE3

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	5.80	7.26	6.09	4.93	6.02 ± 0.96
0.5	8.46	8.47	8.17	8.16	8.32 ± 0.17
1	16.99	17.00	16.41	16.40	16.70 ± 0.34
1.5	25.90	26.19	25.60	25.59	25.82 ± 0.29
2	35.77	36.38	35.18	34.88	35.55 ± 0.66
3	51.10	52.16	51.99	51.98	51.92 ± 0.62
4	66.64	65.16	65.14	64.83	65.44 ± 0.81
5	77.55	77.86	74.83	74.82	76.27 ± 1.67
6	83.74	84.06	82.21	83.70	83.43 ± 0.83
7	91.80	86.07	86.32	86.92	87.78 ± 2.71
8	95.07	92.64	92.93	95.00	93.91 ± 1.30

14) Cumulative Percentages of Naproxen Sodium Released from Batch NE1

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	88.85	85.58	89.18	86.73	87.59 ± 1.72
0.5	90.33	89.33	89.19	90.81	89.91 ± 0.78
1	96.23	94.57	98.19	93.44	95.61 ± 2.07
1.5	98.89	97.22	98.73	94.28	97.28 ± 2.14
2	100.57	100.04	100.09	101.83	100.63 ± 0.83
3	102.76	102.38	98.99	101.40	101.38 ± 1.69
4	102.00	103.76	105.75	103.59	103.77 ± 1.54
5	104.19	104.97	103.54	103.82	104.13 ± 0.62
6	105.24	103.90	106.05	105.19	105.10 ± 0.89

15) Cumulative Percentages of Naproxen Sodium Released from Batch NE2

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	78.87	77.73	77.40	81.49	78.87 ± 1.86
0.5	84.71	87.49	86.67	83.91	85.69 ± 1.67
1	89.76	90.10	92.38	90.43	90.67 ± 1.18
1.5	100.73	96.16	98.78	95.50	97.79 ± 2.42
2	98.82	95.21	96.05	97.50	96.90 ± 1.60
3	102.96	100.96	102.14	101.47	101.88 ± 0.87
4	104.50	104.78	105.31	105.29	104.97 ± 0.40
5	107.03	106.50	108.66	107.82	107.50 ± 0.94
6	108.42	109.19	108.42	110.04	109.02 ± 0.77

16) **Cumulative Percentages of Naproxen Sodium Released from Batch NE3**

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	42.05	49.58	50.73	44.84	46.80 ± 4.06
0.5	75.67	76.37	77.35	75.69	76.27 ± 0.79
1	89.02	89.06	89.07	89.36	89.13 ± 0.16
1.5	93.43	93.48	94.47	94.27	93.91 ± 0.53
2	94.40	97.27	96.96	96.42	96.76 ± 0.42
3	98.24	99.43	99.45	99.08	99.05 ± 0.57
4	100.37	100.79	100.48	99.62	100.41 ± 0.54
5	101.28	101.01	101.51	101.46	101.32 ± 0.23
6	102.31	101.88	102.06	101.84	102.02 ± 0.22

17) **Cumulative Percentages of Naproxen Sodium Released from Batch NE4**

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	16.20	17.02	16.20	15.05	16.21 ± 0.81
0.5	36.58	38.06	36.09	35.59	36.58 ± 1.06
1	61.98	62.32	61.82	60.34	61.62 ± 0.88
1.5	69.04	67.41	65.92	67.05	67.36 ± 1.29
2	74.82	73.51	72.99	73.15	73.62 ± 0.83
3	80.46	80.30	79.94	80.42	80.28 ± 0.24
4	85.32	84.50	82.83	82.33	83.75 ± 1.40
5	86.93	84.47	83.61	84.09	84.77 ± 1.48
6	86.74	86.56	85.04	86.76	86.25 ± 0.81

18) Cumulative Percentages of Naproxen Sodium Released from Batch DE4

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	18.95	14.27	16.32	14.85	16.10 ± 2.09
0.5	31.41	23.15	24.92	24.62	26.03 ± 3.67
1	53.53	39.50	42.19	40.40	43.91 ± 6.51
1.5	70.89	53.99	56.41	54.01	58.83 ± 8.21
2	80.34	65.06	66.91	64.78	69.27 ± 7.44
3	91.74	78.36	79.63	78.37	82.03 ± 6.50
4	99.50	90.00	90.08	87.90	91.87 ± 5.19
5	96.50	89.03	94.28	92.94	93.19 ± 3.14
6	98.88	94.12	94.84	93.86	95.43 ± 2.34
7	101.63	100.43	101.44	101.09	101.15 ± 0.53
8	101.87	101.03	102.32	102.59	101.95 ± 0.68

19) Cumulative Percentages of Naproxen Sodium Released from Batch NC80

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	17.02	17.35	16.85	17.67	17.22 ± 0.36
0.5	24.64	24.97	24.97	25.30	24.97 ± 0.27
1	35.41	35.42	35.41	35.75	35.50 ± 0.17
1.5	44.44	44.78	44.77	45.27	44.82 ± 0.34
2	52.22	52.55	52.55	53.05	52.59 ± 0.34
3	63.79	64.13	64.13	64.63	64.17 ± 0.34
4	73.47	73.81	74.13	74.31	73.93 ± 0.37
5	81.07	81.90	82.23	82.41	81.90 ± 0.59
6	86.75	86.93	87.26	87.27	87.05 ± 0.26
7	91.31	92.47	92.15	91.84	91.94 ± 0.49
8	94.26	94.77	94.77	94.62	94.61 ± 0.24

20) Cumulative Percentages of Naproxen Sodium Released from Batch NC81

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.27	12.93	12.93	12.60	12.68 ± 0.31
0.5	16.27	16.60	16.93	16.92	16.68 ± 0.31
1	23.72	23.73	24.22	24.55	24.05 ± 0.40
1.5	30.73	31.06	31.55	31.06	31.10 ± 0.34
2	36.95	36.96	37.62	37.29	37.20 ± 0.32
3	47.79	47.14	48.30	48.13	47.84 ± 0.51
4	56.56	56.07	57.23	56.90	56.69 ± 0.50
5	64.07	63.74	65.40	64.58	64.45 ± 0.72
6	72.11	71.78	73.29	72.46	72.41 ± 0.65
7	77.74	77.41	78.92	78.09	78.04 ± 0.65
8	83.39	82.57	83.93	82.93	83.21 ± 0.59

21) Cumulative Percentages of Naproxen Sodium Released from Batch NC82

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	13.75	14.89	13.75	14.56	14.24 ± 0.58
0.5	16.93	19.06	18.24	18.24	18.12 ± 0.88
1	23.90	27.35	25.87	26.53	25.91 ± 1.47
1.5	30.41	34.70	33.21	33.87	33.05 ± 1.86
2	36.47	40.46	39.61	40.11	39.16 ± 1.83
3	44.52	49.19	47.85	47.86	47.36 ± 1.99
4	50.99	56.49	54.98	55.49	54.49 ± 2.42
5	57.65	63.02	61.66	61.68	61.00 ± 2.33
6	62.38	67.29	65.27	66.11	65.26 ± 2.09
7	66.64	72.24	70.04	70.39	69.83 ± 2.33
8	70.77	76.23	74.35	74.54	73.97 ± 2.30

22) Cumulative Percentages of Naproxen Sodium Released from Batch NC83

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	13.75	13.42	14.07	13.09	13.58 ± 0.42
0.5	17.42	17.75	17.75	17.75	17.67 ± 0.16
1	24.55	25.05	24.72	24.72	24.76 ± 0.21
1.5	31.07	31.24	31.08	31.07	31.11 ± 0.08
2	36.48	36.97	36.97	36.81	36.81 ± 0.23
3	46.17	46.99	47.00	46.66	46.71 ± 0.39
4	54.44	54.62	54.62	54.44	54.53 ± 0.10
5	61.12	61.62	61.62	61.12	61.37 ± 0.29
6	67.67	68.34	68.01	67.67	67.92 ± 0.32
7	73.27	74.77	74.44	73.93	74.10 ± 0.65
8	79.23	79.75	79.75	79.23	79.49 ± 0.30

23) Cumulative Percentages of Naproxen Sodium Released from Batch NC84

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.24	14.56	14.89	15.05	14.69 ± 0.36
0.5	17.75	17.92	18.25	18.57	18.12 ± 0.36
1	26.20	26.20	26.69	26.70	26.45 ± 0.29
1.5	33.21	33.22	34.04	34.37	33.71 ± 0.59
2	39.29	38.96	40.12	40.45	39.70 ± 0.70
3	49.97	50.63	51.79	51.80	51.05 ± 0.90
4	59.41	59.42	61.08	60.92	60.21 ± 0.92
5	66.61	66.94	68.28	68.12	67.49 ± 0.84
6	72.54	73.69	75.04	74.22	73.87 ± 1.05
7	78.98	80.14	81.17	81.01	80.33 ± 1.00
8	83.83	85.16	86.52	86.03	85.38 ± 1.18

24) Cumulative Percentages of Naproxen Sodium Released from Batch NC85

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.24	14.07	14.07	13.42	13.95 ± 0.36
0.5	20.53	20.21	20.70	20.20	20.41 ± 0.25
1	30.30	30.14	31.12	30.30	30.42 ± 0.44
1.5	39.47	38.81	39.64	39.46	39.35 ± 0.37
2	46.07	45.73	46.24	46.06	46.03 ± 0.21
3	60.07	59.73	59.75	59.73	59.82 ± 0.17
4	69.23	68.89	69.56	68.90	69.15 ± 0.32
5	77.79	77.62	77.80	77.78	77.75 ± 0.09
6	85.74	85.07	85.75	85.08	85.41 ± 0.39
7	90.79	90.45	91.12	91.10	90.87 ± 0.32
8	95.70	94.86	95.38	94.87	95.20 ± 0.41

25) Cumulative Percentages of Naproxen Sodium Released from Batch NC86

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	9.82	9.49	9.82	9.82	9.74 ± 0.16
0.5	13.80	12.98	14.29	14.13	13.80 ± 0.58
1	19.77	18.29	19.93	19.93	19.48 ± 0.80
1.5	24.62	23.13	25.12	25.12	24.50 ± 0.94
2	29.18	27.52	30.00	29.67	29.09 ± 1.10
3	37.68	35.36	38.84	38.51	37.60 ± 1.57
4	45.09	42.75	46.74	45.59	45.04 ± 1.68
5	51.39	48.88	53.71	52.22	51.55 ± 2.02
6	58.54	54.87	59.40	58.89	57.92 ± 2.07
7	64.10	60.24	65.28	64.12	63.43 ± 2.20
8	70.50	66.29	72.18	70.52	69.87 ± 2.51

26) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 of Size Range 421-850 μm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	16.85	17.02	16.85	17.02	16.94 ± 0.09
0.5	24.15	24.48	23.82	23.82	24.07 ± 0.31
1	34.92	35.74	34.26	34.92	34.96 ± 0.60
1.5	41.66	43.14	41.65	42.47	42.23 ± 0.72
2	48.92	50.57	49.08	49.74	49.52 ± 0.75
3	60.15	61.81	59.82	60.82	60.65 ± 0.88
4	69.32	70.99	68.99	70.15	69.86 ± 0.90
5	77.06	79.07	77.05	77.73	77.73 ± 0.95
6	83.04	84.73	83.36	83.39	83.63 ± 0.75
7	87.58	89.61	87.91	88.42	88.38 ± 0.89
8	91.33	93.37	91.82	91.85	92.09 ± 0.88

27) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 of Size Range 1401-2000 μm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	11.78	11.45	11.45	12.11	11.70 ± 0.31
0.5	14.30	14.63	14.30	14.96	14.55 ± 0.31
1	21.09	20.76	20.76	21.10	20.93 ± 0.19
1.5	26.61	26.60	26.28	27.10	26.65 ± 0.34
2	32.32	31.66	31.33	32.32	31.91 ± 0.50
3	40.68	40.51	39.85	41.01	40.51 ± 0.49
4	48.43	48.42	48.25	49.58	48.67 ± 0.61
5	57.36	57.52	57.02	58.36	57.57 ± 0.52
6	62.58	62.91	62.24	63.43	62.79 ± 0.50
7	68.49	68.65	68.47	69.50	68.78 ± 0.49
8	74.59	74.91	74.57	75.76	74.96 ± 0.56

28) Cumulative Percentages of Naproxen Sodium Released from Batch NC81a

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	11.78	11.78	11.45	10.96	11.50 ± 0.39
0.5	16.27	16.10	16.26	16.10	16.18 ± 0.10
1	24.70	24.70	25.03	24.53	24.74 ± 0.21
1.5	32.69	32.36	33.18	32.36	32.65 ± 0.39
2	38.11	38.76	38.11	37.61	38.15 ± 0.47
3	49.12	49.12	49.45	48.29	48.99 ± 0.49
4	59.86	59.86	60.52	59.03	59.82 ± 0.61
5	66.90	67.22	67.39	66.38	66.97 ± 0.44
6	73.31	73.81	73.82	72.47	73.35 ± 0.63
7	78.95	78.95	79.13	78.10	78.78 ± 0.46
8	83.79	83.80	83.97	82.29	83.46 ± 0.79

29) Cumulative Percentages of Naproxen Sodium Released from Batch NC81b

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.07	14.07	13.75	14.56	14.11 ± 0.34
0.5	17.91	17.91	17.75	18.24	17.96 ± 0.21
1	26.20	26.20	25.87	26.53	26.20 ± 0.27
1.5	33.87	33.87	33.86	34.04	33.91 ± 0.09
2	39.62	39.78	40.10	40.44	39.99 ± 0.37
3	49.98	50.31	50.31	50.65	50.31 ± 0.27
4	59.42	59.51	59.74	60.25	59.83 ± 0.35
5	67.76	68.09	68.09	67.78	67.93 ± 0.19
6	75.00	75.01	75.01	75.02	75.01 ± 0.01
7	81.14	81.47	81.47	81.16	81.31 ± 0.19
8	85.67	86.00	86.33	86.01	86.00 ± 0.27

30) Drug Release Rates of Batch NC81

TIME (HOURS)	DRUG RELEASE RATES				MEAN ± SD
	S1	S2	S3	S4	
1	23.72	23.73	24.22	24.55	24.06 ± 0.40
2	13.23	13.23	13.40	12.74	13.15 ± 0.28
3	10.84	10.18	10.68	10.84	10.64 ± 0.31
4	8.77	8.93	8.93	8.77	8.85 ± 0.09
5	7.51	7.67	8.17	7.68	7.76 ± 0.29
6	8.04	8.04	7.89	7.88	7.96 ± 0.09
7	5.63	5.63	5.63	5.63	5.63 ± 0.00
8	5.65	5.16	5.01	4.84	5.17 ± 0.35

31) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Basket Method at 100 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.24	13.75	14.07	13.75	13.95 ± 0.25
0.5	18.57	18.89	19.06	18.89	18.85 ± 0.21
1	25.55	27.02	27.35	27.02	26.73 ± 0.81
1.5	33.54	34.04	35.03	34.69	34.32 ± 0.66
2	37.65	37.99	38.98	38.48	38.28 ± 0.58
3	47.84	48.18	49.18	48.35	48.39 ± 0.57
4	56.61	56.63	57.30	57.29	56.96 ± 0.39
5	63.63	63.32	64.65	64.15	63.94 ± 0.59
6	69.38	69.72	71.06	70.06	70.05 ± 0.73
7	74.83	74.51	75.86	74.86	75.01 ± 0.59
8	80.47	79.82	80.69	80.17	80.29 ± 0.37

32) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Bottle Method at 50 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.27	10.64	12.93	13.09	12.23 ± 1.12
0.5	17.41	15.44	18.24	18.24	17.53 ± 1.32
1	27.49	25.51	28.65	28.97	27.65 ± 1.57
1.5	35.99	33.99	37.48	37.48	36.23 ± 1.65
2	44.04	42.04	45.37	45.21	44.17 ± 1.54
3	56.72	55.19	58.71	58.72	57.34 ± 1.71
4	67.01	65.48	69.18	68.36	67.51 ± 1.62
5	74.74	73.86	77.25	77.25	75.77 ± 1.74
6	82.51	81.46	83.73	84.21	82.98 ± 1.24
7	87.38	86.48	89.09	88.27	87.81 ± 1.12
8	91.13	91.37	93.50	93.17	92.29 ± 1.22

33) Drug Release Rates of Batch NC81 Using the Rotating Basket Method at 100 rpm

TIME (HOURS)	DRUG RELEASE RATES				MEAN ± SD
	S1	S2	S3	S4	
1	25.55	27.02	27.35	27.02	26.74 ± 0.81
2	12.10	10.97	11.63	11.46	11.54 ± 0.47
3	10.19	10.19	10.20	9.87	10.11 ± 0.16
4	8.77	8.45	8.12	8.94	8.57 ± 0.36
5	7.02	6.69	7.35	6.86	6.98 ± 0.28
6	5.75	6.40	6.41	5.91	6.12 ± 0.34
7	5.45	4.79	4.80	4.80	4.96 ± 0.33
8	5.64	5.31	4.83	5.31	5.27 ± 0.33

34) Drug Release Rates of Batch NC81 Using the Rotating Bottle Method at 50 rpm

TIME (HOURS)	DRUG RELEASE RATES				MEAN ± SD
	S1	S2	S3	S4	
1	27.49	25.51	28.65	28.97	27.66 ± 1.56
2	16.55	16.53	16.72	16.24	16.51 ± 0.20
3	12.68	13.15	13.34	13.51	13.17 ± 0.36
4	10.29	10.29	10.47	9.64	10.17 ± 0.37
5	7.73	8.38	8.07	8.89	8.27 ± 0.49
6	7.77	7.60	6.48	6.69	7.20 ± 0.59
7	4.87	5.02	5.39	4.06	4.83 ± 0.55
8	3.75	4.89	4.41	4.90	4.49 ±0.54

35) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Paddle Method at 50 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	13.09	12.93	13.42	12.93	13.09 ± 0.23
0.5	17.91	18.24	18.24	17.91	18.07 ± 0.19
1	25.54	25.86	25.54	25.53	25.62 ± 0.16
1.5	32.39	33.04	32.39	32.38	32.55 ± 0.33
2	38.45	38.95	38.46	38.13	38.50 ± 0.34
3	48.97	49.15	48.98	48.64	48.94 ± 0.21
4	57.42	58.09	57.26	57.26	57.51 ± 0.39
5	65.27	65.28	64.61	64.11	64.82 ± 0.56
6	71.84	72.18	71.35	70.52	71.47 ± 0.72
7	77.30	77.48	76.97	76.14	76.97 ± 0.60
8	82.63	83.46	82.13	80.64	82.22 ± 1.19

36) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Paddle Method at 150 rpm

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	10.96	8.35	13.42	11.13	10.96 ± 2.07
0.5	21.66	21.65	21.67	20.19	21.29 ± 0.74
1	30.94	30.28	30.63	29.46	30.33 ± 0.64
1.5	39.46	38.62	39.15	37.97	38.80 ± 0.65
2	46.88	45.71	46.56	45.22	46.09 ± 0.76
3	57.94	56.76	56.80	55.61	56.78 ± 0.95
4	66.27	65.91	65.95	64.75	65.72 ± 0.66
5	73.51	71.67	72.36	71.49	72.26 ± 0.91
6	78.16	77.62	77.66	77.11	77.64 ± 0.43
7	82.84	81.97	82.50	81.62	82.23 ± 0.54
8	87.05	86.18	86.71	85.83	86.44 ± 0.54

37) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Basket Method at 50 rpm

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	13.75	13.75	13.75	13.42	13.66 ± 0.16
0.5	19.39	18.89	19.39	19.38	19.26 ± 0.25
1	27.84	27.34	27.51	28.33	27.76 ± 0.43
1.5	34.05	33.55	33.88	34.37	33.96 ± 0.34
2	39.31	38.97	38.81	39.80	39.22 ± 0.44
3	49.01	49.00	48.35	49.18	48.89 ± 0.37
4	56.64	55.82	56.14	56.98	56.40 ± 0.52
5	63.01	62.83	63.00	64.16	63.25 ± 0.61
6	69.24	68.41	68.58	69.26	68.87 ± 0.44
7	74.20	73.69	73.69	74.54	74.03 ± 0.42
8	78.20	77.85	77.69	78.71	78.11 ± 0.45

38) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Using the Rotating Basket Method at 150 rpm

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	9.82	9.82	10.15	10.64	10.10 ± 0.39
0.5	14.95	14.62	14.62	14.95	14.78 ± 0.19
1	24.68	24.52	23.86	24.20	24.32 ± 0.36
1.5	33.16	32.67	31.52	32.68	32.51 ± 0.70
2	40.55	40.38	39.22	39.73	39.97 ± 0.61
3	51.73	51.73	50.57	50.75	51.19 ± 0.62
4	62.16	61.83	60.17	61.01	61.29 ± 0.89
5	70.52	70.19	68.85	69.36	69.73 ± 0.76
6	77.45	77.44	75.77	76.28	76.74 ± 0.85
7	83.11	83.10	81.74	82.26	82.55 ± 0.67
8	87.32	87.64	86.44	86.80	87.05 ± 0.53

39) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in Hydrochloric Acid Buffer pH 1.5

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	1.37	1.37	1.31	1.28	1.33 ± 0.05
0.5	2.13	2.13	1.81	2.30	2.09 ± 0.21
1	2.80	2.64	2.64	3.13	2.80 ± 0.23
1.5	3.80	3.63	3.80	3.96	3.80 ± 0.13
2	4.15	4.14	3.98	4.64	4.23 ± 0.29
3	4.99	5.15	4.98	5.16	5.07 ± 0.10
4	4.52	5.67	5.83	5.35	5.34 ± 0.58
5	6.18	6.52	6.19	6.36	6.31 ± 0.16
6	6.55	6.39	7.53	7.05	6.88 ± 0.52
7	7.07	6.75	7.08	6.76	6.92 ± 0.19
8	7.60	7.44	6.46	6.96	7.12 ± 0.51

40) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in Phosphate Buffer pH 4.5

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	0.62	0.62	0.74	0.83	0.70 ± 0.10
0.5	1.80	1.36	1.64	1.64	1.16 ± 0.18
1	3.12	2.79	3.12	3.29	3.08 ± 0.21
1.5	4.12	3.79	3.96	3.80	3.92 ± 0.16
2	4.80	4.47	4.47	4.47	4.55 ± 0.16
3	5.81	5.64	5.48	5.64	5.64 ± 0.13
4	6.49	6.16	6.16	6.00	6.20 ± 0.21
5	6.69	6.85	7.01	6.85	6.85 ± 0.13
6	7.55	7.37	7.22	7.54	7.42 ± 0.16
7	7.92	8.23	7.58	7.58	7.83 ± 0.31
8	8.45	8.77	8.77	8.28	8.57 ± 0.24

41) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in Phosphate Buffer pH 6.9

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	9.98	9.65	9.98	9.98	9.90 ± 0.16
0.5	14.29	13.64	13.96	13.96	13.96 ± 0.27
1	20.26	19.93	19.93	19.93	20.01 ± 0.17
1.5	25.94	25.44	25.44	25.44	25.57 ± 0.25
2	30.66	29.83	30.16	30.16	30.21 ± 0.34
3	38.68	37.69	38.18	38.18	38.19 ± 0.41
4	45.11	44.11	44.61	44.61	44.61 ± 0.41
5	50.60	49.92	51.07	50.26	50.46 ± 0.49
6	56.76	55.92	56.75	56.26	56.42 ± 0.41
7	59.85	59.00	59.84	59.18	59.47 ± 0.44
8	62.80	61.78	62.62	61.79	62.25 ± 0.54

42) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in Phosphate Buffer pH 7.4

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	13.84	14.16	14.49	14.49	14.25 ± 0.31
0.5	17.66	17.66	17.34	17.67	17.58 ± 0.16
1	26.81	26.81	26.81	27.14	26.90 ± 0.16
1.5	33.37	33.70	33.37	33.70	33.54 ± 0.19
2	40.63	40.64	40.47	40.97	40.68 ± 0.21
3	53.72	53.72	53.23	53.56	53.56 ± 0.23
4	61.54	61.21	61.04	61.05	61.21 ± 0.23
5	67.60	67.44	67.10	67.60	67.44 ± 0.23
6	73.04	72.71	72.70	72.72	72.29 ± 0.16
7	78.02	77.52	77.52	77.69	77.69 ± 0.23
8	82.86	82.36	82.52	82.86	82.65 ± 0.25

43) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in Phosphate Buffer pH 8.0

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	15.55	15.22	14.73	15.22	15.18 ± 0.34
0.5	21.52	21.19	20.86	21.52	21.28 ± 0.32
1	32.61	32.27	31.45	32.60	32.23 ± 0.54
1.5	41.29	40.47	40.30	41.29	40.84 ± 0.53
2	47.25	46.75	46.41	48.07	47.12 ± 0.72
3	59.13	57.97	57.96	59.29	58.59 ± 0.72
4	67.47	66.63	66.62	68.29	67.25 ± 0.80
5	73.24	71.58	71.89	73.24	72,49 ± 0.88
6	76.91	76.38	76.86	77.73	76.97 ± 0.56
7	80.25	79.58	80.23	80.61	80.25 ± 0.48
8	82.67	82.14	82.95	83.01	82.69 ± 0.40

44) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 in the Various pH Gradients Used to Simulate the Gastrointestinal Milieu

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	0.92	0.85	0.97	0.91	0.91 ± 0.05
0.5	1.81	1.64	1.81	1.81	1.76 ± 0.08
1	2.63	2.47	2.80	2.80	2.67 ± 0.16
1.5	3.68	3.84	4.06	4.39	3.99 ± 0.31
2	4.76	4.77	5.10	4.94	4.89 ± 0.16
3	21.61	21.95	23.26	22.61	22.36 ± 0.73
4	31.36	33.01	34.49	33.02	32.97 ± 1.28
5	48.39	50.36	52.16	50.86	50.44 ± 1.56
6	58.62	61.58	63.06	62.74	61.50 ± 2.02
7	67.28	71.23	72.38	72.39	70.82 ± 2.42
8	78.24	82.52	83.67	84.34	82.19 ± 2.74
12	94.77	99.54	101.34	102.18	99.46 ± 3.31

45) Drug Release Rates of Batch NC81 in Phosphate Buffer pH 7.4

TIME (HOURS)	DRUG RELEASE RATES				MEAN ± SD
	S1	S2	S3	S4	
1	26.81	26.81	26.81	27.14	26.89 ± 0.17
2	13.82	13.83	13.66	13.83	13.79 ± 0.08
3	13.09	13.08	12.76	12.59	12.88 ± 0.25
4	7.82	7.49	7.81	7.49	7.65 ± 0.19
5	6.06	6.23	6.06	6.55	6.23 ± 0.23
6	5.44	5.27	5.60	5.12	5.36 ± 0.21
7	4.98	4.81	4.82	4.97	4.90 ± 0.09
8	4.84	4.84	5.00	5.17	4.96 ± 0.16

46) Drug Release Rates of Batch NC81 in Various pH Gradients Used to Simulate the Gastrointestinal Milieu

TIME (HOURS)	DRUG RELEASE RATES				MEAN ± SD
	S1	S2	S3	S4	
1	2.63	2.47	2.80	2.80	2.68 ± 0.16
2	2.13	2.30	2.30	2.14	2.22 ± 0.10
3	16.85	17.18	18.16	17.67	17.47 ± 0.57
4	9.75	11.06	11.23	10.41	10.61 ± 0.67
5	17.03	17.35	17.67	17.84	17.47 ± 0.36
6	10.23	11.22	10.90	11.88	11.06 ± 0.69
7	8.66	9.65	9.32	9.65	9.32 ± 0.47
8	10.69	11.29	11.29	11.95	11.37 ± 0.42
12	4.13	4.26	4.42	4.46	4.32 ± 0.15

47) The Effect of Storage Conditions on the Potency of Microspheres of Batch NC81

STORAGE PERIOD (WEEKS)	STORAGE CONDITION AND POTENCY			
	ASSAY 1 (mg)	ASSAY 2 (mg)	ASSAY 3 (mg)	MEAN ± SD (mg)
ROOM TEMPERATURE (21 ± 1°C)				
0	278.91	277.81	275.80	277.51 ± 1.58
4	276.72	275.70	274.83	275.73 ± 0.97
8	274.15	273.53	274.28	273.99 ± 0.40
12	269.50	273.70	270.71	271.30 ± 2.16
40°C				
4	271.83	272.38	274.43	272.88 ± 1.37
8	267.76	269.62	264.51	267.30 ± 2.59
12	264.09	258.04	264.78	262.30 ± 3.71
37°C WITH 80% RELATIVE HUMIDITY				
4	273.21	270.68	273.83	272.57 ± 1.67
8	265.52	267.34	270.63	267.83 ± 2.59
12	256.87	264.67	258.98	260.17 ± 4.03
5 ± 1°C				
4	276.90	275.11	277.26	276.42 ± 1.15
8	275.04	273.13	275.79	274.65 ± 1.37
12	274.82	273.12	276.59	274.84 ± 1.74

48) The Effect of Storage Conditions on the Moisture Content of Microspheres of Batch NC81

STORAGE PERIOD (WEEKS)	STORAGE CONDITION AND MOISTURE CONTENT			
	ASSAY 1 (% w/w)	ASSAY 2 (% w/w)	ASSAY 3 (% w/w)	MEAN ± SD (% w/w)
ROOM TEMPERATURE (21 ± 1°C)				
0	0.491	0.602	0.682	0.592 ± 0.096
4	0.374	0.365	0.403	0.381 ± 0.020
8	0.606	0.567	0.653	0.609 ± 0.043
12	0.510	0.508	0.606	0.541 ± 0.056
40°C				
4	0.604	0.649	0.673	0.642 ± 0.035
8	0.577	0.636	0.834	0.682 ± 0.135
12	0.495	0.432	0.539	0.489 ± 0.054
37°C WITH 80% RELATIVE HUMIDITY				
4	1.254	1.417	1.242	1.304 ± 0.098
8	1.047	1.203	1.097	1.116 ± 0.080
12	1.531	1.575	1.507	1.538 ± 0.034
5 ± 1°C				
4	0.791	1.055	0.934	0.927 ± 0.132
8	1.090	1.115	1.024	1.076 ± 0.047
12	1.281	0.964	0.994	1.080 ± 0.175

49) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 Prior to Storage Under the Various Simulated Conditions (0 Weeks)

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	13.42	13.42	13.42	12.60	13.21 ± 0.41
0.5	18.57	18.89	18.24	17.91	18.40 ± 0.42
1	27.50	27.5	27.01	26.68	27.18 ± 0.40
1.5	35.51	35.84	35.18	34.68	35.30 ± 0.50
2	42.09	42.58	41.59	41.25	41.88 ± 0.58
3	53.12	53.62	53.11	51.95	52.95 ± 0.71
4	61.76	62.75	61.91	61.89	62.08 ± 0.45
5	69.78	70.62	69.94	69.76	70.02 ± 0.40
6	75.56	77.06	76.21	75.54	76.09 ± 0.71
7	81.21	82.06	81.86	80.69	81.45 ± 0.62
8	86.07	86.59	86.07	84.73	85.86 ± 0.80

50) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 2 Weeks at 21 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.60	13.42	13.42	12.93	13.09 ± 0.40
0.5	19.05	18.89	19.38	18.56	18.97 ± 0.34
1	28.16	28.16	28.65	28.16	28.28 ± 0.25
1.5	36.00	36.33	36.67	35.84	36.21 ± 0.37
2	42.58	43.24	43.25	41.76	42.71 ± 0.70
3	54.44	54.77	55.27	53.94	54.60 ± 0.56
4	64.39	65.05	65.55	63.89	64.72 ± 0.73
5	71.94	73.10	73.44	71.93	72.60 ± 0.78
6	78.88	79.55	80.06	78.37	79.22 ± 0.74
7	83.56	84.08	84.58	82.89	83.78 ± 0.72
8	87.45	87.80	88.31	86.94	87.63 ± 0.58

51) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 4 Weeks at 21 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.60	12.93	13.42	12.93	12.97 ± 0.34
0.5	18.56	18.89	19.71	19.71	19.22 ± 0.58
1	28.15	28.16	28.66	28.33	28.32 ± 0.24
1.5	35.02	35.02	36.34	36.34	35.68 ± 0.76
2	41.59	42.09	43.74	43.41	42.71 ± 1.03
3	54.76	55.08	56.25	56.25	55.58 ± 0.78
4	63.56	64.22	65.07	64.41	64.32 ± 0.62
5	71.92	71.94	72.79	71.96	72.15 ± 0.43
6	79.19	79.85	80.39	79.55	79.75 ± 0.51
7	83.22	83.72	83.77	83.26	83.49 ± 0.29
8	87.43	87.45	87.49	86.65	87.26 ± 0.40

52) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 8 Weeks at 21 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.24	13.75	13.09	13.42	13.62 ± 0.49
0.5	18.24	17.91	17.42	17.91	17.87 ± 0.34
1	28.16	28.16	27.33	28.16	27.95 ± 0.41
1.5	36.66	36.82	35.50	36.33	36.33 ± 0.59
2	43.74	43.73	42.90	43.40	43.44 ± 0.40
3	55.10	55.26	53.93	54.77	54.77 ± 0.59
4	64.24	65.06	63.88	64.39	64.39 ± 0.49
5	72.49	72.99	71.91	72.77	72.63 ± 0.20
6	78.50	78.83	77.98	78.49	78.45 ± 0.35
7	84.00	83.35	83.15	83.34	83.46 ± 0.37
8	87.90	87.41	87.04	87.39	87.43 ± 0.35

53) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 12 Weeks at 21 ± 1°C

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	12.11	13.42	12.93	12.93	12.85 ± 0.54
0.5	17.09	18.57	18.24	17.42	17.83 ± 0.69
1	25.03	25.87	24.23	24.55	24.92 ± 0.71
1.5	31.88	31.57	30.42	30.74	31.15 ± 0.69
2	38.44	37.31	37.29	37.62	37.67 ± 0.54
3	49.78	49.13	48.62	48.30	48.96 ± 0.65
4	61.01	60.53	59.85	59.85	60.31 ± 0.57
5	69.04	68.88	67.71	68.03	68.42 ± 0.65
6	76.94	76.29	75.77	76.10	76.27 ± 0.49
7	80.63	80.96	80.11	80.11	80.45 ± 0.42
8	88.76	88.11	87.25	86.76	87.72 ± 0.89

54) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 2 Weeks at 40°C

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	12.27	11.78	11.45	11.13	11.66 ± 0.49
0.5	16.60	16.92	16.92	16.92	16.84 ± 0.16
1	23.72	23.89	23.88	23.72	23.80 ± 0.09
1.5	29.42	30.24	29.91	29.58	29.78 ± 0.36
2	35.96	36.13	35.64	35.30	35.76 ± 0.37
3	44.67	44.67	44.67	44.99	44.75 ± 0.16
4	53.26	53.75	53.26	53.58	53.46 ± 0.25
5	61.57	61.90	61.24	61.56	61.57 ± 0.27
6	67.47	67.15	67.46	67.95	67.51 ± 0.33
7	73.23	73.57	73.23	73.89	73.48 ± 0.31
8	79.19	78.38	78.37	79.20	78.79 ± 0.47

55) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 4 Weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.60	12.93	12.93	12.11	12.64 ± 0.39
0.5	15.78	15.78	15.45	15.12	15.53 ± 0.31
1	22.25	21.92	22.25	21.91	22.08 ± 0.19
1.5	27.61	27.12	27.12	27.11	27.24 ± 0.25
2	31.36	31.19	31.19	30.86	31.15 ± 0.21
3	39.71	39.38	39.05	38.88	39.26 ± 0.37
4	46.48	45.65	46.30	46.29	46.18 ± 0.36
5	52.29	51.46	51.47	51.46	51.67 ± 0.42
6	58.63	58.13	57.80	57.63	58.05 ± 0.44
7	63.20	62.86	62.86	62.36	62.82 ± 0.35
8	67.64	67.13	67.29	67.11	67.29 ± 0.24

56) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 8 Weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	11.78	12.11	12.11	12.27	12.07 ± 0.21
0.5	15.77	16.10	16.10	16.27	16.06 ± 0.21
1	23.06	22.74	23.07	22.74	22.90 ± 0.19
1.5	27.93	28.43	28.27	28.43	28.26 ± 0.23
2	32.02	32.84	32.51	32.84	32.55 ± 0.39
3	40.21	40.55	40.54	41.04	40.58 ± 0.34
4	46.48	47.15	46.82	47.32	46.94 ± 0.37
5	52.30	52.97	52.64	53.14	52.76 ± 0.37
6	57.00	57.84	57.34	58.80	57.67 ± 0.65
7	62.55	62.90	62.89	63.40	62.94 ± 0.35
8	67.63	67.66	67.32	68.00	67.75 ±0.28

57) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 12 Weeks at 40°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	10.64	10.31	9.82	10.96	10.43 ± 0.49
0.5	14.30	14.95	14.62	15.77	14.91 ± 0.63
1	20.76	21.41	21.08	21.91	21.29 ± 0.49
1.5	26.69	26.77	26.60	26.78	26.69 ± 0.10
2	30.84	31.33	31.16	32.00	31.33 ± 0.49
3	38.86	39.85	38.86	39.37	39.24 ± 0.48
4	46.76	48.25	46.27	46.46	46.94 ± 0.90
5	52.58	53.42	52.91	52.61	52.88 ± 0.39
6	57.78	58.46	57.29	57.80	57.83 ± 0.48
7	62.51	63.36	62.83	62.37	62.77 ± 0.44
8	66.12	65.17	66.12	66.47	65.97 ± 0.56

58) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 2 Weeks at 37°C With 80% Relative Humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.60	12.11	12.60	12.27	12.40 ± 0.25
0.5	17.09	16.59	17.09	16.92	16.92 ± 0.23
1	25.53	24.21	25.53	25.03	25.08 ± 0.62
1.5	32.21	31.22	32.21	32.21	31.96 ± 0.50
2	38.12	37.28	38.12	38.11	37.91 ± 0.42
3	47.82	47.14	47.82	48.14	47.73 ± 0.42
4	57.24	56.40	57.41	57.40	57.11 ± 0.48
5	65.25	64.56	64.92	65.41	65.04 ± 0.37
6	71.33	70.15	71.33	71.66	71.12 ± 0.66
7	77.45	76.59	77.28	77.77	77.27 ± 0.50
8	83.10	81.75	82.61	83.43	82.72 ± 0.73

59) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 4 Weeks at 37°C With 80% Relative Humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.24	13.09	14.24	13.42	13.75 ± 0.58
0.5	17.92	16.93	17.10	17.91	17.46 ± 0.52
1	25.05	24.22	24.72	26.52	25.13 ± 0.99
1.5	31.90	31.06	31.89	33.54	32.10 ± 1.04
2	37.64	36.80	38.94	39.29	38.17 ± 1.16
3	46.19	46.33	45.54	48.67	46.68 ± 1.37
4	53.81	52.96	54.13	56.95	54.46 ± 1.73
5	60.15	59.31	60.48	63.64	60.90 ± 1.90
6	66.37	65.52	66.70	70.04	67.16 ± 1.99
7	75.24	74.88	76.06	80.24	76.61 ± 2.47
8	76.96	75.94	76.96	81.00	77.72 ± 2.24

60) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 8 Weeks at 37°C With 80% Relative Humidity

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	12.93	12.60	12.27	12.60	12.06 ± 0.27
0.5	17.74	17.09	16.92	16.92	17.17 ± 0.39
1	25.04	24.71	24.22	24.55	24.63 ± 0.34
1.5	30.74	30.25	29.91	29.92	30.21 ± 0.39
2	35.99	35.65	35.31	35.32	35.57 ± 0.32
3	45.02	44.19	44.18	44.18	44.39 ± 0.42
4	52.79	52.12	51.62	51.63	52.04 ± 0.55
5	58.81	58.30	57.96	58.29	58.34 ± 0.35
6	65.51	64.67	64.00	64.66	64.71 ± 0.62
7	70.45	69.93	69.59	69.92	69.97 ± 0.36
8	75.08	74.40	74.22	74.39	74.52 ± 0.38

61) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 12 Weeks at 37°C With 80% Relative Humidity

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	12.60	13.42	12.60	12.93	12.89 ± 0.39
0.5	16.27	17.09	16.60	16.93	16.72 ± 0.36
1	23.27	24.71	23.40	23.40	23.81 ± 0.62
1.5	28.27	29.43	29.95	27.95	28.40 ± 0.71
2	33.99	34.50	33.17	32.52	33.55 ± 0.88
3	42.69	43.86	41.86	41.86	42.57 ± 0.94
4	48.48	50.15	48.47	48.31	48.85 ± 0.87
5	55.95	57.46	55.12	55.12	55.91 ± 1.10
6	62.96	64.32	62.13	61.80	62.80 ± 1.12
7	67.89	69.58	66.88	66.23	67.64 ± 1.46
8	73.82	75.03	72.32	71.82	73.25 ± 1.46

62) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage For 2 Weeks at 5 ± 1°C

TIME	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
(HOURS)	S1	S2	S3	S4	
0.25	13.42	13.75	13.75	14.07	13.75 ± 0.27
0.5	18.24	17.75	18.24	17.91	18.04 ± 0.24
1	26.68	26.68	27.01	27.01	26.85 ± 0.19
1.5	34.03	34.03	34.04	34.36	34.12 ± 0.17
2	42.56	42.56	42.57	43.22	42.73 ±0.33
3	50.65	50.65	50.82	51.15	50.82 ± 0.24
4	59.77	59.93	59.77	59.94	59.85 ± 0.10
5	67.29	67.46	67.30	67.80	67.46 ± 0.24
6	72.57	73.06	72.90	73.40	72.93 ± 0.35
7	77.54	78.37	78.20	78.39	78.12 ± 0.40
8	83.20	83.86	83.86	84.04	83.74 ± 0.37

63) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 4 Weeks at 5 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	11.45	13.09	13.42	13.42	12.85 ± 0.94
0.5	16.59	17.91	18.24	17.75	17.62 ± 0.72
1	24.54	25.04	25.05	25.05	24.92 ± 0.25
1.5	31.55	32.71	31.24	31.24	31.68 ± 0.70
2	38.10	38.13	37.63	38.12	37.99 ± 0.24
3	45.35	45.54	45.53	45.04	45.36 ± 0.23
4	51.32	51.68	51.01	51.34	51.34 ± 0.27
5	61.58	61.94	61.60	62.09	61.80 ± 0.25
6	69.94	70.46	70.12	70.94	70.36 ± 0.44
7	79.32	79.68	78.84	79.34	79.30 ± 0.34
8	84.66	85.02	84.18	85.01	84.72 ± 0.39

64) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 8 Weeks at 5 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	14.89	15.05	13.75	14.24	14.48 ± 0.60
0.5	21.68	21.85	19.39	21.02	20.99 ± 1.12
1	31.78	32.11	28.17	31.12	30.80 ± 1.80
1.5	39.49	40.47	36.67	39.15	38.94 ± 1.62
2	46.90	48.22	42.92	46.89	46.24 ± 2.30
3	58.78	59.61	53.47	57.95	57.45 ± 2.74
4	68.76	69.60	62.60	68.74	67.42 ± 3.24
5	74.53	76.08	69.16	75.66	73.84 ± 3.19
6	83.45	84.13	75.59	83.76	81.73 ± 4.11
7	88.81	89.50	81.23	88.80	87.90 ± 3.91
8	96.98	92.11	83.96	92.06	91.28 ± 5.39

65) Cumulative Percentages of Naproxen Sodium Released from Batch NC81 After Storage for 12 Weeks at 5 ± 1°C

TIME (HOURS)	CUMULATIVE PERCENTAGE RELEASED				MEAN ± SD
	S1	S2	S3	S4	
0.25	15.71	15.38	15.05	14.89	15.26 ± 0.36
0.5	21.36	20.70	21.03	20.54	20.91 ± 0.36
1	31.79	30.96	31.45	30.96	31.29 ± 0.40
1.5	40.47	39.97	39.97	39.48	39.97 ± 0.41
2	47.08	47.06	47.39	46.56	47.02 ± 0.34
3	59.61	58.94	59.60	58.44	59.15 ± 0.57
4	69.59	69.24	69.58	68.41	69.21 ± 0.55
5	78.15	77.64	77.81	76.81	77.60 ± 0.57
6	84.30	84.12	84.62	83.28	84.08 ± 0.57
7	89.67	89.16	89.66	90.28	89.69 ±0.46
8	93.75	95.20	93.58	92.89	93.86 ± 0.97

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