PREPARATION OF NOVEL MODIFIED-RELEASE DOSAGE FORMS OF DICLOFENAC SODIUM AND IBUPROFEN

JOMJAI SUJJA-AREEVATH

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

School of Pharmacy
The Robert Gordon University
Aberdeen
United Kingdom

October 1997

แด่ แม่และพ่อ

สำหรับความรักและความเข้าใจที่มีให้เสมอมา

To mum and dad

for their love and understanding

ACKNOWLEDGEMENT

I greatly appreciate the advice, encouragement and understanding of Dr. P. J. Cox and Dr. D. L. Munday throughout this study. I would also like to thank Mr. H. J. Fletcher for his help with photographic techniques and Dr. R. R. Moody for his guidance on UV spectrophotometry. My thanks are also due to Prof. K. A. Khan and Dr. A. Smith for their useful advice.

The warm welcome afforded by Prof. R. M. E. Richards on arrival in Aberdeen greatly encouraged me. The unfailing support from academic and technical staff of the School of Pharmacy, namely, Mrs. P. Ewen, Mr. D. Bain and Mr. O. Shakoor, was greatly appreciated throughout this study. I am also grateful to all my friends for their assistance and encouragement.

The financial support by the Robert Gordon University and Knoll Pharmaceuticals (formerly Boots) is gratefully acknowledged.

ABSTRACT

Mini-matrix multiple unit dosage forms (MUDFs) of diclofenac sodium and S(+) ibuprofen have been prepared. Normal tabletting techniques were used to form the mini-matrices prior to their enclosure in hard gelatin capsules. Four natural hydrophilic gums, namely xanthan, karaya, locust bean and carrageenan gums as well as hydroxypropyl methylcellulose (HPMC) were used as the principle release-retarding agents. Various excipients - lactose, Encompress®, cellulose acetate phthalate (CAP), Veegum F® and Avicel PH101® - were added in different proportions to further modify drug release.

The diclofenac sodium mini-matrices (4.5 mm in diameter) were produced by the wet granulation method. The release profiles from several encapsulated mini-matrices in phosphate buffer solution (pH 7.0) showed that xanthan, karaya and locust bean gums could sustain the release of diclofenac sodium while the carrageenan gum did not produce a satisfactory sustaining effect. The rank order of decreasing swelling rate in both axial and radial dimensions was xanthan > karaya > locust bean gum and each of these gums showed almost Fickian swelling behaviour. The solvent penetration rates were consistent with the swelling rates. However, the order of decreasing drug release and erosion rates was locust bean > xanthan > karaya gum. For each of these gums, the release behaviour was anomalous indicating that both Fickian drug diffusion and polymer relaxation were involved in the release process. The dominant mechanism depended on the nature and content of the gum, as well as the stage in the dissolution period. The study involving xanthan gum showed that the diclofenac sodium release rate declined linearly with a progressive increase in the gum content, without changing the release behaviour. However, for high drug: xanthan gum ratio (2:1), the release kinetics changed to Super Case II. Solubility differences

between the excipients did not affect the release rate, but increasing proportions of each excipient produced a faster release rate with the release mechanism changing from anomalous to Case II and then to Super Case II transport. Mini-matrices containing HPMC produced faster drug release than those containing the three natural gums. There was no synergistic effect between xanthan and locust bean gums on the release of diclofenac sodium from mini-matrices. Variation in the stirring speed (used in the dissolution apparatus) and matrix volume had little effect on drug release, whereas the pH of the dissolution medium greatly affected the release of diclofenac sodium.

Following on from the studies involving diclofenac sodium, xanthan and karaya gums were used to produce mini-matrices of S(+) ibuprofen. Excipients with good compressibility characteristics such as lactose, Encompress® and Avicel PH101® were needed in the formulations. At pH 7, higher drug release rates were obtained with karaya gum (Super Case II mechanism) compared with xanthan gum (anomalous behaviour). Solubility differences between the excipients slightly affected the release rate. Compression forces (11 - 26 kN) slightly affected the crushing strength. The mini-matrices were relatively stable to variation in temperature (5 - 37°C) and relative humidity (10 - 75%) over a 2 month time period.

These studies have shown that near zero-order release of diclofenac sodium and S(+) ibuprofen can be achieved using encapsulated mini-matrices formulations. The release mechanisms and release rates can be adjusted by variation of the type and content of gums and/or excipients.

CONTENTS

CHAPTER 1

INTRODUCTION

1.1 ORAL SUSTAINED-RELEASE DRUG DELIVERY SYSTEMS

Oral delivery is the most acceptable route for delivery of drug to patients, whether this be in the form of liquid or solid preparations. By this route, the tablet and the capsule are the most commonly prescribed dosage forms because they offer a convenient form of drug administration, provide dosage uniformity, are stable over extended and diverse storage conditions and can be produced on high-speed equipment (Lieberman et al. 1990; Deshpande et al. 1996).

Normal drug dosing may follow a "sawtooth" kinetic profile (Figure 1.1). During the early periods of dosing there may be insufficient drug to generate a favourable biological response. The following doses may lead to a toxic level (over the desired therapeutic level), which then falls to a subclinical level, and on subsequent dosing rises to dangerously high level, falling again to ineffective concentrations, in continuous cycles of excessive-ineffective levels. Several technical advancements have been developed in order to control the rate of drug delivery, sustain the duration of therapeutic activity, eliminate dangerous side effects, and/or target the delivery of drug to a tissue (Martin 1993; Chien 1992; Lee and Robinson 1979; Lordi 1986).

The term "sustained release" is used to describe a drug delivery system that delays and/or prolongs the release of drug. It also implies delayed therapeutic action and sustained duration of therapeutic effect. The term "controlled release" has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability and reproducibility in the drug release kinetics. In other words, sustained-release dosage forms provide medication over an extended time period whereas

controlled release systems attempt to control drug concentrations in the target tissue (Chien 1992; Ansel et al. 1995). But Lordi (1986) states that the terms "sustained release", "sustained action", "prolonged action", "controlled release", "extended action", "timed release", "depot" and "repository" dosage forms all describe the same delay in release of drug.

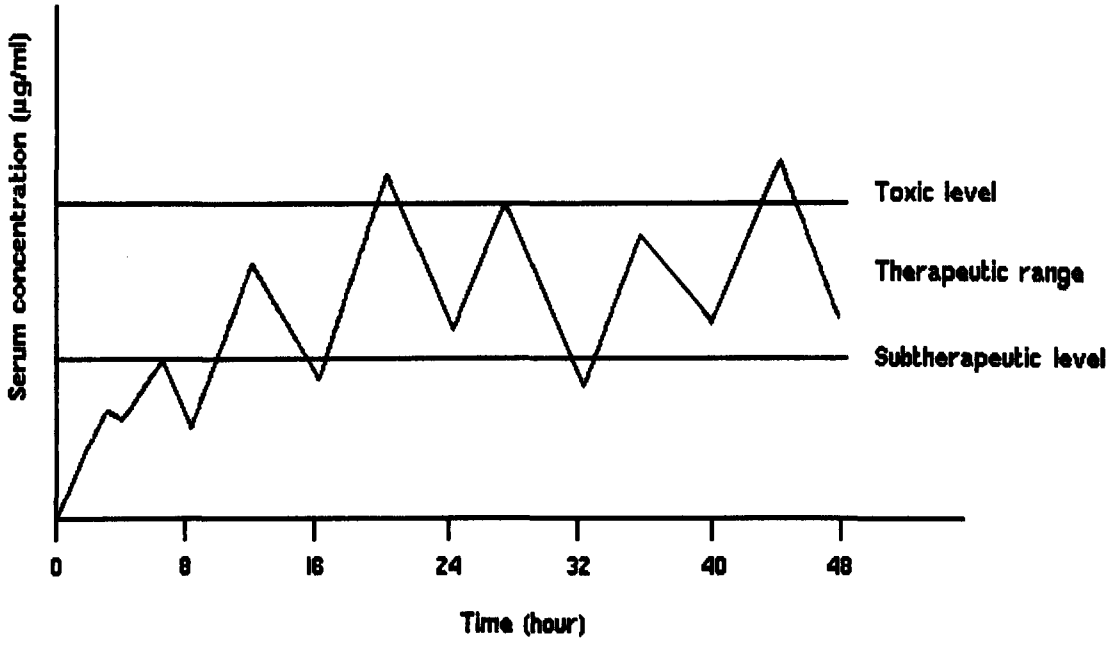


Figure 1.1. Undesirable sawtooth kinetic profile under conditions of normal dosing.

1.2 DESIGNS OF ORAL SUSTAINED-RELEASE DRUG DELIVERY SYSTEMS

Two general methods have been developed for implementation of practical sustained-release dosage form designs: 1) methods based on modification of the physical and/or chemical properties of the drug and 2) methods based on modification of the drug release rate characteristics of the dosage that effect bioavailability (Lordi 1986).

Controlled-release drug delivery systems based on dosage form modification can be classified into three categories.

1. Rate-preprogrammed drug delivery systems. The release of drug molecules from the delivery systems has been preprogrammed at specific rate profiles. This is accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system.

2. Activation-modulated drug delivery systems. The release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

3. Feedback-regulated drug delivery systems. The release of drug molecules from the delivery systems is activated by a triggering agent, such as a biochemical substance, in the body and also regulated by its concentration via some feedback mechanism. The rate of drug release is controlled by the concentration of triggering agent detected by a sensor in the feedback-regulated mechanism.

All three categories of controlled-release drug delivery systems consist of the following common structural features: 1) drug reservoir compartment, 2) rate-controlling element, and 3) energy source.

The rate-preprogrammed drug delivery system can be viewed as the first generation of controlled-release drug delivery systems, providing the technological basis for the later development of activation-modulated drug delivery systems, as the second generation, and of feedback-regulated drug delivery systems, as the third generation.

Rate-preprogrammed drug delivery systems are constructed from the two basic types of controlled-release drug delivery systems (Chien 1992).

1) Polymer membrane permeation-controlled drug delivery systems.

In this system the drug reservoir compartment is encapsulated inside a polymeric membrane, which acts as a rate-controlling element and the release of drug is controlled by its permeation through the rate-controlling membrane (Figure 1.2).

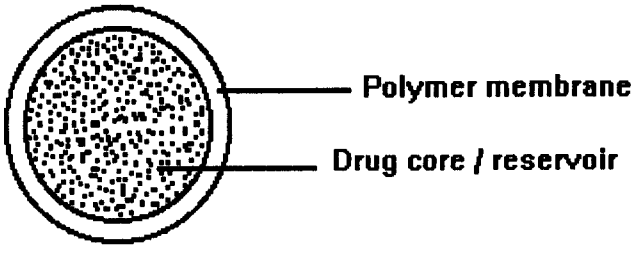


Figure 1.2. Polymer membrane permeation-controlled drug delivery systems.

2) Polymer matrix diffusion-controlled drug delivery systems.

In this system the drug substance is homogeneously dispersed throughout a polymer matrix, which acts as rate-controlling element, and the release of drug is thus controlled by its diffusion through the rate-controlling polymer matrix (Figure 1.3). This system was used in this study in the form of a hydrophilic matrix.

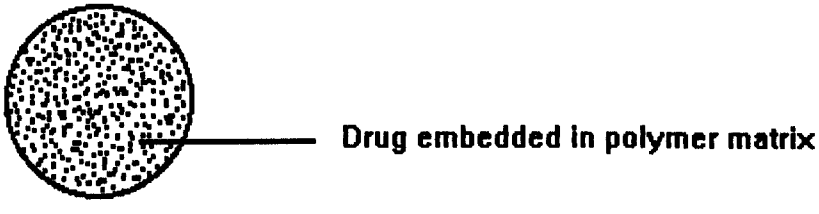


Figure 1.3. Polymer matrix diffusion-controlled drug delivery systems.

1.2.1 Properties of drugs used in sustained-release formulations

In general, the drugs best suited for incorporation into a sustained release product should have certain characteristics.

1) They should exhibit neither very slow nor very fast rates of absorption and excretion. Drugs with slow rates of absorption and excretion are usually inherently long-acting and their preparation into sustained-action type dosage forms is not necessary. Similarly, a drug with a short half life, i.e., < 1 hours, should not be formulated into a sustained release product because such a delivery system would require unacceptably large release rates and doses.

2) They should be uniformly absorbed from the gastrointestinal tract. Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for sustained-release products, because their drug release and therefore drug absorption will fluctuate, depending upon the position of the drug in the gastrointestinal tract and the dosage form's rate of movement within the tract.

3) They should be administered in relatively small doses. Drugs with large single doses frequently are not suitable for the preparation of the sustained-action product because the individual dosage unit needed to maintain the extended therapeutic blood level of the drug would have to be too large for the patient to easily swallow.

4) They should possess a good margin of safety. Those drugs which are potent in very small doses or possess very narrow or small therapeutic indices are poor candidates for formulation into controlled-release formulations because of technological limitations of precise control over release rates.

5) They should be used in the treatment of chronic rather than acute conditions. Drugs for acute conditions generally require more physician control of the dosage than that provided by sustained-release products (Ansel et al. 1995; Lordi 1986).

1.2.2 Hydrophilic matrix (HM)

The hydrophilic matrix (a polymer matrix diffusion-controlled drug delivery system) is defined as an homogeneous mixture of substances, substantially comprising polymers which are slowly dissolved in water. They are converted into a well defined form by compression or encapsulation. When a HM tablet is in contact with water or aqueous based dissolution media such as the gastro-intestinal juices, the hydrophilic polymers form a gelatinous surface layer, through which water slowly penetrates, hydrating and swelling the polymer. Then the polymer in the gel form, gradually goes into solution, first the outermost layer and thereafter the inner layers, until it is totally dissolved. The active substance is slowly released by two contemporaneous mechanisms, namely diffusion through the gelatinous layer and gel erosion. While the first of these release mechanisms prevails when the drug is very soluble in the dissolution medium, the second prevails in case of poorly soluble drugs (Calanchi et al. 1987).

HM tablets have been used extensively to produce sustained drug delivery by the gastro-intestinal (GI) route (Huber and Christenson 1968; Lapidus and Lordi 1968 and Mockel and Lippold 1993) because they are relatively simple, inexpensive, versatile and utilise conventional processing equipment. Various types of swellable polymers have been used to produce hydrophilic matrices for sustained release formulations. Hydroxypropyl methylcellulose (HPMC) alone or in combination with other polymers, is frequently used as mentioned in the reviews by Hogan (1989) and Alderman (1984). It has been used mostly in the form of matrix tablets and matrix pellets (Tapia et al., 1993).

Drug release from a hydrophilic matrix is determined by a diverse range of factors that can be classified into 3 main categories: a) polymer variables, b) formulation and manufacturing, and c) environmental conditions. The mechanisms of

drug release from a HPMC matrix were extensively investigated (Sung et al. 1996; Wan et al. 1993; Pham and Lee 1994). In the case of polymer variables, the effect of polymer content (Ford et al. 1985a; Ford et al. 1985b; Hogan 1989; Panomsuk et al. 1995b; Kabanda et al. 1994; Michell et al. 1993; Sung et al. 1996; Xu and Sunada 1995) and type (Sheu et al. 1992; Lapidus and Lordi 1968; Panomsuk et al. 1995b; Kabanda et al. 1994; Sung et al. 1996) on drug release was considered. Polymer molecular weight (often expressed as solution viscosity) is generally accepted to be a controlling factor (Chang and Parrot 1991). However, this is only valid when dealing with a single type of polymer. Also important are the rheological properties of the polymer. In the case of formulation and manufacturing, the effect of drug type (Ford et al. 1987), drug particle size (Ford et al. 1985a; Ford et al. 1985b; Hogan 1989), drug content (Mitchell et al. 1993; Xu and Sunada 1995), excipient type (Lapidus and Lordi 1968; Ford et al. 1987; Hogan 1989; Panomsuk et al. 1995b; Kabanda et al. 1994; Feely and Davis 1988a; Feely and Davis 1988b; Sheskey et al. 1995), compression force (Ford et al. 1985a; Kabanda et al. 1994; Vazquez et al. 1992) and matrix size and shape (Ford et al. 1987; Hogan 1989; Panomsuk et al. 1995b) on drug release has been investigated. Environmental conditions, for example, the effect of added salt, dissolution medium pH (Sheu et al. 1992) and temperature (Larpidus and Lordi 1968) on drug release has also been investigated. It can be concluded from these works that in a properly developed formulation, HPMC is a good matrix material for sustaining drug release. However, there is a report that certain ionic salts and drugs, e.g., diclofenac sodium, cause failure of sustained release of HPMC matrices because they substantially depress the thermal gelation temperature of HPMC (Rajabi-Siahboomi et al. 1993). In addition, one study showed burst release of propranolol hydrochloride from HPMC matrix at low content of drug (20 mg per 150 mg HPMC) (Mitchell et al. 1993). Therefore other hydrophilic materials have been examined to overcome these

problems. Among these, xanthan gum is an interesting substance (Talukda and Plaizier-Vercammen 1993; Talukda and Kinget 1995; Lu et al. 1991; Dhopeshwarkar and Zatz 1993; Talukdar et al. 1996). It is a high molecular weight heteropolysaccharide. The viscosity of its gel is nearly independent of pH, ionic strength and temperature (see also Chapter 2). Xanthan gum is compatible with virtually all salts. For these reasons, it has been chosen for production of diclofenac sodium and S(+) ibuprofen matrices in this study. The other three hydrophilic gums used were karaya gum, locust bean gum and carrageenan.

1.2.3 Mechanisms of drug release

Modelling of controlled release of drugs from polymeric devices has been the subject of considerable research over the past 20 years. Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system

$$\frac{M_t}{M_\alpha} = kt^n \quad \text{.....(1.1)}$$

where M_t / M_α is the fraction of drug released, t is the release time, k is a kinetic constant (with units of t^{-n}) incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. This equation can be used to analyze the first 60% of a release curve where the release is linearly related to t^n, regardless of geometric shape.

Sinclair and Peppas (1984) and Peppas (1985) have also shown that two competing release mechanisms, a Fickian diffusional release and a Case-II relaxational release, are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or

biological fluids. This term also includes polymer entanglement and erosion. Table 1.1 describes the limits of this analysis for cylindrical shape e.g. a tablet. The value of the exponent for case-II transport mechanism is twice that of pure Fickian diffusional mechanism.

Table 1.1. Diffusion exponent and solute release mechanism for cylindrical shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

Following a heuristic approach first developed by Alfrey et al. (1966) for the case of solvent transport in a polymer, the two phenomena controlling the release can be considered as additive. Therefore, Equation 1.1 may be extended (Peppas and Sahlin 1989)

$$\frac{M_t}{M_\alpha} = k_1 t^m + k_2 t^{2m} \quad \text{.....(1.2)}$$

where the first term of the right-hand side is the Fickian contribution, the second term being the Case-II relaxational contribution. The coefficient *m* is the purely Fickian diffusion exponent for a device of any geometric shape which exhibits controlled release. This coefficient was given for any shape, including cylinders, tablets and films by a diagram (Figure 1.4).

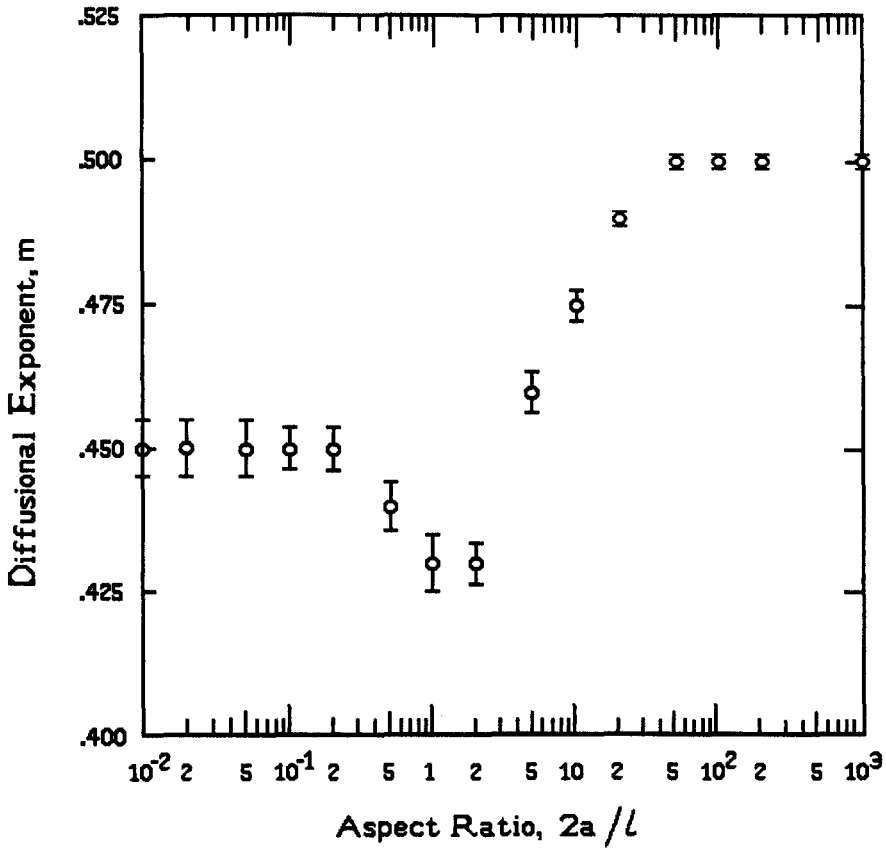


Figure 1.4. Diffusional exponent, *m*, of Equation 1.2 for Fickian diffusional drug release from mini-matrices as a function of their aspect ratio; a ratio of diameter (2a) to thickness of the tablet (l) (From Peppas and Sahlin 1989. Int J Pharm, 57, 169-172.).

Equation 1.2 can be rewritten as:

$$\frac{M_t}{M_\alpha} = k_1 t^m [1 + \frac{k_2}{k_1} t^m] \quad \text{.....(1.3)}$$

The percentage of drug release due to the Fickian mechanism, *F*, is clearly calculated as:

$$F = \frac{1}{1 + \frac{k_2}{k_1} t^m} \quad \text{.....(1.4)}$$

which leads to the ratio of relaxational over Fickian contributions as:

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \quad \text{.....(1.5)}$$

Therefore, Equations 1.2 and 1.3 indicate that solute release from any device, irrespective of its geometric shape, can be written in terms of a Fickian and a relaxational contribution. If the Fickian contribution can be expressed as a function of t^m, then the relaxational contribution can be expressed as a function of t^{2m}. By comparison of Equations 1.1 and 1.2 it is concluded that $m=n$ when the relaxational mechanism is negligible.

Although the constant k in Equation 1.1 is one of the measures of the drug release rate, it should not be used for comparison because there are different kinetics in different test conditions. Therefore, to characterize the drug release rate in different experimental conditions, mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold (1993) using Equation 1.6.

$$MDT = \frac{n}{n+1} k^{-1/n} \quad \text{.....(1.6)}$$

For calculation of the release rate of the drug, the data in this study were subjected to the Higuchi equation (Higuchi 1961):

$$Q = (2ADC_s t)^{1/2} \quad \text{.....(1.7)}$$

where Q is the percentage of drug release at time t, A is the total concentration of drug in the mini-matrix, D is the diffusion coefficient of the drug in the mini-matrix and C_s is the solubility of drug in the mini-matrix. This equation may be reduced to a simple equation as:

$$Q = at^{1/2} + c \quad \text{.....(1.8)}$$

Equation 1.8, for release data dependent on the square root of time, would give a straight line release profile, where a is a √time dissolution rate constant and c is a constant. The lag period, prior to the commencement of release, is defined as $(-c/a)^2$.

1.3 ADVANTAGES AND DISADVANTAGES OF SUSTAINED-RELEASE DRUG DELIVERY SYSTEMS

1.3.1 Advantages of sustained-release drug delivery systems

Sustained drug delivery systems are convenient items. They accomplish more efficiently what conventional dosage forms accomplish with real clinical benefits. Some of the potential benefits to be gained from sustained drug delivery are now considered.

1) Enhanced patient compliance and convenience. Patient compliance is a chronic problem for all self-administered drugs and is a sufficiently compelling reason in itself to warrant a prolonged-action delivery system. It is a very important component of successful drug therapy. With less frequency of dose administration the patient is less apt to neglect taking a dose. Rate-controlled products deliver more than a single dose of medication and thus are taken less often than conventional forms.

2) Reduction in amount of drug required. The net effect of reduction in drug use is usually a decrease or elimination of systemic or local side effects. Other advantages are to gain less potentiation or reduction of drug activity with chronic use and minimize drug accumulation with chronic dosing.

3) Improved efficiency in treatment. This is the most important reason for sustained drug delivery. Proper drug delivery should lead to a more prompt cure or control of the condition at hand as well as better management of acute and chronic conditions. This effect has many therapeutic and non-therapeutic ramifications including perhaps a financial saving to the patient in terms of lost work days, less hospitalization, fewer visits to the physician, etc.

4) Reduction in health care costs, i.e., economy. This economy should be viewed in a broad sense, since the unit cost of most sustained and/or controlled drug delivery systems is usually greater than conventional dosage forms because of the

special nature of these products. However, when measured against the total cost savings in health care it seems reasonable to assume that many of these products are already economical to the patient and the savings should be even greater (Lee and Robinson 1979; Ansel et al. 1995; Lordi 1986; Calanchi et al. 1987).

1.3.2 Disadvantages of sustained-release drug delivery systems

Disadvantages of these systems must also be considered.

1) Administration of sustained release medication does not permit the prompt termination of therapy. Immediate changes in drug need during therapy, such as might be encountered if significant adverse effect are noted, cannot be accommodated.

2) The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

3) Sustained release forms are designed for the normal population, i.e., on the basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition, significant patient variation, and so forth are not accommodated.

4) Economic factors must also be assessed, since more costly processes and equipment are involved in manufacturing sustained release forms (Lordi 1986).

1.4 MULTIPLE UNIT DOSAGE FORMS (MUDFs)

Multiple units dosage forms (MUDFs) or multiparticulate dosage forms are those in which a single dose of a therapeutic agent is administered subdivided into many small dosage units. For oral administration, sufficient units to comprise a single therapeutic dose is usually enclosed in a hard gelatin capsule, a disintegrating tablet or in a sachet. MUDFs are widely used for oral pharmaceuticals and whilst occasionally

they may provide immediate release products, by far their major use is as controlled release devices providing delayed or sustained release of drug (Melia 1994).

Some of the common technologies used in the pharmaceutical industry for the production of oral MUDFs are extrusion/spheronisation, non-pareil coating, granulation, tabletting, microencapsulation, spray coating, ion-exchange complexation and macromolecular complexation. The decision to choose a particular technology for the production is influenced by many factors. Some of the principle factors are listed below.

- Drug: dose, stability, physicochemical characteristics, pharmacokinetic profile, compatibility with excipients.
- Dosage form: drug release profile, *in vivo* performance, therapeutic efficacy, stability.
- Manufacturing: equipment availability, capital expenditure, existing expertise, production costs, time and ease of manufacture, batch to batch reproducibility.
- Other: patent protection, patient acceptability, product image.

1.4.1 Advantages of MUDFs

With a move towards 12 or 24 hourly dosing regimes, sustained release preparations must contain greater amounts of drug than the conventional dose form equivalent and consequently the size of the monolithic unit is increased. MUDFs allow much greater dosing flexibility. Incompatible drugs or excipients may be co-administered.

One of the major problems associated with large single controlled release units above a certain size is the variability in the gastric emptying patterns which are displayed both in fasted and fed subjects. MUDFs have much more reproducible gastric emptying patterns leading to more reproducible bioavailability of certain drugs.

The report from Digranes and co-workers (1984) showed that food affects the absorption of erythromycin pellets less than it affects erythromycin stearate enteric-coated tablets. Erythromycin pellets also produced better reproducibility in absorption than the enteric-coated tablets both within and between subjects (Graffner et al. 1986). The absorption of erythromycin from enteric-coated pellets given 1 hour before food is better and more reliable than film-coated erythromycin stearate or enteric-coated erythromycin base (Josefsson et al. 1986). The erythromycin enteric-coated pellets also gave a higher maximum drug concentration than the film coated erythromycin stearate tablet (Josefsson et al. 1982). A study of acetylsalicylic acid showed that encapsulated enteric-coated granules gave more uniform plasma levels and less inter- and intra-individual variation than enteric-coated tablets (Edgar et al. 1984). In the stomach the mixing of the MUDFs with food may avoid the high localised drug concentration associated with release from a large, single monolithic device.

In a patient with normal bowel function, the transit of pellets through the colon is very much slower than with large single units. Pellets are better suited for delivery of drugs to the large bowel as larger units pass through more quickly due to a phenomenon called colonic streaming. In addition where the colon contents are more fluid such as secretory diarrhoea, the sieving function of the ascending colon is lost and all materials travel at the same rate. In these cases the use of high density pellets may prolong residence in the ascending colon.

If a single monolithic dosage form unexpectedly disintegrates within the gastrointestinal tract, for example, as a result of the patient inadvertently chewing a controlled release dosage form, then it will release its payload as a bolus causing 'dose dumping' of the drug. In MUDFs, failure of the unit is unlikely to cause disruption of all the particulates thus the dosage released will be minimal. For this reason MUDFs are associated with a reduced risk of toxicity.

Administering a drug as a multiparticulate reduces the probability of localised mucosal damage to the gastrointestinal tract. If a capsule or tablet sticks in the oesophagus or within the stomach or intestine, then the contents will be released onto a small area of the gut wall (Melia et al. 1994).

1.4.2 Disadvantages of MUDFs

If the technology chosen is new to a pharmaceutical company, then the disadvantages of using a MUDFs are primarily those of the cost and time in its development and introduction. Investment will be required in new plant, capital equipment and modifications to existing pilot and factory production staff and for them to develop "hands on" experience in product manufacture. Considerable time will be required to develop, commission and validate the production process, in which some unit processes may be unfamiliar, this is in addition to the normal time associated with developing the new controlled release product.

Unforeseen difficulties may also arise in stability testing and quality control of the new product as a result of lack of a knowledge base and experience in the new technology. Even if the technology and expertise is well established, production costs and time for manufacture are often higher for MUDFs than for tablets. Many of these problems may be circumvented if development and/or manufacture of a product is subcontracted to a specialist company which offers expertise in a particular technology (Melia et al. 1994).

1.4.3 Technologies used in the production of MUDFs

1.4.3.1 Extrusion/spheronisation

Extrusion/spheronisation is one of the principle manufacturing methods used for production of multiple unit sustained-release dosage forms. The two main unit processes are used to produce spherical, drug-loaded "cores" of uniform diameter (0.5-2.0 mm), which can then be film-coated and filled into hard gelatin capsules (Hodsdon and Melia 1994). It is a mechanical method for mass-production of spheroidal particles from a wet powder mass; in effect, an automated version of the old traditional method of pill production by hand (Rowe 1983). Successful extrusion is highly dependent on the interplay between the formulation, the equipment and the processing conditions. Smooth extrudates will produce spheres of uniform particle size whilst extrudates having uneven density or surface roughness will result, at best, in wider particle size distributions and, at worst, may not successfully spheronise at all.

1.4.3.2 Non-pareil coating

Non-pareil seed coating or multilayer coating is the other main method used for production of multiple unit sustained-release dosage forms. It has a supporting inert core (non-pareil seed), ideally, a spherical granule of diameter 0.7 to 2.0 mm, coated with a homogeneous layer of active drug and excipients. Multilayer formulations may be more complex and a number of layers may be required to provide a drug release profile suitable for the required pharmacological profile (Alighieri et al. 1994). The rotating coating pan is the most extensively utilised type of equipment for the production of multilayer formulations. Careful choice of process control is needed to ensure product reproducibility.

1.4.3.3 Granulation

The granules are produced in a similar way to conventional tablet granules, but they are coated with a release-controlling polymer. Ideally, the granule must be mechanically strong, well densified and resistant to impact-attrition and abrasion. These properties are essential in order to withstand the physical stresses of film coating and any subsequent processing (e.g. encapsulation, tabletting) required to produce the final dosage. Granule morphology is also important because it determines the level of polymer coating that is necessary to achieve uniform granule coverage.

1.4.3.4 Microencapsulation

The polymer is dissolved in an organic solvent, and drug is added to form a solution or suspension. The emulsifier is dissolved in a second liquid that is immiscible with the drug-polymer solution. The drug-polymer mixture is emulsified into the second surfactant-containing liquid phase to form a dispersion of drug-polymer solvent droplets. The solvent is then removed by evaporation, heat or vacuum might be used if necessary. The microsphere size can be controlled by using different mixing techniques. The completed drug polymer microspheres usually have a matrix structure with the drug homogeneously dispersed throughout the polymer.

1.4.3.5 Tabletting

The methods mentioned could be both time consuming and costly to develop. Investment might be required in new equipment. Difficulties in quality control to assure product reproducibility may also arise and this is the important point to be considered. Tabletting is considered a good technique for preparing MUDFs.

Recent investigations (Munday et al. 1991; Colombo et al. 1985) have evaluated the potential of mini-matrices contained within hard gelatin capsules as controlled release oral multiparticulate formulations. In order to get a true multiparticulate dosage form, offering the benefits and advantages, it is necessary for the tablets to be as small as possible. For practical purposes, tablets between 2 mm and 5 mm diameter are used (Meyer et al. 1985). Tablets larger than this could not be contained in a hard gelatin capsule in any great number and tablets smaller than 2 mm would be extremely difficult to manufacture. Studies have shown that tablets of this general size have a similar gastric emptying pattern to standard pellet formulation (Feely et al. 1985).

Most types of tablet (directly compressed, wet granulated, coated, layered etc.) can, in theory, also be produced at this smaller scale. Compression is conducted on standard tablet presses, but often punches containing up to four or even eight punch tips are utilised to increase production rates. These tablets can be filled into capsules using the same processes and equipment used to fill pellets.

There are a number of benefits to be gained from the use of tablets. Tablet technology is widely understood, diverse and offers less constraints than, for example extrusion or spheronisation. Sustained-release tablets can be produced which employ a variety of different release mechanisms, e.g., diffusion, erosion, osmotic, etc., unlike pellets which principally rely on diffusion through a rate controlling polymer coating. Since most companies have a tabletting capacity, multiparticulate products may also be produced without the need for extra capital expenditure. In addition, the mini-matrices would have flexibility in dose adjustment. The dose could be tailored to meet the precise requirements of a particular patient, i.e., adjustment of the precise number of uniform mini-matrices to be enclosed in a capsule. The dose titration might be difficult with beads and pellets because the amount of drug in each particle is not

exactly known, and with granules, the irregular size and shape make dose titration even less precise.

The disadvantages of mini-matrix formulations are that any problems associated with producing a standard size tablet, e.g., poor flow, segregation, capping, lamination, picking, etc., are likely to be amplified when producing a small tablet. Hence consideration of drug loading, excipient selection and formulation are key factors for a successful finished product (Feely and Sims 1994).

Diclofenac sodium hydrophilic matrix tablets using HPMC (Talukdar et al. 1996; Sheu et al. 1992), ethyl cellulose (Chattaraj and Das 1996) or xanthan gum (Talukdar et al. 1996) as matrix materials had been studied. In order to achieve the benefits from both hydrophilic matrix and multiple unit dosage forms, the formulation of diclofenac sodium and also S(+) ibuprofen in the form of mini-matrix MUDFs is the main work in this study.

1.5 TABLET MANUFACTURE

The three basic methods for the preparation of compressed tablets are the wet granulation method, the dry granulation method and direct compression.

1.5.1 Wet granulation

Wet granulation is a widely employed method for the production of compressed tablets. For the powder mixture to flow evenly and freely from the hopper into the dies, it is usually necessary to convert the powder mixture to free-flowing granules by a process known as granulation. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granules, then passing them through a second screen of

smaller mesh to reduce further the size of the granules. The binding agent present in the tablets also contributes to the adhesion of the granules to one another, maintaining the integrity of the tablet after compression.

1.5.2 Dry granulation

In this method the granules are formed by compacting large masses of the mixture and subsequently crushing and sizing these pieces into smaller granules. By this method, either the active ingredient or the diluent must have cohesive properties in order for the large masses to be formed. This method is especially applicable to materials that cannot be prepared by the wet granulation method due to their degradation by moisture or to the elevated temperatures required for drying

1.5.3 Direct compression

Some granular chemicals possess free flowing as well as cohesive properties that enable them to be compressed directly in a tablet machine without the requirement of either wet or dry granulation. The tablet excipients used must be materials with properties of fluidity and compressibility (Ansel et al. 1995).

1.6 *IN VITRO* ASSESSMENT OF ORAL SOLID DOSAGE FORMS

In addition to the physical appearance and the uniformity of dosage unit, the most widely accepted reference method to assess the quality of the final product is the *in vivo* bioavailability testing; measuring drug levels in body fluids at various times after ingestion. However, this method has limitations. First, the body fluid drug levels do not necessarily correlate quantitatively with pharmacological response. Second, the data tend to be study-specific; the data from one set of patients and study conditions may

not be comparable to those of another set of patients and study conditions. Third, it is expensive and time consuming. So, the bioavailability test is used for reference purposes rather than for routine monitoring.

The pharmaceutical industry has sought a rapid, inexpensive and precise means of measuring the pharmacological effectiveness of different formulations and batches of solid oral dosage forms. The *in vitro* dissolution test is used, i.e., the rate that the drug passes from the dosage forms into the solution is determined under controlled conditions. This test attempts to simulate the digestive process in a simplistic way. It is understood that this technique should not be used to make *in vivo* predictions unless the parameter chosen permit a correlation with bioavailability data. Caution must be exercised in selecting dissolution methodology for evaluating and optimizing formulations and for monitoring batch consistency (Dash et al. 1988). Under proper investigation, it is possible to create dissolution methodology which is so sensitive that it can detect differences which are not meaningful from a bioequivalence standpoint.

1.7 OBJECTIVES OF THIS STUDY

Most of the sustained-release diclofenac sodium products commercially available are the enteric-coated tablets. Several reports showed that this kind of tablet have failed to provide therapeutic plasma levels (Levy and Jusko 1967; Wagner et al. 1973). Some showed delay in absorption compared with immediate release preparations (Leonard an Levy 1965) or with the fed state (Fischer et al. 1985). A potential factor influencing the onset of tablet disintegration is the delayed gastric emptying time (Wilding et al. 1992), resulting from food intake.

In order to overcome the bioavailability problems outlined above, a tabletted mini-matrix formulation containing diclofenac sodium was produced and a precise number of mini-matrices enclosed in a hard gelatin capsule was used as a MUDF.

In addition, no oral S(+) ibuprofen products, neither immediate nor sustained release products, are available in the market. Many studies showing that the dose of S(+) ibuprofen can be reduced by 25-50% compared to the dose of racemic ibuprofen (Romero et al. 1991; Stock et al. 1991; Klein et al. 1992). Racemic ibuprofen is handled differently in patients with impaired liver function, suggesting that metabolic inversion of the inactive R(-) ibuprofen to the active S(+) ibuprofen may be affected by cirrhosis (Li et al. 1993). Hepatic elimination of ibuprofen is also impaired. Direct administration of S(+) ibuprofen may be advantageous because the metabolic load to the human body is reduced, the R(-) ibuprofen is potentially toxic and patients are more likely to comply with the smaller doses of S(+) ibuprofen (Li et al. 1993; Stock et al. 1991). The formulation of S(+) ibuprofen in the form of mini-matrix MUDFs is therefore worthy of investigation.

The overall objective of this study was to prepare diclofenac sodium and S(+) ibuprofen oral sustained-release mini-matrix MUDFs. The physico-chemical properties of the drugs; diclofenac sodium and S(+) ibuprofen, and hydrophilic gums used in the formulation were investigated. Diclofenac sodium was the first model drug used to prepare mini-matrix MUDFs using the tabletting technique. The *in vitro* release profiles of these products were studied using the dissolution apparatus. The results were fitted with various equations to investigate the mechanism of drug release. The effect of certain factors; gum type, gum concentration, added excipients, swelling, solvent penetration front, erosion, etc., on drug release were also examined. The knowledge gained from these experiments was used to prepare S(+) ibuprofen mini-matrix MUDFs. The release profiles and mechanisms of S(+) ibuprofen products were also

studied. The stress storage test was applied with the S(+) ibuprofen finished product. The *in vitro* release profiles of commercially available products of diclofenac sodium and racemic ibuprofen were investigated and compared with the prepared products. The compatibility between model drugs and excipients (used in the successful preparations) were performed using DSC.

CHAPTER 2

MATERIALS

2.1 NATURAL HYDROPHILIC GUMS AND SYNTHETIC HYDROPHILIC POLYMER

Natural hydrophilic gums; xanthan gum, karaya gum, locust bean gum and carrageenan gum, were purchased from Sigma Chemical Company (St. Louis, USA). Synthetic hydrophilic polymer, hydroxypropyl methylcellulose (HPMC), was purchased from Dow Chemical (Michigan, USA). The polymer and gums were the principal materials used to form mini-matrices and their physical properties are summarized in Table 2.1.

2.1.1 Xanthan gum

Xanthan gum is a high molecular-weight natural carbohydrate. It is a polysaccharide produced in a pure culture fermentation by the micro-organism *Xanthomonas campestris*, an organism originally isolated from the rutabaga plant (Cottrell et al. 1980). It occurs as a cream or white-coloured, odourless, free-flowing, fine powder (Daskalakis 1994).

Table 2.1. Physical properties of four natural hydrophilic gums and HPMC.

Property	Xanthan gum	Karaya gum	Locust bean gum	Carrageenan	HPMC
M.W.	2×10^6	-	3.1×10^5	No sharp M.W., $2.6\text{-}3.2\times10^5$ for Kappa and $3.3\text{-}7.9\times10^5$ for Lambda-carrageenan	$1\text{-}150\times10^4$
Solubility	Soluble in cold and warm water, insoluble in ethanol and ether	Soluble in water	Soluble in water, full hydration when heated at 80°C for 10 min	Soluble in hot water (>75°C), solubility depends on the type of carrageenan	Soluble in cold water, mixtures of ethanol/methanol and dichloromethane, insoluble in hot water, chloroform, ether
Viscosity	1000 centipoises[a] (1 Pa.s.)	-	-	-	0.005-75 Pa.s.[b], depends on the type of HPMC
Rheology	Pseudoplastic	Non-Newtonian	Pseudoplastic	Thixotropic	Pseudoplastic
Effect of temperature on viscosity	Stable at temperature range 10-70°C	Boiling reduces the viscosity	Thins out reversibly when heat is applied and degrades irreversibly with time when elevated temperature is maintained	Viscosity reduces progressively when temperature increases	Viscosity reduces when temperature increases, reversible sol to gel transformation upon heating and cooling, respectively
Effect of pH on viscosity	Stable at pH range 6-9, pH range 1-11 slightly affects viscosity	Addition of acid or alkali reduces the viscosity	pH range 3-11 slightly affects viscosity	Rate of hydration more rapid at low pH, considerably slower at pH 6 and above	Stable at pH range 3-11

Table 2.1. Physical properties of four natural hydrophilic gums and HPMC. (continued)

Property	Xanthan gum	Karaya gum	Locust bean gum	Carrageenan	HPMC
Incompatibility	Cationic surfactants, polymers, and preservatives, polyvalent metal ions (under highly alkaline condition), borate (<300 ppm), oxidising agent, sodium CMC, dried $Al(OH)_3$ gel	Electrolyte e.g. Na^+, Ca^{2+}, $AlCl_3$, $Al_2(SO_4)_3$	Some inorganic cations, basic salts, high concentration of calcium salt (under alkaline condition)	High and low concentration of divalent cations decreases and increases viscosity, respectively	Some oxidizing agents

a; 1% aqueous solution, measured at 60 rpm, 25°C.

b; 2% aqueous solution, measured at 20°C.

2.1.1.1 Chemical structure

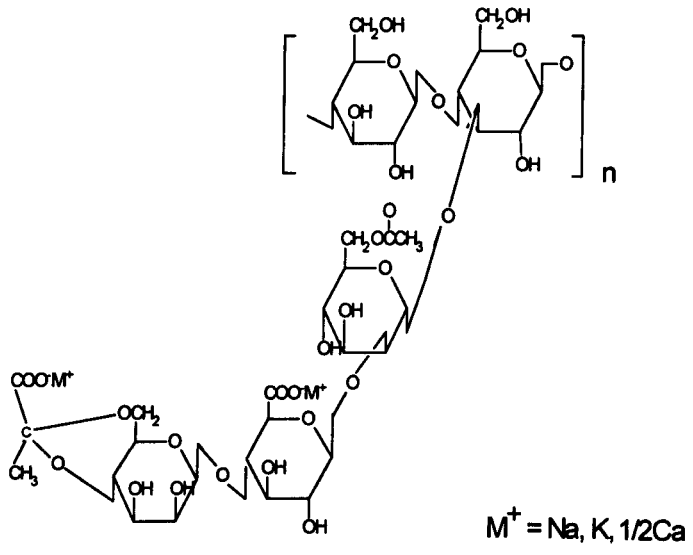


Figure 2.1. The repeating-unit structure of xanthan gum.

Xanthan gum is a heteropolysaccharide, containing mannose, glucose and glucuronic acid (as a mixed potassium, sodium and calcium salt). The molecular weight is approximately 2×10^6 and has been reported to be as high as 13 - 50×10^6. These differences in measurement are probably caused by association phenomena occurring between polymer chains. Figure 2.1 illustrates the repeating-unit structure of xanthan gum. Each repeating block has five sugar units: two glucose, two mannose and one glucuronic acid. The polymer backbone is made up of β-D-glucose units linked through the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan gum from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. Most of the terminal D-mannose residues carry a pyruvic acid residue linked ketalically to the 4 and 6 positions. The non-terminal D-mannose unit on the side chain has an acetyl group at the 6 position. The pyruvate and glucuronate groups account for the anionic nature of the polymer (Jansson et al. 1975; McNeely and Kang 1973; Cottrell et al. 1980).

The shielding of the backbone of xanthan gum by its side chain could explain its extraordinary resistance to enzymes. Also unique among the natural gums are the unvarying chemical structure and the uniformity of chemical and physical properties of xanthan gum (Cottrell et al. 1980, Daskalakis 1994, Fitzpatrick 1995).

2.1.1.2 Physical properties

Solubility. Xanthan gum is practically insoluble in ethanol and ether, and soluble in cold or warm water (Daskalakis 1994). A 1% aqueous solution has pH 6-8 and a viscosity of about 1000 centipoises (1 Pa.s.) when measured at 60 rpm with a Brookfield model LVF viscometer at 25°C. Aqueous solutions of xanthan gum are highly pseudoplastic (McNeely and Kang 1973).

Effect of temperature. The viscosity of its aqueous solution is nearly independent of temperature over a wide temperature range. Between 10 and 70°C, a xanthan gum solution having a viscosity of 1000 cps will decrease in viscosity by not more than 100 cps (McNeely and Kang 1973).

Effect of pH. The viscosity of aqueous solutions of xanthan gum is nearly independent of pH, between pH 6 and 9, and shows only minor variation in viscosity over a pH range of 1 to 11 (McNeely and Kang 1973).

Compatibility. Xanthan gum has unusually good compatibility with high concentration of many salts and it will dissolve directly in moderate concentrations of a wide range of salts. Xanthan gum is compatible with most synthetic and natural viscosity-increasing agents (McNeely and Kang 1973).

Incompatibility. Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers and preservatives since precipitation

occurs. Anionic and amphoteric surfactants at concentrations above 15% cause precipitation of xanthan gum from a solution (Daskalakis 1994).

Under highly alkaline conditions polyvalent metal ions, such as calcium, cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant (McNeely and O'Connell 1966). Long-chain quaternary ammonium salts or amines with more than eight carbon atoms in the main chain may precipitate it (Rogovin and Albrecht 1964). The presence of low levels of borate (<300 ppm) can also cause gelation. This may be avoided by increasing the borate ion concentration or by lowering the pH of a formulation to less than pH 5. The addition of ethylene glycol, sorbitol, or mannitol may also prevent this gelation.

Xanthan gum solutions are stable in the presence of up to 60% water-miscible organic solvents such as acetone, methanol, ethanol or propan-2-ol. However, above this concentration precipitation or gelation occurs (Daskalakis 1994).

Xanthan gum is also incompatible with oxidising agents, some tablet film-coatings (Evans and Fenton-May 1986), carboxymethylcellulose sodium (Walker and Wells 1982), dried aluminium hydroxide gel (Zatz et al. 1986) and some active ingredients such as amitriptyline, tamoxifen and verapamil (Bumphrey 1986).

Stability to heat. Xanthan gum is remarkably resistant to degradation by heat. Long exposures to temperature as high as 80°C appear to have little effect on xanthan gum solutions. The resistance to degradation by heat is improved by the presence of salts (McNeely and Kang 1973).

2.1.1.3 Reaction with locust bean gum

Locust bean gum reacts strongly in solution with xanthan polysaccharide. The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the

presence of locust bean gum, guar gum and magnesium aluminium silicate (Kovac 1973). This effect is most pronounced in deionized water and reduced by the presence of salt. This interaction may be desirable in some instances and can be exploited to reduce the amount of xanthan gum used in a formulation.

2.1.1.4 Applications

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent (Bumphrey 1986; Evans and Fenton-May 1986). Recently, it has been reported that xanthan gum can be used alone or in the combination with other gums as an effective excipient for sustained-release formulations (Lu et al. 1991; Dhopeshwarkar and Zatz 1993; Talukdar and Plaizier-Vercammen 1993).

2.1.2 Karaya gum

Karaya gum or sterculia gum is a complex water-soluble polysaccharide. It is a hydrophilic colloid prepared from the exudate of *Sterculia urens* Roxb and other species of *Sterculia* (Department of Health 1993). It is a finely ground white powder with a faint odour of acetic acid (Budavari 1996).

2.1.2.1 Chemical structure

Karaya gum is a partially acetylated polymer of galactose, rhamnose and glucuronic acid with a high molecular weight. It contains approximately 8% acetyl groups and around 37% uronic acid residues (Meer 1980).

2.1.2.2 Physical properties

Karaya gum absorbs water very rapidly to form viscous mucilages at low concentration. The adhesive property of karaya gum is not related to its viscosity (Meer 1980).

Effect of temperature. The viscosity of a fully hydrated karaya gum solution decreases when the temperature is gradually raised from 20 to 85°C. Boiling reduces the viscosity of karaya gum solution, particularly when it is held at this temperature for more than 2 minutes. A higher maximum viscosity is obtained by cold hydration of karaya gum than is afforded by hot hydration (Goldstein and Alter 1973). The reduction in viscosity that is obtained by cooking karaya gum suspensions, especially under pressure, is accompanied by an increase in the solubility of the gum. Under these conditions, it forms a smooth, homogeneous, translucent, colloidal dispersion (Goldstein and Alter 1973).

Effect of concentration. In dilute solutions of karaya gum, the viscosity increases linearly as the concentration increases up to about 0.5%. Thereafter, karaya gum dispersions exhibit non-Newtonian flow characteristics (Goldstein and Alter 1973).

Effect of pH. Karaya gum maintains its solubility with changes in pH; the viscosity decreases upon addition of acid or alkali. Higher viscosities and pH stability over a wider range are obtainable when the gum is hydrated prior to pH adjustment. The solution colour lightens in acidic media and darkens in alkaline solutions because of the presence of tannins (Meer 1980).

Incompatibility. The viscosity of karaya gum dispersions decreases when electrolytes, such as sodium, calcium, and aluminium chlorides and aluminium sulphate, are added (Meer 1980).

Stability. The viscosity of karaya gum suspensions remains constant for several days. Increased stability can be provided by the addition of preservatives. Karaya gum experiences a loss in viscosity when stored in the dry state; the loss is greater for a powdered material than for the crude gum (Money 1951). This decrease is most noticeable in the first few weeks after the gum has been ground, especially if it is stored under conditions of high humidity and temperature. Cold storage inhibits this degradation. It has been suggested that the decrease in viscosity is related to the loss of acetic acid (Meer 1980; Goldstein and Alter 1973).

2.1.2.3 Applications

Karaya gum is used as a bulk laxative and for adjusting faecal consistency. It has adhesive properties and is used in the fitting of ileostomy and colostomy appliances and in dental fixative powders. It is also used as an emulsifier and stabiliser in foods (Reynold 1996).

2.1.3 Locust bean gum

Locust bean gum is the ground kernel endosperms of the tree pod of *Ceratonia siliqua* L., *Leguminosae* (St John's bread). Its molecular weight is about 310,000. It is a yellow-green powder, odourless and tasteless but acquires a leguminous taste when boiled in water (Budavari 1996).

2.1.3.1 Chemical structure

Locust bean gum is a carbohydrate polymer containing galactose and mannose as the structural building blocks. The ratio of the two components may vary slightly depending on the origin of the seed, but the gum is generally considered to contain

one galactose unit for every four mannose units (Seaman 1980). Its structure is a linear chain of β-D-mannopyranosyl units linked 1, 4 with single-membered α-D-galactopyranosyl units occurring as side branches. The α-D-galactopyranosyl units are linked 1, 6 with the main chain. The side branches are not spaced uniformly (Seaman 1980).

2.1.3.2 Physical Properties

Solubility. Locust bean gum has limited solubility in water at ambient temperature. The gum will hydrate and develop its properties when its solutions are heated. It will reach full hydration when heated for 10 minutes at 80°C. Upon cooling, it remains in solution in dissociated, extended molecular form, where it can serve as a thickener or chemical reagent (Seaman 1980).

Effect of temperature and pH. Its solutions exhibit pseudoplastic flow behaviour. They thin out reversibly when heat is applied and degrade irreversibly with time when an elevated temperature is maintained. The solutions resist shear degradation but will degrade progressively under high shear (Seaman 1980).

Because it is a neutral polysaccharide, pH range from 3-11 has little effect on viscosity (Rol 1973).

Compatibility. Strong reactions are obtained with solutions of certain inorganic cations. The addition of a high concentration of calcium salt, under alkaline conditions, will cause a gel to form. If dry powder is added to the salt solution, the gum will not hydrate and thicken (Seaman 1980). Neutral salts will not precipitate the gum (Bryant 1941), but certain basic salts, such as basic lead acetate, will cause precipitation (Williams 1928). It is also precipitated by tannin (Rol 1973).

2.1.3.3 Applications

It is used as stabiliser, thickener and binder in food and cosmetics (Budavari 1996).

2.1.4 Carrageenan gum

Carrageenans are water-soluble gums which occur in certain species of red seaweeds of the *Gigartinaceae*, *Solieriaceae*, *Phyllophoraceae*, and *Hypneaceae* families. They are cream-coloured to light brown powders (Guiseley *et al.* 1980).

2.1.4.1 Chemical structure

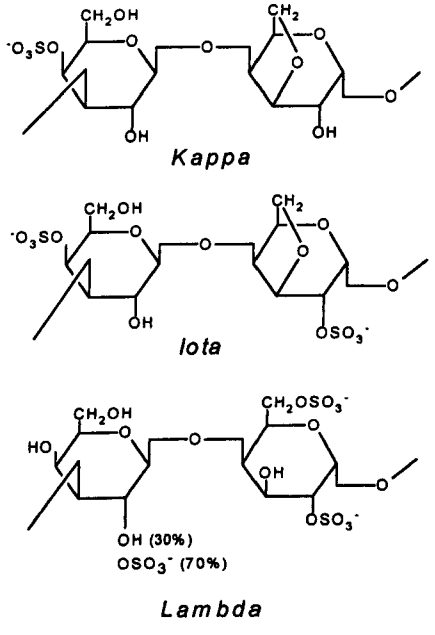


Figure 2.2. Chemical structure of carrageenan gum.

Carrageenan gum consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers (Figure 2.2). These hexoses are alternately linked α-1,3 and β-1,4 in the polymer. The prevalent copolymers in the hydrocolloid are designated *kappa*-, *iota*-, and *lambda*-carrageenan. *Kappa*-carrageenan is mostly the alternating polymer of D-galactose-4-

sulfate and 3,6-anhydro-D-galactose. *Iota*-carrageenan is similar, except that the 3,6-anhydrogalactose is sulfated at carbon 2. Between *kappa*-carrageenan and *iota*-carrageenan there is a continuum of intermediate compositions differing in degree of sulfation at carbon 2. In *lambda*-carrageenan, the alternating monomeric units are mostly D-galactose-2-sulfate (1,3-linked) and D-galactose-2,6-disulfate (1,4-linked). The ester sulfate content for carrageenan ranges from 18% to 40%. In addition, it contains inorganic salts that originate from the process of recovery from the extract (USP XXIII 1994).

Carrageenans do not have sharply defined molecular weights, but rather have average molecular weights representing a distribution of molecular species identical in structure but of varying chain length (Guiseley et al. 1980). Molecular weight values of $2.6\text{-}3.2\times10^5$ and $3.3\text{-}7.9\times10^5$ have been reported for *kappa*- and *lambda*-carrageenans (Goring and Young 1955; Cook et al. 1951; Masson and Caines 1954; Smith et al. 1955). Molecular weights are dependent upon the extraction conditions used (Towle 1973).

2.1.4.2 Physical properties

Solubilities. The carrageenans are soluble in hot (>75°C) water. The solubility in water is influenced by several factors, including temperature, the presence and type of counter-ion associated with the polymer, the presence of other water-soluble organic compounds and salts, and the type of carrageenan. Most important in controlling water solubility is the hydrophilicity of the molecule, related to the sulfate half-ester groups, and the galactopyranosyl unit, as opposed to the presence of the more hydrophobic 3,6-anhydrogalactopyranosyl unit. Thus, *lambda*-carrageenan, being void of 3,6-anhydrogalactopyranosyl units and having a high percentage of sulfate ester groups, is cold-water soluble in all salt forms. *Kappa*-carrageenan, having

less hydrophilic sulfate ester groups and containing a larger proportion of hydrophobic 3,6-anhydrogalactopyranosyl units, is cold-water soluble only in the sodium salt form. In the presence of hydrophobic cations, such as potassium ion, the delicate balance of solubility versus insolubility is tipped and gel formation ensues. Thus, a spectrum of solubility exists, depending upon the balance of hydrophilicity versus hydrophobicity inherent in the primary structure of various carrageenans. That the primary structure alone is responsible for the solubility characteristics of various carrageenan is, however, an oversimplification. Other factors, such as the location of groups on the polymer chain and the molecular conformation, are also deciding factors in determining solubility characteristics (Towle 1973).

Hydration of carrageenan is more rapid at low pH. The rate of hydration is considerably slower at pH 6 and above (Stoloff 1950). Acid-catalysed hydrolysis of glycosidic linkages becomes significant at low pH, especially at pH 3.0 and below. This depolymerization process is much faster at higher temperatures, and for this reason there are practical limitations beyond which the increased rate of hydration offered by lower pH and higher temperature is offset by a significant drop in solution viscosity (Towle 1973).

Dilute aqueous dispersions of carrageenan are viscous, the viscosity being dependent on concentration, temperature, the presence of other solute molecules, the type of carrageenan, and the molecular weight. As the concentration of carrageenan solution is increased, the viscosity increases nearly logarithmically (Towle 1973).

Effect of temperature. The viscosity of carrageenan solutions decreases progressively with increases in temperature. This change is generally reversible provided that heating at or near the stability optimum at pH 9 and that conditions are such that no thermal degradation occurs (Towle 1973).

Incompatibility. Salts of monovalent cations have little effect on the viscosity of carrageenan solutions. Divalent cations, however, tend to reduce the viscosity significantly at higher concentration, but may produce a viscosity increase at low levels (Towle 1973).

Solutions of carrageenan gum display non-Newtonian, thixotropic flow characteristics, typified mainly by a decrease in viscosity with increasing shear or agitation (Masson and Goring 1955) and a return to normal viscosity with ceasation of agitation.

2.1.4.3 Applications

Carrageenans are used as thickening, suspending, and gelling agents. Typical applications are as thickener or binder in toothpaste, a suspending agent for cocoa in chocolate milk, and a gelling agent for milk puddings, water-gel desserts, and air-freshener gels (Towle 1973). They are also used to induce experimental inflammation in laboratory animals (Budavari 1996).

2.1.5 Hydroxypropyl methylcellulose (HPMC)

HPMC is a synthetic water-soluble hydrocolloid derived from the etherification of cellulose. It is an odourless and tasteless, white or creamy-white coloured fibrous or granular powder (Harwood and Johnson 1994).

2.1.5.1 *Chemical structure*

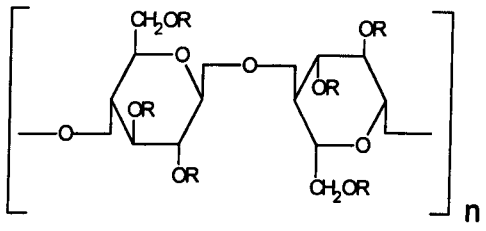


Figure 2.3. Chemical structure of HPMC.

Where R is H, CH_3, or $[CH_3CH(OH)CH_2]$. The degree of substitution (DS) for methyl groups ranges from 0.9 to 1.8 and the molar substitution (MS) of hydroxypropyl groups ranges from 0.1 to 1.0 (Greminger Jr and Krumel 1980).

2.1.5.2 *Physical properties*

Solubility. HPMC is soluble in cold water and insoluble in hot water, practically insoluble in chloroform, ethanol (95%), and ether but soluble in mixtures of ethanol and dichloromethane, and mixtures of methanol and dichloromethane (Harwood and Johnson 1994). Altering the amounts of methyl and hydroxypropyl substitution affects the solubility properties of the cellulose ether (Greminger Jr and Krumel 1980). Commercial products are available in a wide range of viscosities varying from 0.005 to 75 Pa.s. as measured on 2% w/w solutions at 20°C (Greminger Jr and Krumel 1980).

Effect of temperature and pH. A solution of HPMC generally shows pseudoplastic non-thixotropic flow properties at 20°C (Greminger Jr and Krumel 1980). Solutions are stable between pH 3-11. Increasing the temperature reduces the viscosity of solutions. HPMC undergoes a reversible sol to gel transformation upon heating and cooling respectively. The gel point is 50-90°C, depending upon the grade of material (Harwood and Johnson 1994).

Incompatibilities. HPMC is incompatible with some oxidizing agents. Since it is non-ionic, HPMC will not complex with metallic salts and ionic organics to form insoluble precipitates (Harwood and Johnson 1994).

2.1.5.3 Applications

HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, it is primarily used as a tablet binder (Chowhan 1980), in film-coating (Rowe 1977; Rowe 1980; Banker et al. 1981; Okhamafe and York 1982; Alderman and Schulz 1989; Patell 1990) and as an extended release tablet matrix (Hardy et al. 1982; Hogan 1989; Shah et al. 1989; Wilson and Cuff 1989; Dahl et al. 1990).

It is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. It is also used as an emulsifier, suspending and stabilizing agent in topical gels and ointments.

In addition, it is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products (Harwood and Johnson 1994).

2.2 MODEL DRUGS

Diclofenac sodium, a poorly water soluble model drug, was purchased from Sigma Chemical Company (St. Louis, USA). S(+) ibuprofen, pH dependent soluble model drug, was a gift from Boots Pharmaceuticals (Nottingham, UK).

2.2.1 Diclofenac sodium

Chemical structure:

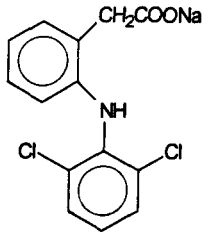


Figure 2.4. Chemical structure of diclofenac sodium.

Chemical formula: $C_{14}H_{10}Cl_2NNaO_2$

Chemical names:

2-[(2,6-Dichlorophenyl) amino] benzeneacetic acid monosodium salt,

[0-(2,6-Dichloroanilino) phenyl] acetic acid sodium salt, or

Sodium [0-[(2,6-dichlorophenyl) amino] phenyl] acetate.

Molecular weight: 318.1

CAS 15307-79-6

2.2.1.1 Physical properties

Diclofenac sodium is an odourless, white to off-white crystalline, slightly hygroscopic powder.

Melting point: 283-285°C for diclofenac sodium and 156-158°C for diclofenac (Lund 1994).

Dissociation constant: pK_a 4.7 in HCl-Na_2HPO_4 buffer solution (Hertzfeldt and Kummel 1983).

Solubility

Effect of pH and temperature

The aqueous solubility of diclofenac sodium is dependent on pH; solubility is poor at low values of pH but when the pH rises above the pK_a, rapid increases in solubility occur. Herzfeldt and Kummel (1983) established a solubility for diclofenac sodium, at room temperature, of less than 4×10^{-4}% w/v at pH 1.2 to 3, whereas in the pH range 4 to 7.5 solubilities are shown in Table 2.2. At 25°C and pH 2 the solubilities of diclofenac sodium has been reported to be 1.5×10^{-6} M (Fini et al. 1986).

Table 2.2. Aqueous solubilities of diclofenac sodium at various pH values, at room temperature.

pH	Solubility (% w/v)
4.0	0.0021
5.0	0.0086
6.0	0.059
7.0	0.187
7.5	0.169

Effect of additives

The presence of cations (sodium ions or potassium ions) markedly affects the solubility of diclofenac sodium. Nishihata et al. (1988) reported solubilities for diclofenac sodium in 0.1 M sodium phosphate buffer (pH 7.2) at room temperature and at 50°C of 13.4 mM and 45.7 mM, respectively. The addition of ethanol 10% w/w to the buffer solution, as a cosolvent, increased the solubility of diclofenac sodium to 51.4 mM at room temperature. As the concentration of either hydroxypropyl-β-cyclodextrin or hydroxypropyl-γ-cyclodextrin was increased (up to about 70 mM) the solubility of

diclofenac sodium, in phosphate buffer pH 7.4 at 25°C, also increased from 30 mM to 85 mM (Backensfeld et al. 1991).

Stability

Crushed diclofenac sodium tablets and diclofenac sodium powder were reported to be stable after storage at 40°C in 50% relative humidity for 28 days. But at 90°C, 55% relative humidity for 20 days the degradation product; 1-[2,6-dichlorophenyl]-2-indolin-2-one; was detected (Kubula et al. 1993).

The suppository formulation was also stable for 24 months at room temperature (Budukova et al. 1989). Diclofenac sodium in biological fluid (serum) can be kept frozen (-20°C) for at least 2 weeks without degradation (El-Sayed et al. 1988).

2.2.1.2 Pharmacokinetics

Diclofenac sodium is rapidly absorbed when given as an oral solution, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although orally-administered diclofenac is almost completely absorbed, it is subject to first-pass metabolism so that about 50% of the drug reaches the systemic circulation in the unchanged form. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may persist even when plasma concentrations fall; diclofenac has been detected in breast milk. The terminal half-life is about 1 to 2 hours. Diclofenac is metabolised to 4'-hydroxydiclofenac, 5-hydroxydiclofenac, 3'-hydroxydiclofenac and 4',5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulphate conjugates, mainly in the urine (about 65%) but also in the bile (about 35%) (Fowler et al. 1983; Maggi et al. 1990).

2.2.1.3 Use and administration

Diclofenac, a phenylacetic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, and following some surgical procedures (Todd and Sorkin 1988).

The usual dose by mouth is 75 to 150 mg of diclofenac sodium daily in divided doses. In children the suggested dose by mouth or rectal for juvenile chronic arthritis is 1 to 3 mg per kg body-weight daily in divided doses (Small 1989).

2.2.1.4 Adverse effects

The commonest side effects occurring during therapy with non-steroidal anti-inflammatory drugs (NSAIDs) are generally gastro-intestinal disturbances. These are usually mild and reversible but in some patients peptic ulcer and severe gastro-intestinal bleeding have been reported. These adverse effects on the gastro-intestinal tract may be associated with inhibition of the form of cyclo-oxygenase known as cyclo-oxygenase-1 (Cox-1). NSAIDs that are highly selective inhibitors of the form known as Cox-2 may have less gastro-intestinal toxicity.

Central nervous system (CNS) related side-effects include headache, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, ashma, and rashes. Hepatotoxicity and aseptic meningitis which occur rarely may also be hypersensitivity reactions. Some patients may experience visual disturbances.

Haematological adverse effects include anaemias, thrombocytopenia, neutropenic, eosinophilia, and agranulocytosis. Inhibition of platelet aggregation is reversible (Reynold 1996).

2.2.2 S(+) Ibuprofen

Chemical structure:

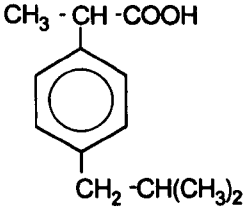


Figure 2.5. Chemical structure of ibuprofen.

Chemical formula: $C_{13}H_{18}O_2$

Chemical names:

2-(4-Isobutylphenyl)propionic acid or

α-Methyl-4-(2-methylpropyl) benzeneacetic acid.

Molecular weight: 206.3

2.2.2.1 Physical properties

A white or almost white powder or crystals with a characteristic odour.

Melting point: 53°C -55°C.

Solubility

Aqueous solubility in phosphate buffer pH 7.7 at 37°C is 6.0 mg/ml. Its solubility in aqueous media is higher than racemic ibuprofen at pH higher than 4.5. The heat of

solution is slightly exothermic at pH 7.7. Intrinsic dissolution rate in USP simulated intestinal fluid at 37°C is 8.1 μg/sec cm^2 (smaller than that of racemic ibuprofen) (Romero and Rhodes 1991). Solubility in aqueous buffer solution at pH 1.5 was twice that of racemic ibuprofen at 20° and 38°C (Burger et al. 1996).

Crystal and molecular structure

Ibuprofen has a chiral centre and can exist in two enantiomeric forms (Freer et al. 1993; McConnell 1974). According to Hutt and Caldwell (1983), on administration of the racemic mixture, the pharmacologically inactive R(-)-enantiomer is converted to the active S(+)-enantiomer. A stereoselective assay is therefore necessary for pharmacokinetic studies.

Stability

Dondoni et al. (1986) used TLC and GLC to identify several products of the oxidative degradation of racemic ibuprofen. In the absence of oxygen, racemic ibuprofen was found to be stable, even at high temperatures (105° to 110°C), for at least four days.

Incompatibility

Interactions between racemic ibuprofen and stearic acid, stearyl alcohol, calcium stearate, and magnesium stearate have been investigated by Gordon and co-workers (1984). Using differential scanning calorimetry, mixtures were heated at a rate of 1.5°C per minute over the temperature range 30°C to 110°C. The formation of a simple eutectic mixture in each case indicated the incompatibility of the stearates with racemic ibuprofen. The effect of these interactions on the chemical stability of racemic ibuprofen was not determined.

Investigations of solid-state mixtures of racemic ibuprofen and magnesium oxide stored at 55°C and 40°C indicated formation of the magnesium salt of ibuprofen (Kararli et al. 1989). No significant interaction was noted at 30°C for up to 80 days. Racemic ibuprofen showed no chemical degradation in the presence of magnesium oxide at 55°C. Solid-state interactions (at 55°C) were also reported between racemic ibuprofen and magnesium hydroxide, sodium bicarbonate, potassium carbonate, or calcium oxide, but not between ibuprofen and magnesium chloride or aluminium hydroxide.

2.2.2.2 Pharmacokinetics

Ibuprofen is absorbed from the gastro-intestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. It is extensively bound (>99%) to plasma proteins (Paliwal et al. 1993) and has a plasma half-life of about 1.77 hours [S(+) ibuprofen (Cheng et al. 1994)] or 1.8 hours [racemic ibuprofen (Li et al. 1993)]. S(+) ibuprofen has higher C_{max}, AUC, mean residence time and renal clearance values compared to racemic ibuprofen (Geisslinger et al. 1993). It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little if any excretion in breast milk.

Ibuprofen contains a chiral carbon atom on the propionic acid side-chain, and therefore exists as two enantiomers. The anti-inflammatory, analgesic and antipyretic activities of ibuprofen, as determined by *in vitro* inhibition of prostaglandin synthesis, resides almost exclusively in the S(+) ibuprofen; 160 times more potent than R(-) ibuprofen (Adams et al. 1976). *In vivo* R(-) ibuprofen is inverted to the S(+) enantiomer (Hutt and Caldwell 1983) to the extent of 57-69% for oral doses (Cheng et al. 1994; Lee et al. 1985) and 69% for IV doses (Cheng et al. 1994) in humans. The bioinversion

of R(-) ibuprofen administered orally is mainly systemic (Cheng et al. 1994; Hall et al. 1993).

Experiments in rats indicate that the liver contributes to the optical isomerization of R(-) ibuprofen to S(+) ibuprofen (Jeffrey et al. 1991). The mechanism probably involves the stereoselective formation of a coenzyme A thioester with the R(-) enantiomer, which subsequently is racemised and hydrolyzed to release the S(+) enantiomer (Hutt and Caldwell 1983; Knihinicki et al. 1991). A large inter-individual variability in the ratio of S(+) to R(-) ibuprofen average concentration at steady-state were observed and probably accounts for the known lack of correlation between racemic ibuprofen concentration and therapeutic efficacy (Oliary et al. 1992). Interestingly, this unidirectional conversion not only has therapeutic implications but might have toxicological consequences, since in rats R(-) ibuprofen forms potentially toxic hybrid triglycerides resulting in adipose depots of slowly eliminated drug (Williams et al. 1986).

Many studies have shown that the dose of S(+) ibuprofen can be reduced from 25-50% compared to the dose of racemic ibuprofen (Romero et al. 1991; Stock et al. 1991; Klein et al. 1992). Racemic ibuprofen is handled differently in patients with impaired liver function, suggesting that metabolic inversion of the inactive R(-) ibuprofen to the active S(+) ibuprofen may be affected by cirrhosis (Li et al. 1993). Hepatic elimination of ibuprofen is also impaired. Direct administration of S(+) ibuprofen may be advantageous because the metabolic load to the human body is reduced, the R(-) ibuprofen is potentially toxic and the patients are more likely to comply with the smaller doses of S(+) ibuprofen (Li et al. 1993; Stock et al. 1991).

2.2.2.3 *Use and administration*

Ibuprofen has analgesic, anti-inflammatory, and antipyretic properties although its anti-inflammatory properties may be weaker than those of some other non-steroidal anti-inflammatory drugs. It is an inhibitor of cyclo-oxygenase.

Ibuprofen is used in mild to moderate pain in conditions such as dysmenorrhoea, migraine, postoperative pain, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile rheumatoid arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorder such as sprains and strains. It is also used to reduce fever.

The usual dose by mouth is 1.2 to 1.8 g daily in divided doses although maintenance doses of 0.6 to 1.2 g daily may be effective in some patients. If necessary the dose may be increased to 2.4 g daily and some sources have suggested that up to 3.2 g daily may be given although others state that 2.4 g daily should not be exceeded. If gastro-intestinal disturbances occur, ibuprofen should be given with food or milk.

2.2.2.4 *Adverse effects*

Its adverse effects are similar to the adverse effects of diclofenac (described in 2.2.1.4). Ibuprofen may be better tolerated than other NSAIDs.

2.3 Excipients

Lactose (Borculor Whey Products, Holland), dicalcium phosphate (Encompress®, Forum Chemical, Surrey, UK), cellulose acetate phthalate (CAP, Eastman, Newcastle, UK), magnesium aluminium silicate (Veegum F®, R.T. Vanderbilt, Norwalk, USA) and microcrystalline cellulose (Avicel®PH101, Honeywill and Stein, Surrey, England) were used as the release regulating excipients.

Magnesium stearate (BDH, Poole, UK), talc (Fisher, Leicestershire, UK) and hydrogenated cottonseed oil (Lubritab®, Forum, Surrey, England) were used as lubricants.

2.4 Buffers, liquids and solutions

Sodium hydroxide and potassium dihydrogen orthophosphate (both were purchased from BDH, Poole, UK) were used to prepare phosphate buffer solutions pH range 6-8 (USP XXIII 1994). Hydrochloric acid (Fisher, Leicestershire, UK) and potassium chloride (BDH, Poole, England) were used to prepare hydrochloric acid buffer solution pH 1.2 (USP XXIII 1994). Sodium phosphate (Fisons, Loughborough, UK) and citric acid (Fisher, Leicestershire, UK) were used to prepare citrate-phosphate buffer solution pH range 3-5.5 (Wade 1980).

Potassium hydroxide (Philip Harris, Shenstone, England), magnesium chloride (Fisher, Leicestershire, UK) and sodium chloride (Fisons, Laughborough, UK) were used to prepare saturated solutions for controlling the relative humidity in the chambers (Wade 1980).

Methanol (Rathburn, Walkerburn, Scotland), ethanol (Haymans, Essex, UK), n-propanol (Fisons, Laughborough, UK), butanol and acetone (both were purchased from Fisher, Leicestershire, UK) were used as solvents for preparing supersaturated diclofenac sodium solutions.

CHAPTER 3

PREFORMULATION STUDIES

3.1 INTRODUCTION

Preformulation is the first learning phase of all new drugs. It focuses on the physico-chemical properties of the compound that could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rational for formulation design.

This part of the research is intended to study the physico-chemical properties of the model drugs; diclofenac sodium and S(+) ibuprofen, that might affect the formulation, the release mechanism and release rate of the drugs from the matrices. Some useful properties that had been published were also gathered in this chapter. The properties of the natural hydrophilic gums: xanthan gum, karaya gum, locust bean gum and carrageenan gum that related to the performance of the mini-matrices, such as particle size distribution and viscosity, were investigated.

3.2 MATERIALS

Natural hydrophilic gums: xanthan gum (X), karaya gum (K), locust bean gum (LB) and carrageenan (C).

Model drugs: diclofenac sodium (D) and S(+) ibuprofen (I).

Excipients: lactose (L), dicalcium phosphate (E, Encompress®), cellulose acetate phthalate (CAP), magnesium aluminium silicate (V, Veegum F®) and microcrystalline cellulose (A, Avicel®).

Lubricants: magnesium stearate, talc and hydrogenated cottonseed oil (Lubritab®).

Buffers, liquids and solutions: sodium hydroxide and potassium dihydrogen orthophosphate were used to prepare phosphate buffer solutions pH 7.0 (USP XXIII 1994), 0.1 M HCl was used as solvent to prepare gum mucilages, and water, methanol, ethanol, propanol, butanol and acetone were used as solvents to prepare supersaturated diclofenac sodium solutions.

3.3 Methods

3.3.1 Crystallinity and polymorphism

3.3.1.1 Preparation of diclofenac sodium crystals

Supersaturated solutions of diclofenac sodium in various solvents; water, methanol, ethanol, propanol, butanol and acetone, were prepared using a water bath. The supersaturated solutions were left to recrystallize by slow cooling (at room temperature) and fast cooling (using an ice bath). The resulting crystals were kept in a desiccator containing silica gel until required. The melting point and evidence for polymorphism of diclofenac sodium crystals were investigated by differential scanning calorimetry. The morphology of these crystals were studied using the scanning electron microscope (SEM).

3.3.1.2 Differential scanning calorimetry (DSC)

Diclofenac sodium crystals were thermally characterised by using a differential scanning calorimeter (Perkin Elmer, DSC 7, USA). The samples (2-10 mg) were weighed directly into flat bottomed aluminium sample pans. These samples were heated in a nitrogen atmosphere. The heat flow rate of 20°C/min was monitored as a function of temperature from 40 to 360°C. The thermograms were recorded.

3.3.1.3 Scanning electron microscope (SEM)

The diclofenac sodium crystals were coated with gold (Polaron sputter coater model SC7640) and scanned using a Cambridge instruments scanning electron microscope (model S90B).

3.3.2 Particle size study

The gum powders (xanthan gum, karaya gum, locust bean gum and carrageenan) were sent to Knoll Pharmaceuticals (Nottingham, UK.) for particle size determination using image analysis (Microscale, Cambridge, England). Each gum was dispersed in liquid paraffin before measuring the size. The photomicrographs were taken and particle size distribution of each gum was plotted.

3.3.3 Viscosity study

A 2% w/w mucilage of natural hydrophilic gums; xanthan gum, karaya gum, locust bean gum and carrageenan, in 0.01 M HCl pH 1.2 and 0.05 M phosphate buffer solution pH 7.0 were prepared. The gum powders were dispersed in the acid or buffer solutions by continuous stirring using magnetic stirrers. The mucilages were left overnight at room temperature for complete hydration of the gums. 2% w/w mucilages of 1:1 natural hydrophilic gums and model drugs; diclofenac sodium or S(+) ibuprofen, and 1:1:1 natural hydrophilic gums, model drugs and lactose in 0.05 M phosphate buffer solution pH 7.0 were also prepared by the same procedure. The rheology of these mucilages was examined at 37°C using a Carri-Med controlled stress rheometer (England).

3.3.4 Solubility study

3.3.4.1 pH solubility profile

The solubility of diclofenac sodium and S(+) ibuprofen at various pH values was determined. Excess drug powders were added to the medium in the double jacketed beaker, connected to the water bath (37°C). The mixtures were stirred with a magnetic stirrer and left to equilibrate for 24 hours. The initial medium used was a dilute acid (0.1 M HCl) pH 1.2 and a certain amount of dilute alkali (0.1 M NaOH) was added successively to produce the required pH. A sample (3 ml) was then removed, filtered using a Whatman® filter paper number 1, and the absorbance of the filtrate was measured using a UV spectrophotometer (Shimadzu, UV160A, Japan). For diclofenac sodium a wavelength of 275 nm was used for pH ≥ 5 and a wavelength of 273 nm was used for pH < 5. For S(+) ibuprofen a wavelength of 231 nm was used at all pH values. The solubilities of the drugs were plotted against pH.

3.3.4.2 Intrinsic dissolution rate

Flat face pure diclofenac sodium discs weighing 350 mg and diameter 11 mm were prepared by direct compression. The powder was manually compressed by a Manesty F3 single punch tablet machine (Manesty Machine Ltd., Liverpool, England). After removal of the die from the machine, the tablet was placed in the 11 mm diameter die such that the surface of the tablet was level to the surface of the die. The other end of the die was sealed with hard paraffin in order to control the contact surface area of the drug. This die was placed in 1000 ml 0.05 M phosphate buffer pH 7.4 maintained at 37°C in a water bath. The dissolution medium was stirred with a paddle (BP 1993 dimensions) at 100 rpm and at the distance of 25±2 mm above the exposed tablet surface. The solution (3 ml) was then taken out every 5 minutes for 65

minute duration, filtered using Whatman® filter paper number 1, and the absorbance of the filtrate was measured using a UV spectrophotometer (Shimadzu, UV160A, Japan) at wavelength 275 nm. The amount of diclofenac sodium dissolved per surface area was calculated and plotted against time.

3.4 RESULTS AND DISCUSSION

3.4.1 Crystallinity and polymorphism

3.4.1.1 Differential scanning calorimetry (DSC)

Differential scanning calorimetry is a thermal analysis method that is valuable in pharmaceutical research and quality control for the characterization and identification of compounds, determination of purity, polymorphism, solvent and moisture content, stability and compatibility with excipients. The theory of DSC is to measure the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. The endothermic (heat-absorbing) processes are referred to fusion, boiling, sublimation, vaporization, desolvation, solid-solid transition and chemical degradation. Crystallization and degradation are usually exothermic process. Quantitative measurements of these processes have many applications in preformulation studies including purity, polymorphism, solvation, degradation and excipient compatibility.

Diclofenac sodium crystals recrystallized from various solvents were white to off-white in colour. The thermograms, i.e. the plot of the difference in energy input required to maintain the sample and the reference at exactly the same temperature against the sample temperature, of all diclofenac sodium crystals had similar profiles with little difference in melting point (extrapolated onset, the temperature corresponding to the intersection of the pre-transition baseline with the extrapolated

leading edge of the endotherm or exotherm of that transition). These indicated no evidence of polymorphism of diclofenac sodium crystals recrystallized from various solvents and at different cooling rates. The thermogram of slow cooling diclofenac sodium crystal from water is shown in Figure 3.1 as a typical example. The thermogram showed an endotherm peak at 298.8°C, with the onset at 292.5°C followed by an exotherm. These endotherm and exotherm peaks indicate melting and decomposition of diclofenac sodium, respectively. In addition, there was a broad endotherm in the range of 30-105°C. This endotherm indicates the evaporation of water from the surface of the sample. The endotherm peak and onset (melting point) of each crystal are shown in Table 3.1.

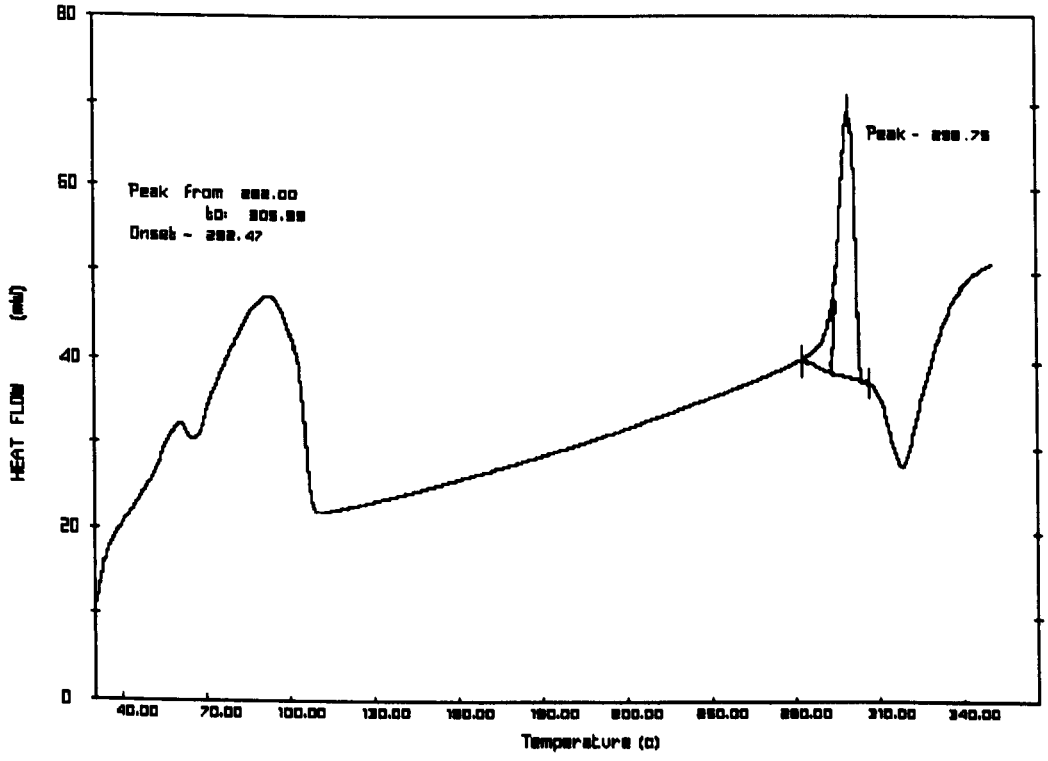


Figure 3.1. DSC thermogram of diclofenac sodium crystal after recrystallization at a slow rate from water showing the endotherm peak at 298.8°C and onset temperature at 292.5°C (heat flow rate 20°C/min).

Table 3.1. DSC thermogram characteristics of diclofenac sodium crystals recrystallized from various solvents and at different cooling rates. The commercial sample of diclofenac sodium had a melting point at 288.7°C and peak of transition at 298.7°C.

Solvent	Fast cooling		Slow cooling	
	Melting point (°C)	Peak of transition (°C)	Melting point (°C)	Peak of transition (°C)
Water	-	-	292.5	298.8
Methanol	297.6	301.5	291.6	298.2
Ethanol	293.8	299.1	293.6	298.1
Acetone	290.5	297.1	292.5	297.5
n-Propanol	293.6	301.8	295.5	303.2
Butanol	295.9	300.5	295.1	300.2

3.4.1.2 Scanning electron microscope (SEM)

SEM is used as a tool for imaging the surface of a material. It has a high resolution capacity, around 0.00001 mm compared to 0.001 mm for a light microscope. The morphology of diclofenac sodium and diclofenac sodium crystals recrystallized from various solvents and at different cooling rates are shown in Figures 3.2-3.10. When a crystal precipitates from a supersaturated solution, the first event that occurs is the creation of a nucleus. This nucleus then grows. If growth is of equal rate in all directions, then a fairly cubical-looking shape will occur. If the growth is inhibited in one direction, then a plate will occur, and if it is inhibited in two directions, then a needle will be the result. Such shape differences do not imply different crystal systems, but are called crystal habits.

The molecular particles of diclofenac sodium (as received from the company) (Figure 3.2) were amorphous. The diclofenac sodium crystals recrystallized from water by fast and slow cooling rates had plate-like shapes (Figures 3.3 and 3.4). As the polarity of the solvents decreased (from methanol to ethanol, acetone, propanol and butanol) the shape of the crystals gradually changed from irregular plates (in methanol and ethanol, fast cooling, Figures 3.5 and 3.6) to a mixture of irregular plates and tabular crystals (in acetone, fast cooling, Figure 3.7), a mixture of tabular and needle-like crystals (in propanol, fast cooling, Figure 3.8) and needle-like crystals (in butanol, fast and slow cooling, Figures 3.9 and 3.10) respectively.

The arrangement of diclofenac sodium crystals recrystallized from water (Figures 3.3 and 3.4) and butanol (Figures 3.9 and 3.10) showed that the cooling rate did not affect the shape of the crystals but did affect the arrangement of the crystals. In a slow cooling environment, the crystals were slowly built up resulting in more regular crystals than in fast cooling. The cooling rate affected the size of the crystals recrystallized from water and butanol in different ways. The size of slow cooling

crystals recrystallized from water was larger than fast cooling crystals and vice versa for the crystals recrystallized from butanol.

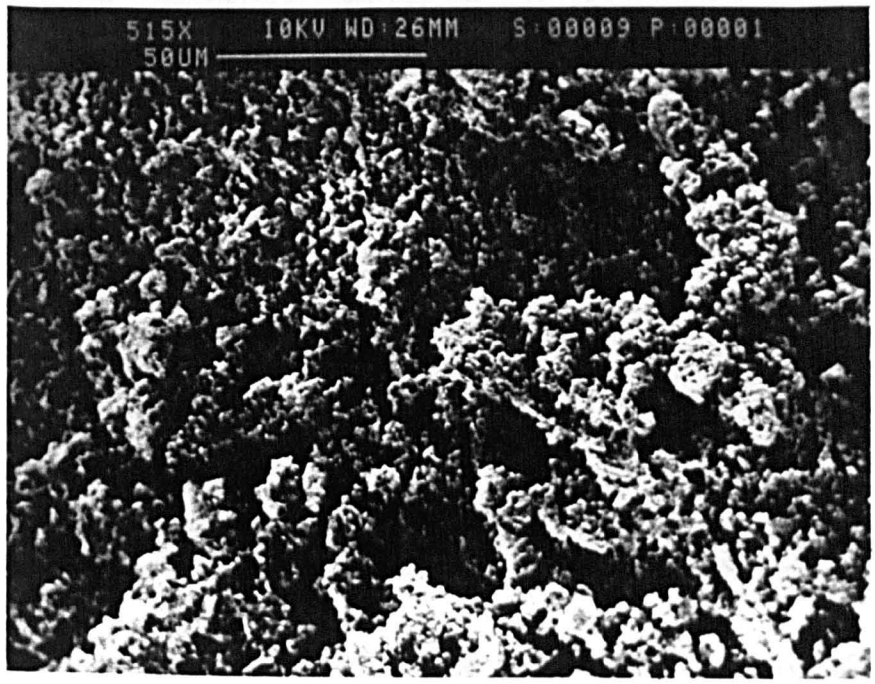


Figure 3.2. SEM photomicrograph of diclofenac sodium as received from the company. Magnification: 515x. Voltage: 10 kV.

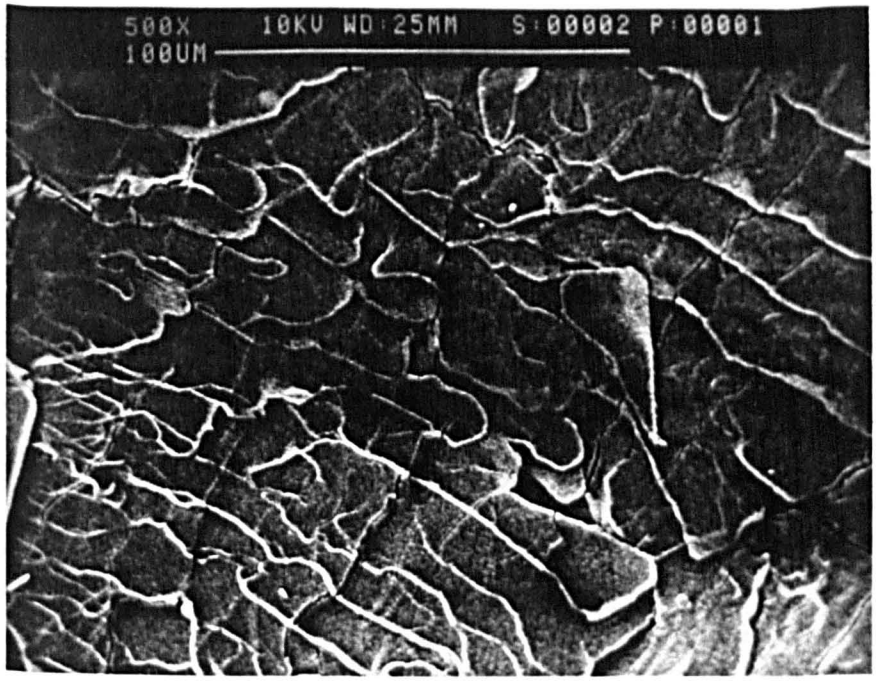


Figure 3.3. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in water (dielectric constant at 20°C = 80) in a fast cooling environment. Magnification: 500x. Voltage: 10 kV.

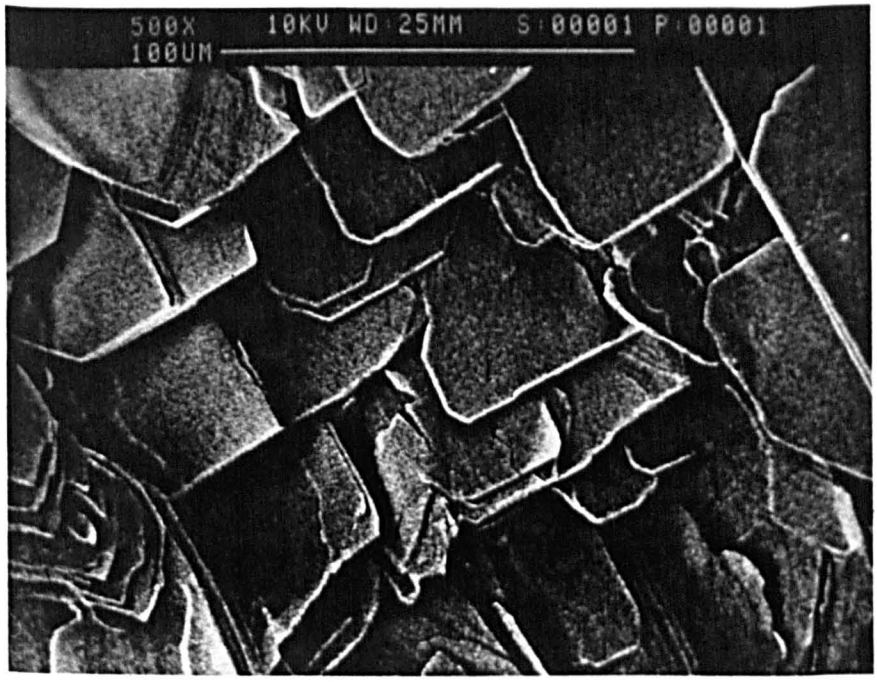


Figure 3.4. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in water (dielectric constant at 20°C = 80) in a slow cooling environment. Magnification: 500x. Voltage: 10 kV.

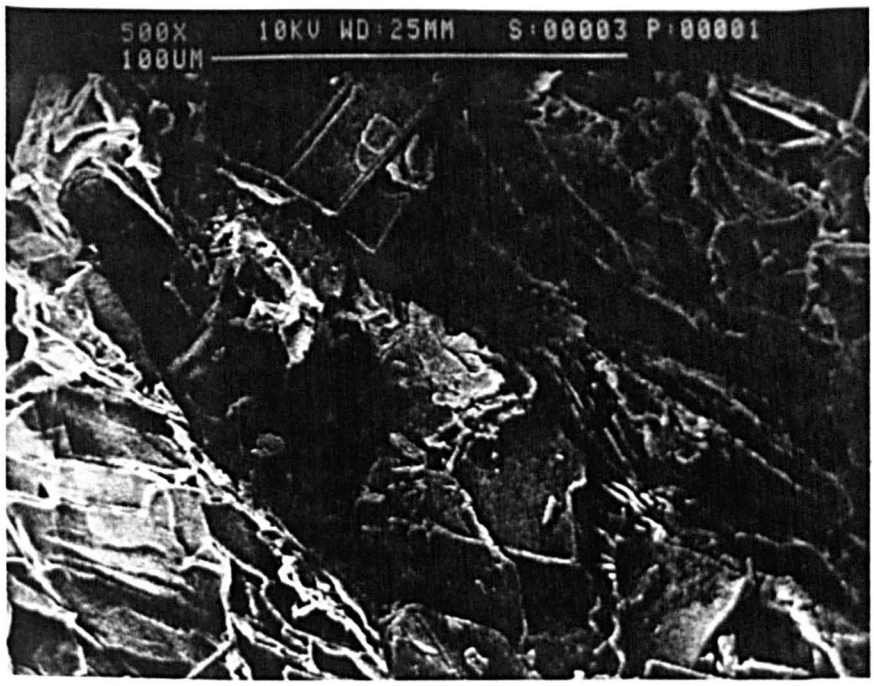


Figure 3.5. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in methanol (dielectric constant at 20°C = 33) in a fast cooling environment. Magnification: 500x. Voltage: 10 kV.

Figure 3.6. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in ethanol (dielectric constant at 20°C = 25) in a fast cooling environment. Magnification: 500x. Voltage: 10 kV.

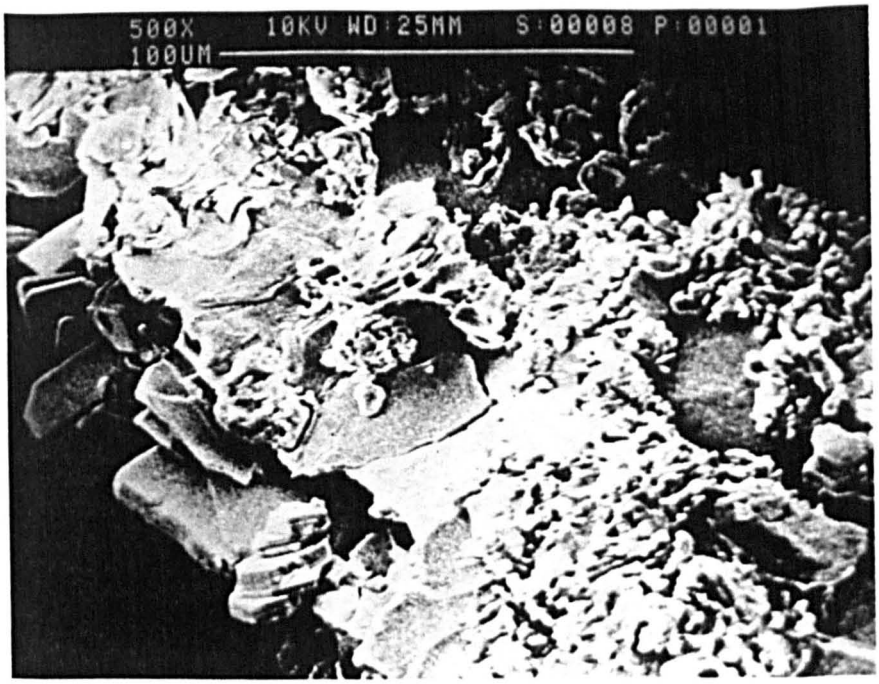


Figure 3.7. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in acetone (dielectric constant at 20°C = 21) in a fast cooling environment. Magnification: 500x. Voltage: 10 kV.

Figure 3.8. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in propanol (dielectric constant at 20°C = 18.62) in a fast cooling environment. Magnification: 500x. Voltage: 10 kV.

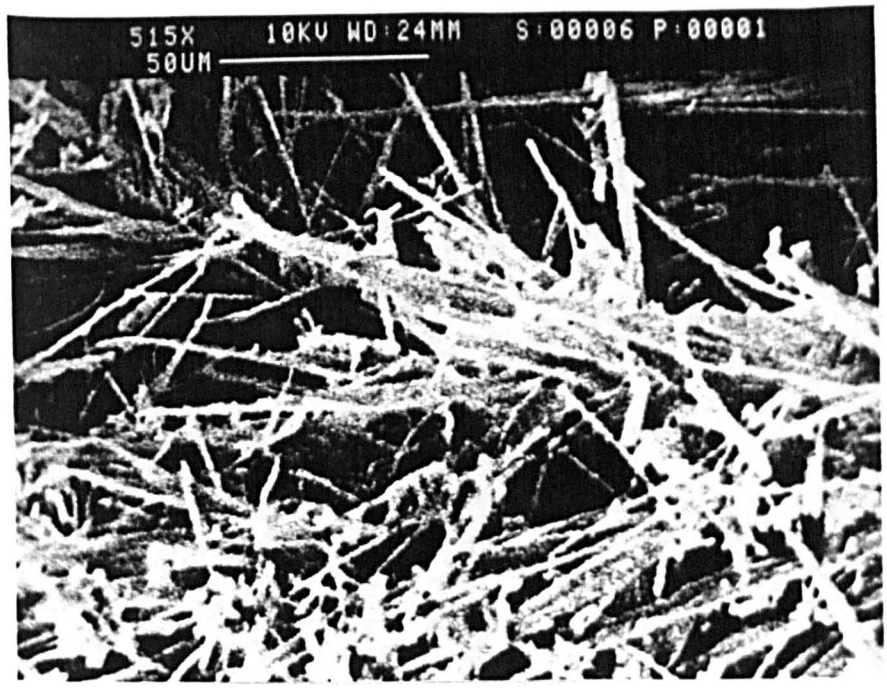


Figure 3.9. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in butanol (dielectric constant at 20°C = 17.1) in a fast cooling environment. Magnification: 515x. Voltage: 10 kV.

Figure 3.10. SEM photomicrograph of diclofenac sodium crystal recrystallized from a supersaturated solution of diclofenac sodium in butanol (dielectric constant at 20°C = 17.1) in a slow cooling environment. Magnification: 500x. Voltage: 10 kV.

3.4.2 Particle size study

The photomicrographs of xanthan gum, karaya gum, locust bean gum and carrageenan are shown in Figures 3.11-3.14 respectively. Xanthan gum, karaya gum and locust bean gum have an irregular shape with different particle sizes. Xanthan gum has a larger particle size than locust bean gum and karaya gum respectively. Carrageenan has a fibrous-like shape. The histogram of particle size distribution of each gum is shown in Figures 3.15-3.18. A logarithmic plot of particle size distribution of these four gums is shown in Figure 3.19. The plot showed that particle size distributions of carrageenan and locust bean gum were very close (Figure 3.19). The

mean sizes are 252.5, 123.4, 121.3 and 60.9 μm for xanthan gum, carrageenan, locust bean gum and karaya gum respectively.

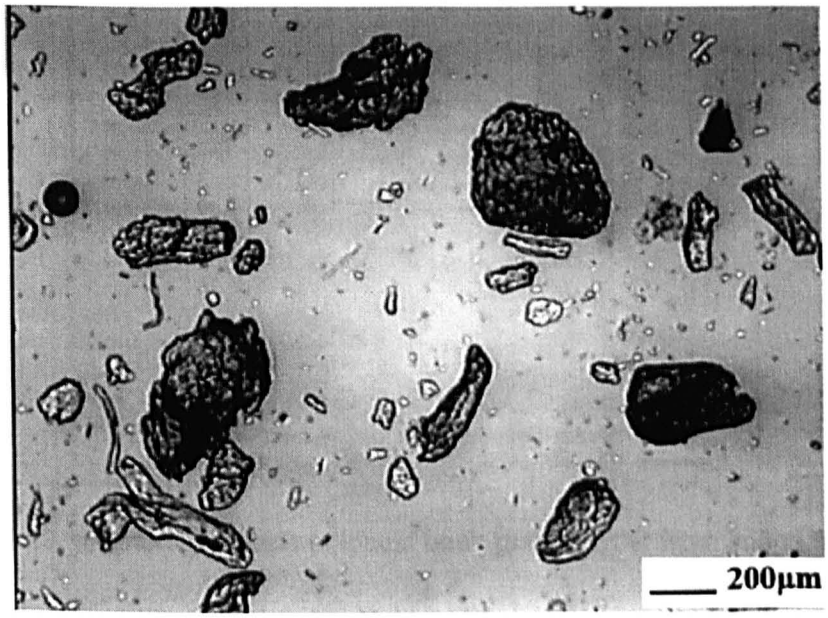


Figure 3.11. Photomicrograph of xanthan gum powder from image analysis.

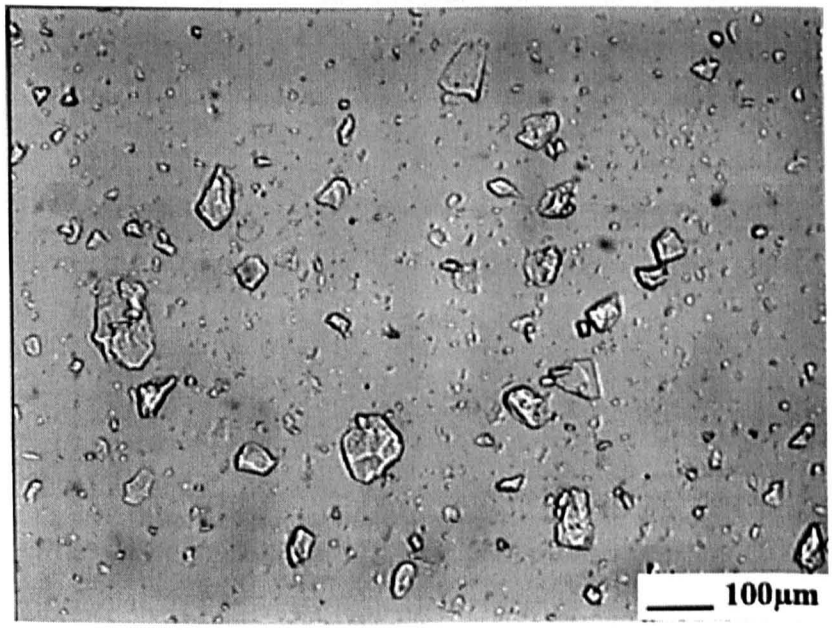


Figure 3.12. Photomicrograph of karaya gum powder from image analysis.

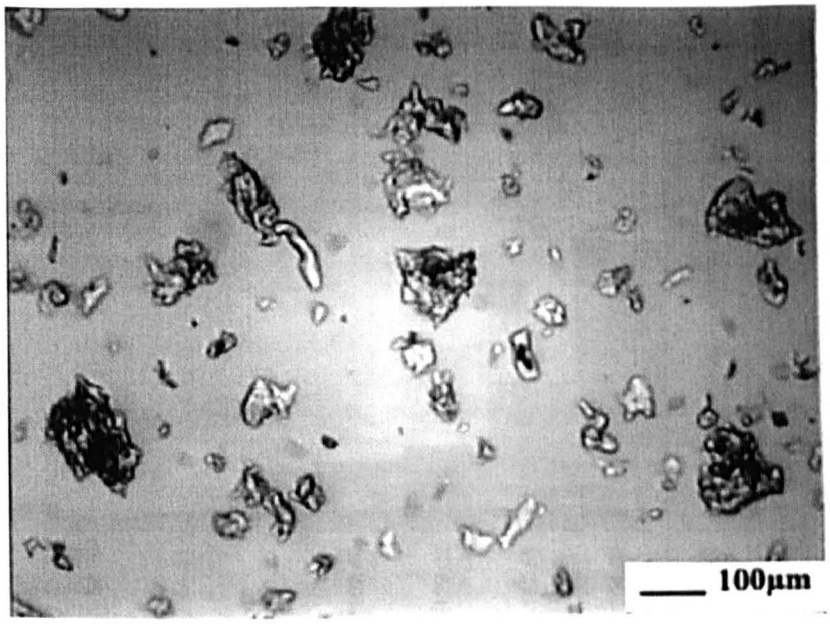


Figure 3.13. Photomicrograph of locust bean gum powder from image analysis.

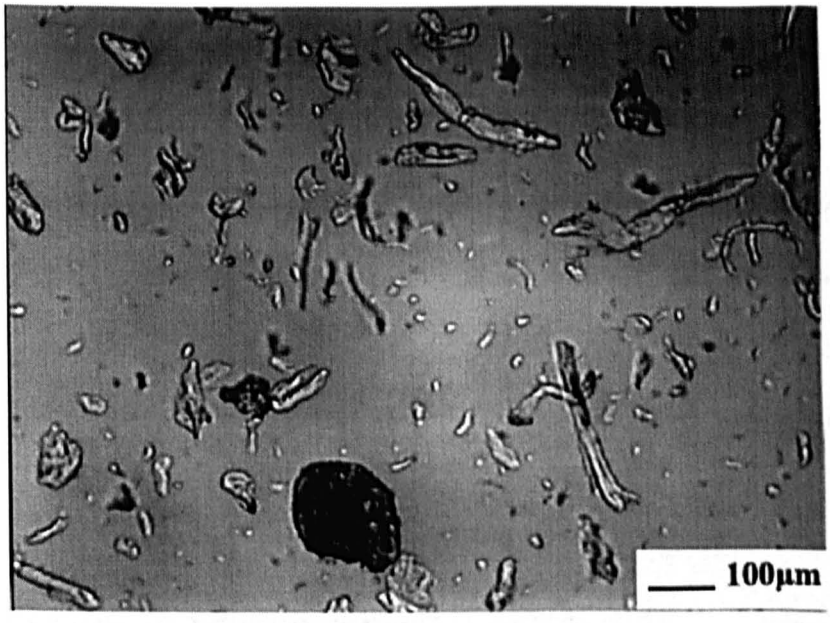


Figure 3.14. Photomicrograph of carrageenan gum powder from image analysis.

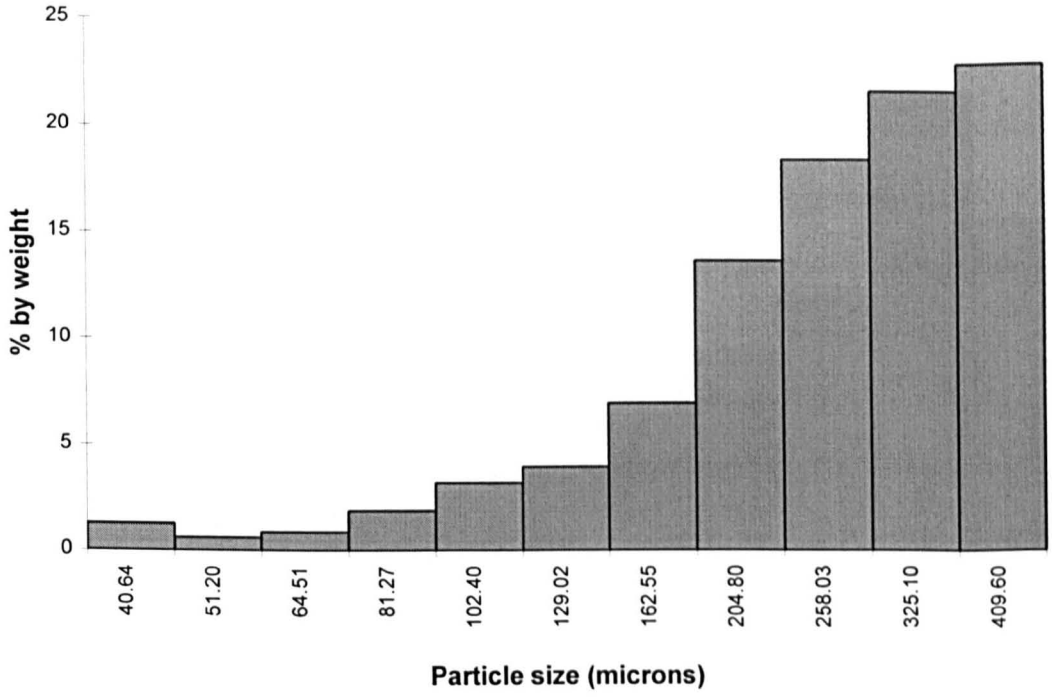


Figure 3.15. Histogram of particle size distribution of xanthan gum from image analysis.

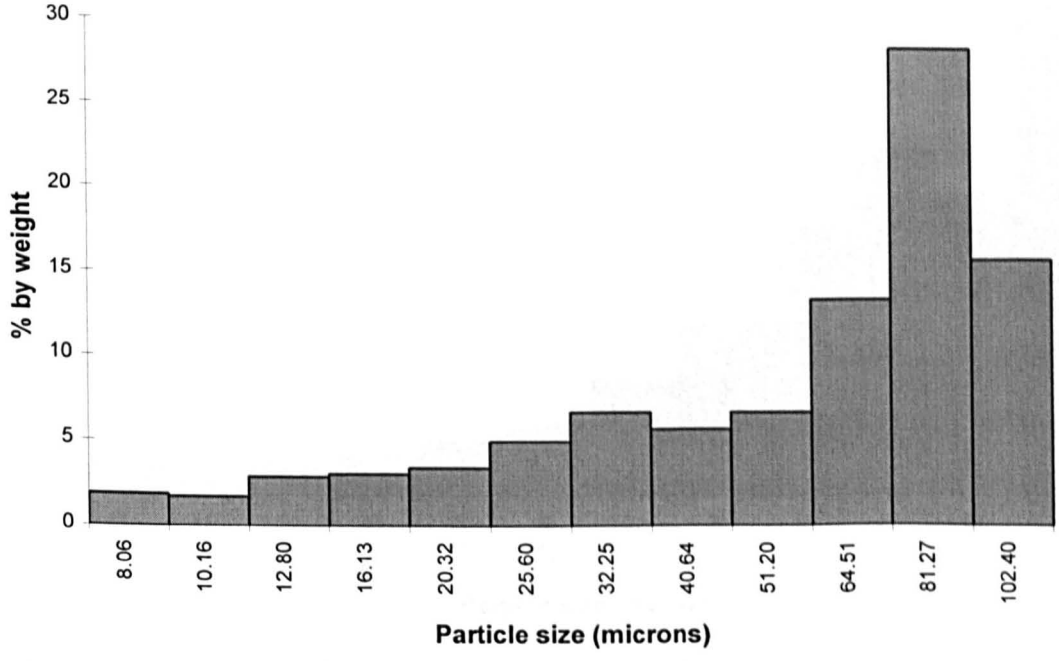


Figure 3.16. Histogram of particle size distribution of karaya gum from image analysis.

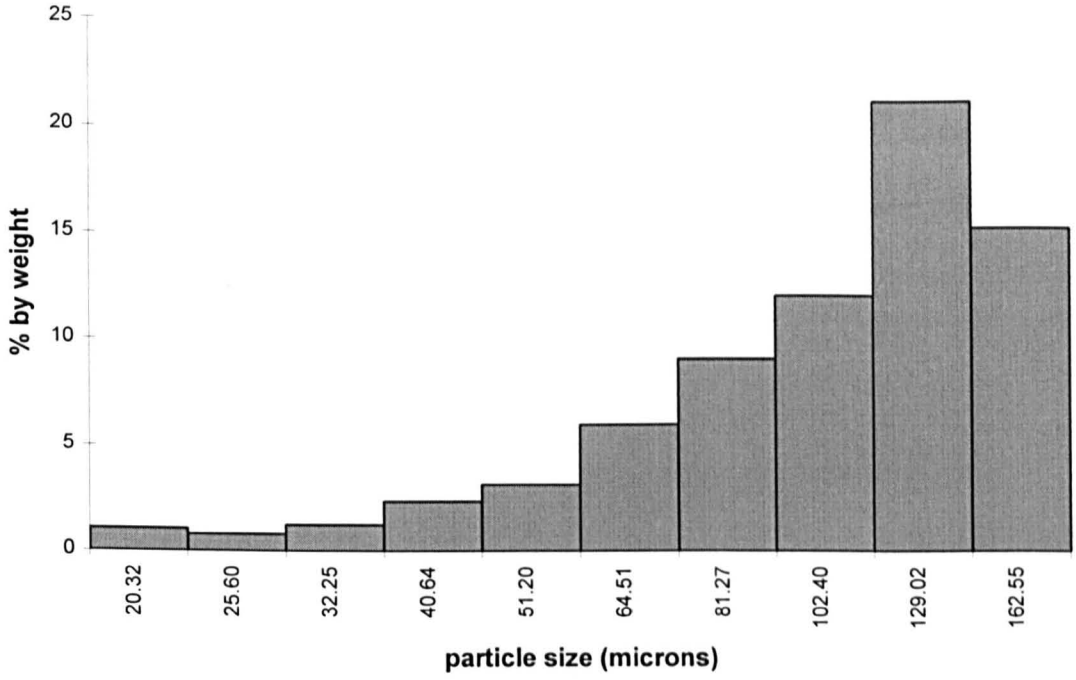


Figure 3.17. Histogram of particle size distribution of locust bean gum from image analysis.

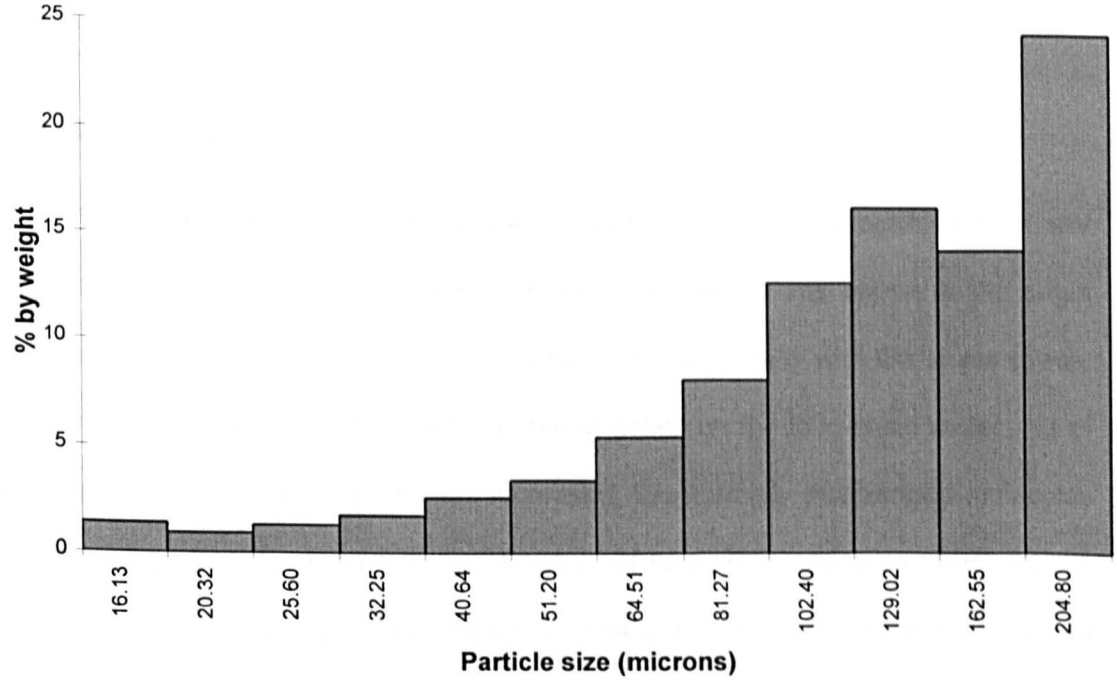


Figure 3.18. Histogram of particle size distribution of carrageenan gum from image analysis.

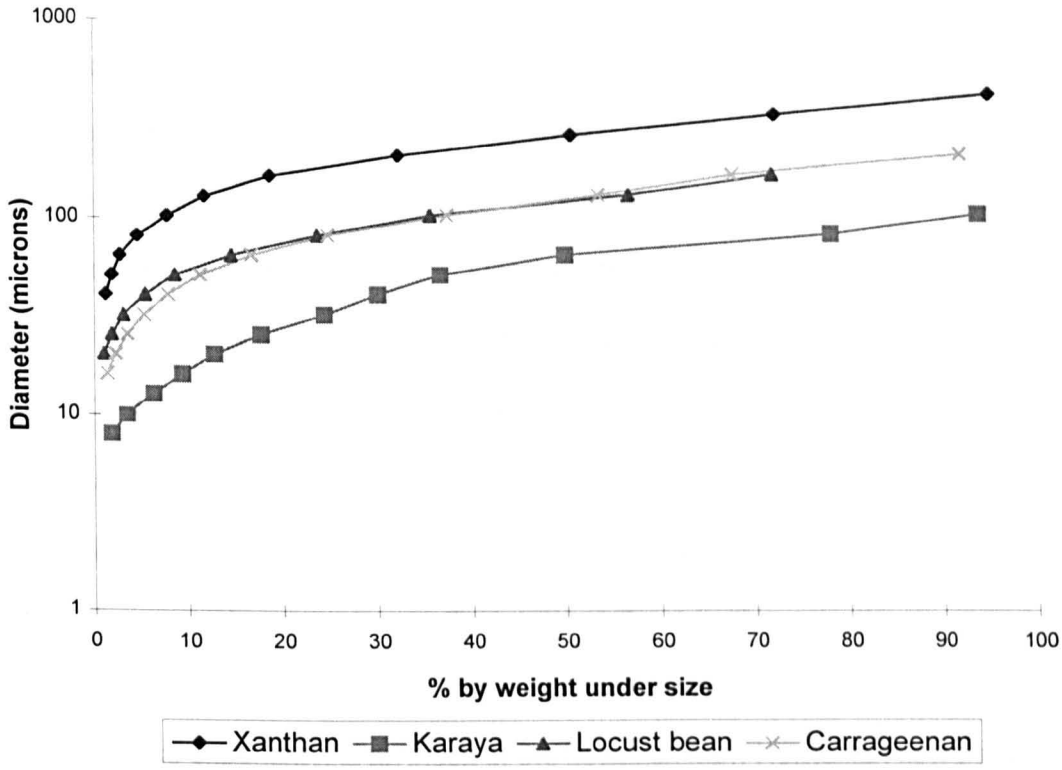


Figure 3.19. A logarithmic plot of particle size distribution of four natural hydrophilic gums against % by weight under size.

3.4.3 Viscosity study

The gum mucilages studied exhibited pseudoplastic flow, except for the 2% w/v karaya gum mucilage containing S(+) ibuprofen. The rheograms began at the origin and were non-linear, i.e. the shear rate did not increase linearly with the shear stress. The curved rheograms resulted from a shearing action on the long-chain molecules of the gums. As the shearing stress was increased, the normally disarranged molecules began to align their long axes in the direction of flow. This orientation reduced the internal resistance of the gum and allowed a greater rate of shear at each successive shearing stress. In addition, some of the solvent associated with the molecules may be

released, resulting in an effective lowering of the concentration and the size of the dispersed molecules. These effected a lowering of the apparent viscosity.

Objective comparisons between different pseudoplastic systems are more difficult than with either Newtonian or plastic systems. Several approaches have been used to obtain meaningful parameters that will allow different pseudoplastic materials to be compared. The empirical power law (Ostwald-de Waele equation) has been used most frequently for pseudoplastic and dilatant systems (Whorlow 1992).

$$\sigma = k\gamma^{n} \quad \text{.....(3.1)}$$

Where σ is the shearing stress, k is a viscosity coefficient and γ is the rate of shear. The particular viscosity coefficient (k) defined in this equation is a constant characteristic of a particular material, but dissimilar to Newtonian and plastic viscosities. The exponent n is an index of the deviation from Newtonian flow behaviour. The exponent n is unity for Newtonian systems, <1 for pseudoplastic systems and >1 for dilatant systems. The more n differs from unity, the more non-Newtonian is the flow behaviour. Following rearrangement, Equation 3.1 may be rewritten in the logarithmic form:

$$\log \sigma = n \log \gamma + \log k \quad \text{.....(3.2)}$$

A plot of log σ versus log γ yielded a straight line of slope = n and intercept = log k. The viscosity coefficient (k), shear rate index (n) and correlation coefficient of 2% w/v mucilage of gums; xanthan gum, karaya gum, locust bean gum or carrageenan, 1:1 gums and drugs; diclofenac sodium or S(+) ibuprofen, and 1:1:1 gums, drugs and lactose in 0.05 M phosphate buffer solution pH 7.0 were calculated according to Equation 3.1 and shown in Table 3.2. For comparison purposes, the histogram of the viscosity index (k) of these mucilages are also shown in Figure 3.20.

The rheogram of 2% w/v S(+) ibuprofen and karaya gum mucilage fitted well with the Herschel-Bulkley model, $\sigma = \sigma_y + k\gamma^n$; where σ_y = yield value. Above the yield stress, the flow curve was non-linear. This mucilage had viscosity coefficient (*k*) = 0.0009, shear rate index (*n*) = 1.215, dynamic yield (σ_y) = 7 Nm^{-2} and correlation coefficient (r) = 0.9941. The shear rate index (*n*) was more than 1 indicating the dilatant or shear thickening system.

Table 3.2. Viscosity parameters from the rheograms of 2% w/v mucilages of gums, model drugs and gums, and model drugs, gums and lactose using Equation 3.1 to derive the viscosity coefficient (k) and shear rate index (n).

2% w/v mucilage of	Viscosity coefficient (k)	Shear rate index (n)	Correlation coefficient (r)
X	47.56	0.13	0.9922
D and X	14.20	0.16	0.9931
D, X and L	6.09	0.22	0.9931
I and X	14.36	0.16	0.9954
I, X and L	5.97	0.22	0.9936
K	0.78	0.57	0.9998
D and K	0.34	0.49	0.9867
D, K and L	0.12	0.55	0.9928
I and K	-	-	-
I, K and L	0.18	0.52	0.9860
LB	15.77	0.45	0.9792
D and LB	1.41	0.60	0.9932
D, LB and L	0.32	0.67	0.9985
I and LB	1.25	0.60	0.9936
I, LB and L	0.34	0.65	0.9992
C	0.21	0.50	0.9964

X; Xanthan gum, K; Karaya gum, LB; Locust bean gum, C; Carrageenan, D; Diclofenac sodium, I; S(+) ibuprofen and L; Lactose.

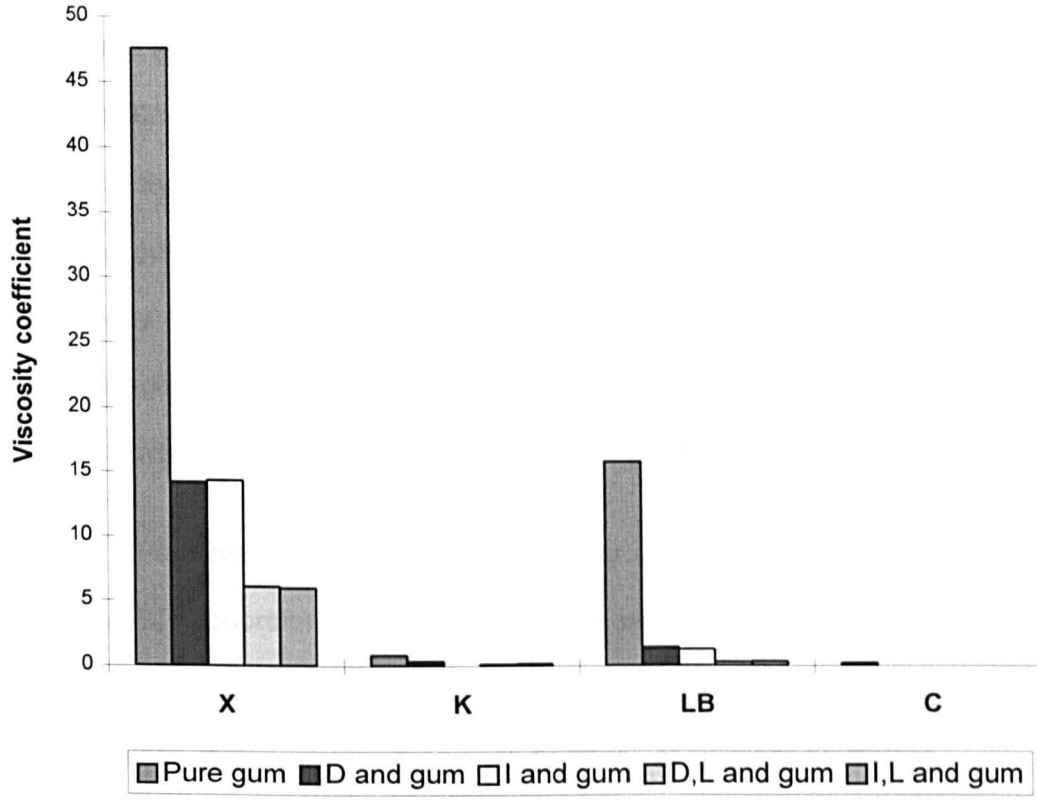


Figure 3.20. Viscosity coefficients of 2% w/v gums, gums and drugs, and gums, drugs and lactose. X; Xanthan gum, K; Karaya gum; LB; Locust bean gum, C; Carrageenan, D; Diclofenac sodium, I; S(+) ibuprofen and L; Lactose.

The percentage decrease in the viscosity coefficient when drugs, or drugs and lactose are used to substitute a portion of the gums are shown in Table 3.3. The viscosity coefficients of 2% w/v xanthan gum, karaya gum, locust bean gum and carrageenan mucilages in 0.05 M phosphate buffer solution pH 7.0 were 47.56, 0.78, 15.77 and 0.21 respectively. The viscosity coefficients of xanthan gum mucilages were decreased about 70% when 50% of the xanthan gum was substituted with diclofenac sodium or S(+) ibuprofen. For karaya gum, the viscosity coefficients decreased by 56% when 50% of the karaya gum was substituted with diclofenac sodium. Although this decrease in viscosity coefficient was less than for xanthan gum, the initial viscosity

coefficient of a 2% w/v solution of karaya gum was very low (0.78) compared with xanthan gum (47.56). For locust bean gum, the viscosity coefficients were decreased by 91 and 92% when 50% of the locust bean gum was substituted with diclofenac sodium and S(+) ibuprofen respectively. When diclofenac sodium or S(+) ibuprofen, lactose and gums were combined in equal parts (1:1:1), the viscosity coefficients were decreased by approximately 87, 78-84 and 98% for xanthan gum, karaya gum and locust bean gum respectively. The experiment was not continued with carrageenan because its initial viscosity coefficient was very low (0.21).

Table 3.3. Percentage decrease in the viscosity coefficient when drugs (diclofenac sodium and S(+) ibuprofen), or drugs and lactose were used to substitute some of the gum in a 2% w/v solution in 0.05 M phosphate buffer pH 7.0.

Composition of 2% w/v solution	% decrease of viscosity coefficient		
	xanthan gum	karaya gum	locust bean gum
D: gum 1:1	70.1	56.0	91.0
I: gum 1:1	69.8	-	92.0
D:L: gum 1:1:1	87.2	84.4	98.0
I:L: gum 1:1:1	87.4	77.5	97.9

*D; Diclofenac sodium, I; S(+) ibuprofen, L; Lactose.

When xanthan gum was substituted with the two different drugs, diclofenac sodium or S(+) ibuprofen, the percentage decrease in viscosity coefficient was not significantly different; 70.1% compared to 69.8%. The result with locust bean gum was similar but the reduction was greater; 91.0% and 92.0% for diclofenac sodium and S(+) ibuprofen respectively. For karaya gum, the flow behaviour changed from pseudoplastic to Herschel-Bulkley when the gum was substituted with S(+) ibuprofen. S(+) ibuprofen is soluble in 0.05 M phosphate buffer pH 7.0. The solubility was approximately 20 mg/ml. The affinity of water with S(+) ibuprofen might be higher than

with karaya gum resulting in not enough water to hydrate the gum. Hence, the flow behaviour was changed and the viscosity coefficient was very low.

The degree of reduction in viscosity coefficient was significantly different when karaya gum was mixed with diclofenac sodium and lactose (84.39%) or S(+) ibuprofen and lactose (77.53%). On the other hand, the degree of reduction in viscosity under similar circumstances for xanthan gum and locust bean gum was not significantly different (see Table 3.3). This indicated that karaya gum flow behaviour and viscosity coefficient were both sensitive to substitution with drugs. Xanthan gum should be the best candidate for formulating both drugs because the flow behaviour is less sensitive to substitution with the two drugs, and the degree of reduction in viscosity coefficient was less than locust bean gum.

The viscosity coefficients of 2% w/v xanthan gum, karaya gum and locust bean gum mucilage in 0.1 M HCl pH 1.2 were lower than in 0.05 M phosphate buffer pH 7.0 by 39.0, 83.3 and 29.0% respectively. In acid medium, these gums underwent hydrolysis resulting in lower viscosity (Cottrell et al. 1980; Meer 1980). On the other hand, the viscosity coefficient of carrageenan in 0.1 M HCl was much higher (86.6%) than in 0.05 M phosphate buffer pH 7.0 because the hydration of carrageenan is more rapid at low pH. These results were consistent with findings of Stoloff (1950), in which it was shown that the rate of hydration is considerably slower at pH 6 and above.

3.4.4 Solubility study

3.4.4.1 pH solubility profile

The pH solubility profiles of diclofenac sodium and S(+) ibuprofen are shown in Figures 3.21 and 3.22. For diclofenac sodium (Figure 3.21), the solubility at pH<5.2 was very low, and increased slightly from pH 5.2 to 6.5. The solubility rapidly increased

from pH 6.5 to 8. For S(+) ibuprofen (Figure 3.22), the solubility at pH<4 was very low, and increased slightly from pH 4 to 5.7. The solubility rapidly increased from pH 5.7 to 8.

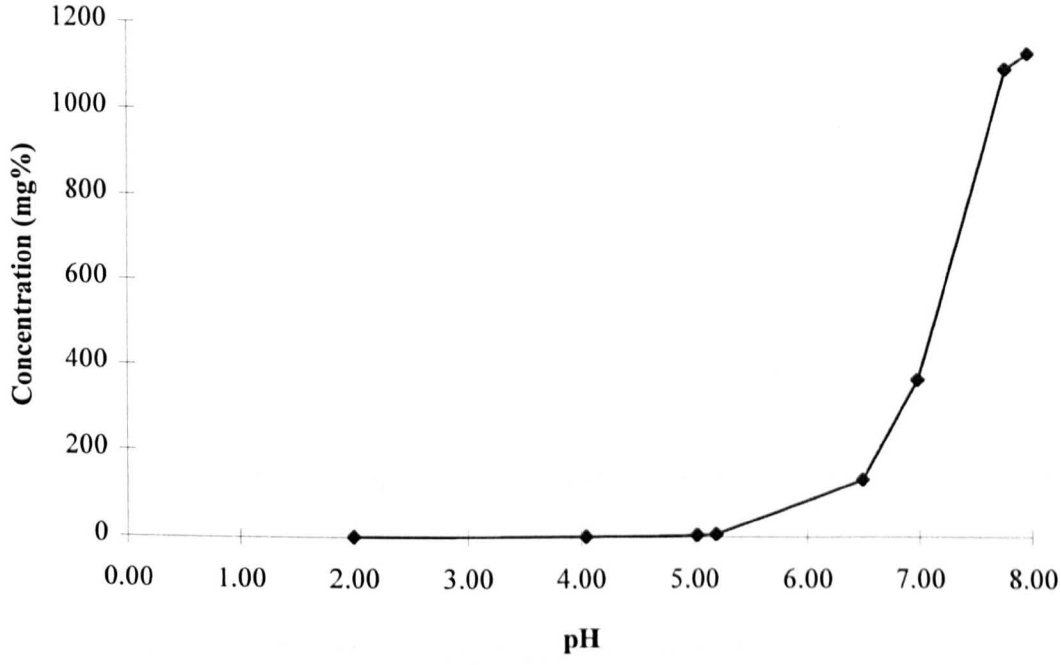


Figure 3.21. pH solubility profile of diclofenac sodium powder at 37°C.

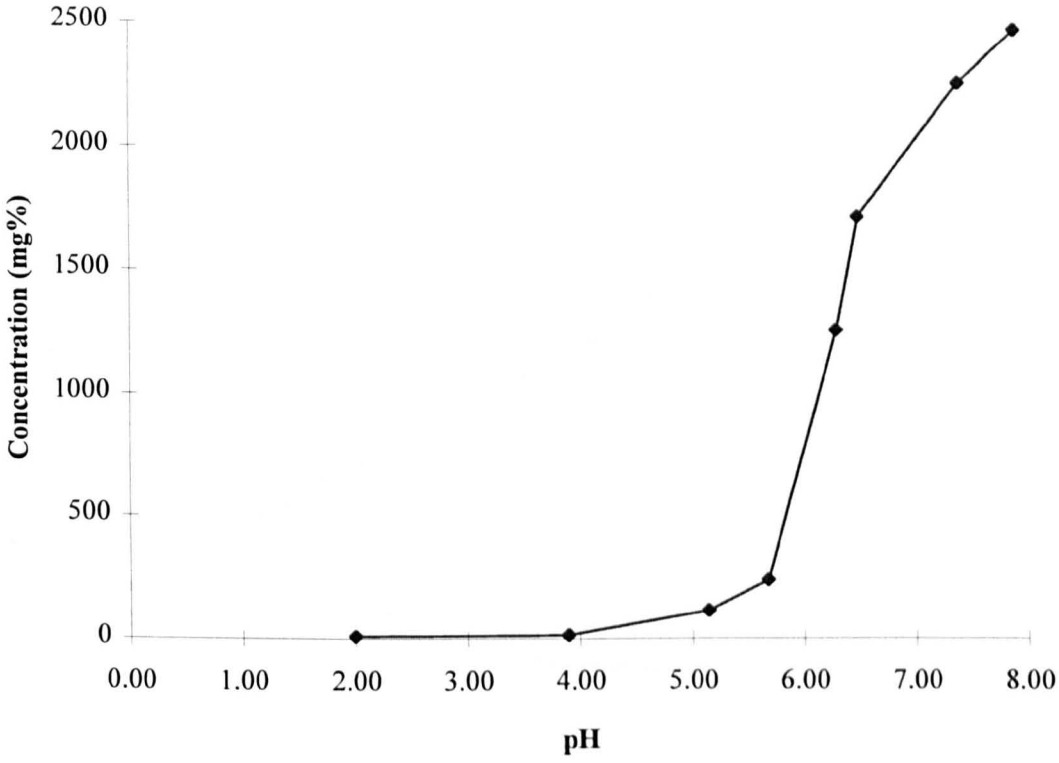


Figure 3.22. pH solubility profile of S(+) ibuprofen powder at 37°C.

3.4.4.2 Intrinsic dissolution rate (IDR)

The plot of the amount of diclofenac sodium dissolved per unit surface area against time at 37°C in 0.05 M phosphate buffer medium pH 7.4 is shown in Figure 3.23. The IDR, calculated from the slope of this chart, is 0.92 mg/cm^{2}min.

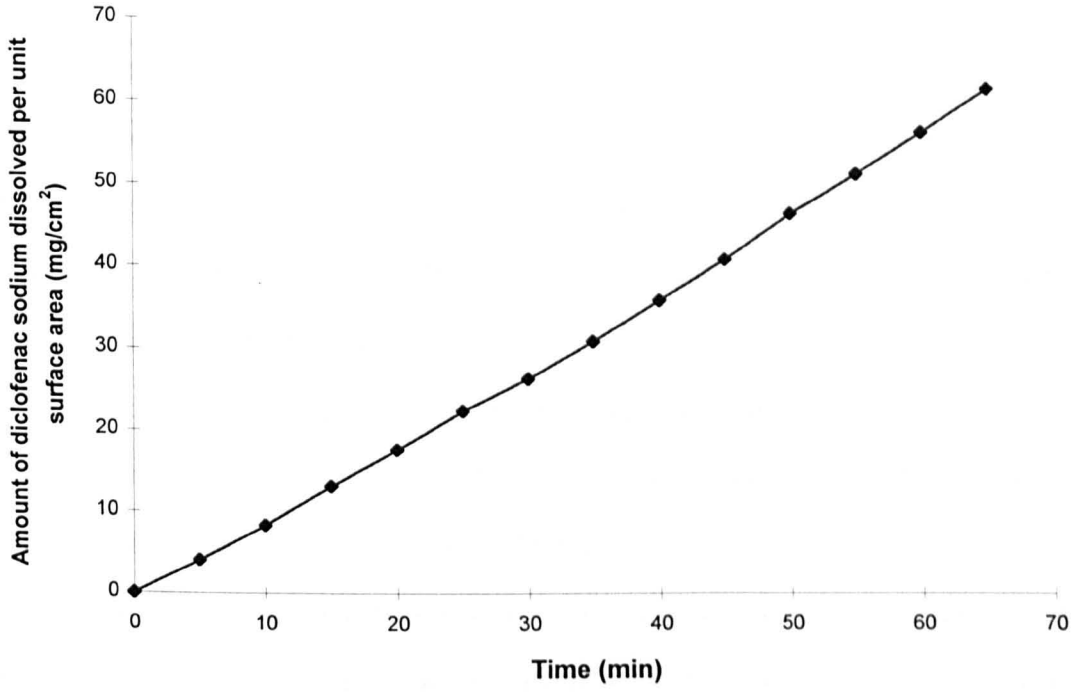


Figure 3.23. Amount of diclofenac sodium dissolved (mg/cm^2) against time (min) at 37°C in 0.05 M phosphate buffer medium pH 7.4, speed of rotation 100 rpm.

Similar work carried out by Romero and Rhodes (1991) reported an intrinsic dissolution rate for S(+) ibuprofen of 0.486 mg/cm^2min using 500 ml USP simulated intestinal fluid at 37±0.8°C, speed of rotation 100 rpm. It has been reported that a IDR of < 1 mg/cm^2min for a drug would be likely to produce bioavailability problems because absorption would be dissolution rate limited (Kaplan 1972). The IDR of S(+) ibuprofen was lower than that of diclofenac sodium. However, comparison should be made with caution because the experimental conditions were different in each case. In general, the higher the IDR, the better the *in vivo* performance, e.g., bioavailability, could be expected.

3.5 CONCLUSION

Diclofenac sodium crystals recrystallized from various solvents and at different cooling rates were white to off-white in colour with a melting point of 293.8±2.1°C. There was no evidence of polymorphism under these recrystallisation conditions. The type of the solvents affected the shape of the crystals while the cooling rate affected the arrangement of the crystals.

Xanthan gum, locust bean gum and karaya gum had irregularly shaped particles with mean sizes of 252.5, 121.3 and 60.9 μm respectively. Carrageenan had a fibrous-like shape with a mean size of 123.4 μm.

The gum mucilages exhibited pseudoplastic flow. The rheology patterns were still the same when these gums were partially substituted with the model drugs and lactose, except when karaya gum and S(+) ibuprofen were combined in the ratio of 1:1. The viscosity coefficients decreased to various degrees for each gum, in accordance with the decrease of gum concentration. The flow behaviour of xanthan gum was least sensitive to the type of substituted drug and the degree of reduction in viscosity coefficient was less than locust bean gum. Xanthan gum would be a good candidate in formulating diclofenac sodium and S(+) ibuprofen hydrophilic matrices.

The solubility of both drugs greatly depended on the pH of the medium. The higher the medium pH, the greater the solubility.

The intrinsic dissolution rate of diclofenac sodium in 0.05 M phosphate buffer pH 7.4 at 37°C was 0.92 mg/cm^{2}min. The intrinsic dissolution rate of S(+) ibuprofen in USP simulated intestinal fluid at 37°C was 0.486 mg/cm^{2}min (Romero and Rhodes 1991). These two values cannot be compared because of the different experimental condition used.

CHAPTER 4

HYDROPHILIC MINI-MATRICES CONTAINING DICLOFENAC SODIUM AND NATURAL GUMS: PREPARATION AND EVALUATION OF *IN VITRO* RELEASE

4.1 INTRODUCTION

Diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID), is a drug of choice for chronic arthritis. Its short half-life, about 1-2 hours (Fowler et al. 1983), makes it a good candidate for sustained-release formulation. The multiple units dosage forms (MUDFs) were chosen for this study in order to achieve uniform plasma levels (Edgar et al. 1984) and reproducible bioavailability (Graffner et al. 1986) (see also Chapter 1). The mini-matrices were the units enclosed in the hard gelatin capsules of the MUDFs. The production of mini-matrices uses a tabletting technique that is widely understood, diverse and offers less constraints than, for example extrusion or spheronisation. It does not require extra capital expenditure because most companies already have a tabletting capacity. In addition, the mini-matrices also have dosing flexibility. The aim of this chapter is to prepare diclofenac sodium mini-matrix MUDFs and subsequently evaluate their *in vitro* release profiles.

4.2 MATERIALS

Natural hydrophilic gums: xanthan gum (X), karaya gum (K), locust bean gum (LB), and carrageenan gum (C).

Synthetic hydrophilic polymer: hydroxypropyl methylcellulose (HPMC).

Model drug: diclofenac sodium (D).

Excipients: lactose (L), dicalcium phosphate (E, Encompress®), cellulose acetate phthalate (CAP), and magnesium aluminium silicate (V, Veegum F®).

Lubricant: magnesium stearate.

Buffers, liquids and solutions: sodium hydroxide and potassium dihydrogen orthophosphate were used to prepare phosphate buffer solutions pH 6, 6.5, 7, 7.4 and 8 (USP XXIII 1994), sodium phosphate and citric acid were used to prepare citrate-phosphate buffer solution pH 3, 4, 5 and 5.5 (Wade 1980).

4.3 METHODS

4.3.1 Tablet manufacture

All materials were passed through a mesh sieve with an aperture of 250 μm before use. Mini-matrices were prepared by the wet granulation method. The composition of the formulations are presented in Tables 4.1 and 4.2. All materials, with the exception of lubricant (magnesium stearate), were thoroughly mixed in a tumbling mixer for 5 minutes and then wetted in a mortar with 50% v/v ethanol (except for formula 2 which was wetted with 70% v/v ethanol). The wet mass was then passed through a 500 μm mesh sieve and dried at a temperature not greater than 60°C for 18 hours (except for formula 2 which was dried at room temperature). The dried granules were then rescreened through a 300 μm mesh sieve, lubricated with magnesium stearate 1% w/w and compressed into flat-faced mini-matrices of diameter 4.5 mm, weighing 30 mg (except as indicated in Table 4.1), and containing 15 mg of diclofenac sodium. Diclofenac sodium: xanthan gum in the ratio of 1:1 (Formulation 1, Table 4.1) was also compressed to 3 and 5.5 mm diameter tablets, weighing 20 and 40 mg and containing 10 and 20 mg of diclofenac sodium respectively, in order to study the effect of tablet volume on drug release. An instrumented Manesty F3 single punch tablet

machine (Manesty Machines Ltd., Liverpool, England) was used to compress the mini-matrices. Since the influence of compression pressure on the drug release rate from hydrophilic matrices is reported to be negligible (Hogan 1989; Huber and Christenson 1968; Lapidus and Lordi 1968; Ford et al. 1985a; Talukdar and Plaizier-Vercammen 1993), the effect of the pressure was not studied here. However the mini-matrices produced were in the range of 15-44 N crushing strength depending on the composition in the formulas. The crushing strength of 20 tablets was individually measured (Erweka TBH 28 Tablet Hardness Tester, F.R.G.). The mean crushing strength and standard deviation were calculated. Six mini-matrices containing a total dose of 90 mg of diclofenac sodium were encapsulated in size 1 hard gelatin capsules to produce a MUDF.

Table 4.1. Composition (%) of the mini-matrices containing diclofenac sodium and four hydrophilic gums or HPMC.

	Formulation								
	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	7[b]	8[c]	9[d]
Diclofenac sodium	49.5	49.5	49.5	49.5	49.5	49.5	66	39.6	33
Xanthan gum	49.5	-	-	-	-	24.75	33	59.4	66
Karaya gum	-	49.5	-	-	-	-	-	-	-
Locust bean gum	-	-	49.5	-	-	24.75	-	-	-
Carrageenan	-	-	-	49.5	-	-	-	-	-
HPMC K4M	-	-	-		49.5	-	-	-	-
Magnesium stearate	1	1	1	1	1	1	1	1	1

Weight of each mini-matrix: [a]30.2±1.1 mg; [b]22.5±1.0 mg; [c]37.5±1.0 mg; [d]45.0±1.0 mg.

Table 4.2. Composition (%) of the mini-matrices containing diclofenac sodium, xanthan gum and various excipients.

	Formulation				
	10A-D*	11A-D*	12A-D*	13A-D*	14A-D*
Diclofenac sodium	49.5	49.5	49.5	49.5	49.5
Xanthan gum	41.25	33	24.75	16.5	8.25
Excipients (lactose, Encompress®, CAP and Veegum F®)	8.25	16.5	24.75	33	41.25
Magnesium stearate	1	1	1	1	1

*A, B, C and D series for each formulation number contain lactose, Encompress®, CAP and Veegum F® respectively.

4.3.2 Mini-matrix dissolution studies

The USP XXIII basket method (Copley Dissolution System and Drive Control, Copley Instruments, Nottingham, England) was used with a constant temperature water bath at 37±0.5°C. The dissolution medium was 0.05 M phosphate buffer (pH 7.0). The speed of rotation was 100±1 rpm. The dissolution apparatus was connected to a flow-through UV spectrophotometer (Ultrospec II, LKB Biochrom Ltd., England) via a peristaltic pump. The absorbance was measured automatically at 275 nm in a 10 mm cell at 30 minute time intervals over a 12 hour period.

The effect of rotating speed was also studied by varying the speed of rotation from 50 to 100 and 150 rpm.

The studies were carried out in triplicate. The cumulative percentage of diclofenac sodium released was calculated and plotted against time. The release rates were calculated from a Higuchi plot (Equation 1.8). The values of n and k were calculated from log fraction of drug release against log time plot (Equation 1.1). The

Fickian and relaxational contributions were calculated according to Equations 1.2, 1.4 and 1.5.

The release profiles of commercially available diclofenac sodium sustained-release products; Diclomax Retard® (Park-Davis, 100 mg/capsule) and Motifene® (Panpharma, 75 mg/capsule), were also studied. In order to study the effect of dissolution medium on release characteristics of these products, various dissolution media; citrate-phosphate buffer pH 3, 4, 5, and 5.5, and 0.05 M phosphate buffer pH 6, 6.5, 7, 7.4 and 8, were used. The absorbance of the solutions was measured at wavelength 271 nm for the dissolution medium pH $\leq$ 4 and at wavelength 275 nm for the others.

4.4 RESULTS AND DISCUSSION

4.4.1 Effect of gum type on release characteristics

The four natural hydrophilic gums used showed greatly different *in vitro* dissolution profiles for diclofenac sodium from the encapsulated mini-matrices using a buffered dissolution medium (pH 7.0) and at drug: gum ratios of 1:1. The studies were carried out using hard gelatin capsules each containing six mini-matrices (4.5 mm diameter, 30 mg weight) of each gum formulation (Formulations 1-4 of Table 4.1). As seen in Figure 4.1, the times for 50% release ($t_{50\%}$ values) are 30, 165, 280 and 630 minutes for carrageenan, locust bean, xanthan and karaya gums respectively. The Type 1 carrageenan gum used, which contains predominantly *kappa*- and lesser amounts of *lambda*-carrageenan, does not produce sufficient sustained release of diclofenac sodium in spite of the fact that *kappa*-carrageenan is reported (suppliers' literature) to form rather rigid gels. On the other hand locust bean, xanthan and karaya gums do show variable degrees of sustained release.

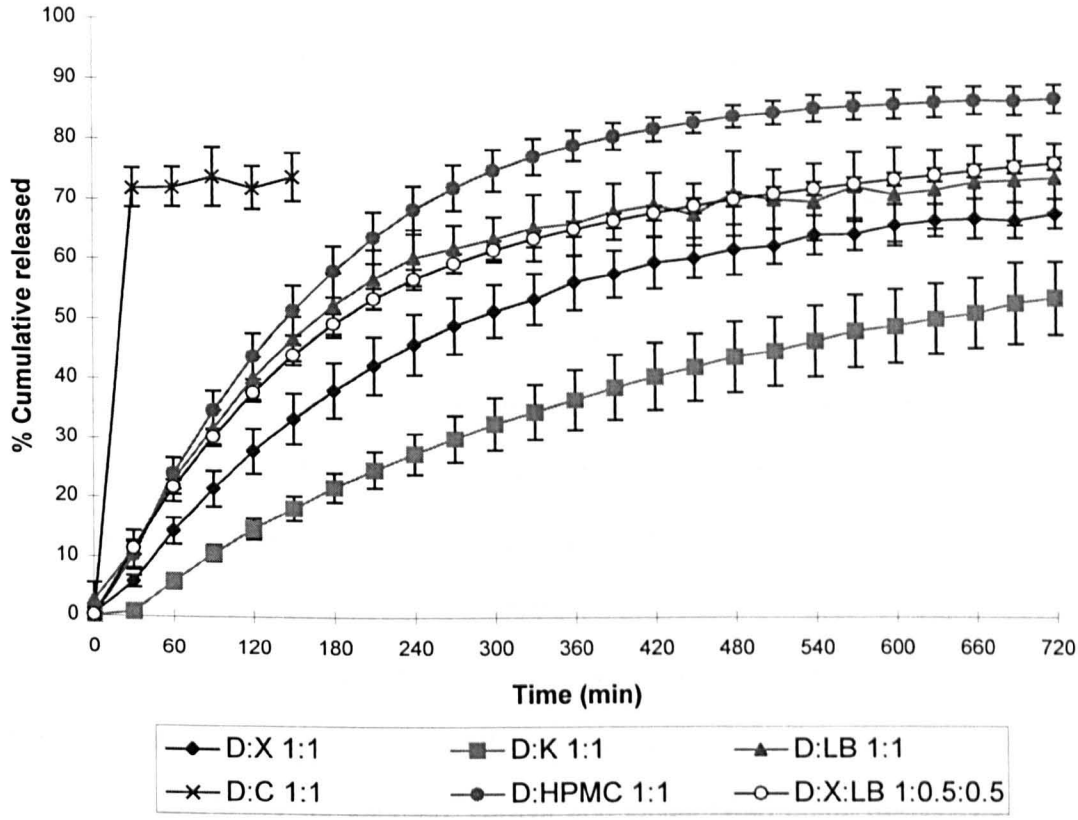


Figure 4.1. Percentage of diclofenac sodium released against time from 6 mini-matrices (4.5 mm diameter) containing diclofenac sodium (D) and various hydrophilic gums; xanthan (X), karaya (K), locust bean (LB) and carrageenan (C), or HPMC enclosed in a hard gelatin capsule (mean values±SD, n=3).

The maximum amount of accumulated drug released is about 75% for carrageenan and locust bean gums whereas for xanthan and karaya gums the maximum amount released after 12 hours was 66% and 54% respectively. However in the case of the latter two gums the drug was still being released slowly from the hydrated matrices after 12 hours. After 24 hours this amount had risen to 77 and 71% respectively.

HPMC can sustain the release of diclofenac sodium but has a lesser sustaining effect when compared with locust bean gum, xanthan gum and karaya gum (see

Figure 4.1). The maximum amount of accumulated drug released at 12 hour is 86% and $t_{50\%}$ is 150 min. This result is not totally unexpected because there is a study which showed that diclofenac sodium causes failure of HPMC matrices because it substantially depresses the thermal gelation temperature of HPMC (Rajabi-Siahboomi et al. 1993).

The values for release exponent (n), kinetic constant (k), $t_{50\%}$ value, mean dissolution time and release rate together with the correlation coefficient (r) for mini-matrices containing diclofenac sodium and each gum are given in Table 4.3. A value of $n = 0.45$ indicates Case I or Fickian diffusion, $n = 0.89$ indicates Case II transport, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion and $n > 0.89$ for Super Case II transport (Ritger and Peppas 1987). The release behaviour of each of the three gums displaying sustained release was clearly anomalous (non-Fickian) with values of $n = 0.703$, 0.731 and 0.777 for xanthan, karaya and locust bean gums respectively. This suggests that these gums (particularly locust bean) are in moving boundary conditions, since the swelling and dissolution of the gum continuously modify the effective diffusivity of the drug. The release behaviour of HPMC was Super Case II transport with a n value of 0.913. This implies that the release of HPMC is nearly time independent and erosion is more dominant than diffusion.

It is commonly known that locust bean gum can react strongly in solution with xanthan gum (Kovac 1973), so mini-matrices containing diclofenac sodium: xanthan gum: locust bean gum in the ratio of 1:0.5:0.5 (Formulation 6, Table 4.1) were also produced in order to investigate whether such a combination would produce any significant effect on drug release from the solid mini-matrices. The release profile of diclofenac sodium: xanthan gum: locust bean gum in the ratio of 1:0.5:0.5 resembles the profile of diclofenac sodium: locust bean gum in the ratio of 1:1 (Figure 4.1). The time for 50% release ($t_{50\%}$) was 160 min. The dissolution results did not therefore

provide any clear evidence for a synergistic effect between xanthan gum and locust bean gum on the rate of diclofenac sodium release from solid mini-matrices.

The percentage contributions of Fickian diffusion (F) and Relaxation (R) over the first 60% of drug release for each of the three gums and HPMC are shown graphically in Figures 4.2a, b, c and d. In the case of xanthan gum and karaya gum, Fickian diffusion predominates for the first half of the dissolution period, gradually decreasing until polymer relaxation becomes predominant in the second half. During the dominant Fickian diffusion period, the thickness of the viscous gel layer around the matrix will increase with time creating a longer path length for the drug to diffuse into the external dissolution medium. Thereafter the polymer chains increasingly relax, disentangle and dissolve. It is noted that drug release due to relaxation takes over from the declining diffusional release mechanism about half way through the dissolution time period, thus facilitating an approach toward zero-order release. On the other hand, with locust bean gum and HPMC the contribution of Fickian diffusion (F) is relatively small whilst release due to Relaxation (R) is dominant for the entire dissolution time period. These findings are consistent with the calculated n values (Table 4.3) and with the erosion and swelling studies reported in Chapter 5.

Table 4.3. Release parameters from the encapsulated mini-matrices using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). Mean dissolution time (min) was calculated from Equation 1.6. The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values±SD, n=3).

Mini-matrices Composition*	Release exponent (n)	Kinetic constant (k) $(min^{-n})\times10^{-3}$	Correlation coefficient (r)	$t_{50\%}$ value (min)	Mean dissolution time (min)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X 1:1	0.703±0.017	9.27±1.63	0.988	280	329±60	3.53±0.34	0.994
D:LB 1:1	0.777±0.092	10.21±4.44	0.994	165	180±36	5.10±0.52	0.997
D:K 1:1	0.731±0.009	4.70±0.62	0.991	630	655±120	2.46±0.30	0.997
D:HPMC 1:1	0.913±0.093	5.78±2.35	0.995	137	147±20	6.02±0.43	1.000
D:X 2:1	0.906±0.030	4.30±0.76	0.999	189	196±4	5.55±0.06	0.999
D:X 1:1	0.703±0.017	9.27±1.63	0.988	280	329±60	3.53±0.34	0.994
D:X 2:3	0.705±0.021	6.92±0.67	0.988	423	483±36	2.87±0.14	0.995
D:X 1:2	0.671±0.035	7.91±1.57	0.990	480	558±20	2.63±0.09	0.993

*D, Diclofenac sodium; X, Xanthan gum; LB, Locust bean gum; K, Karaya gum; HPMC, Hydroxypropyl methylcellulose.

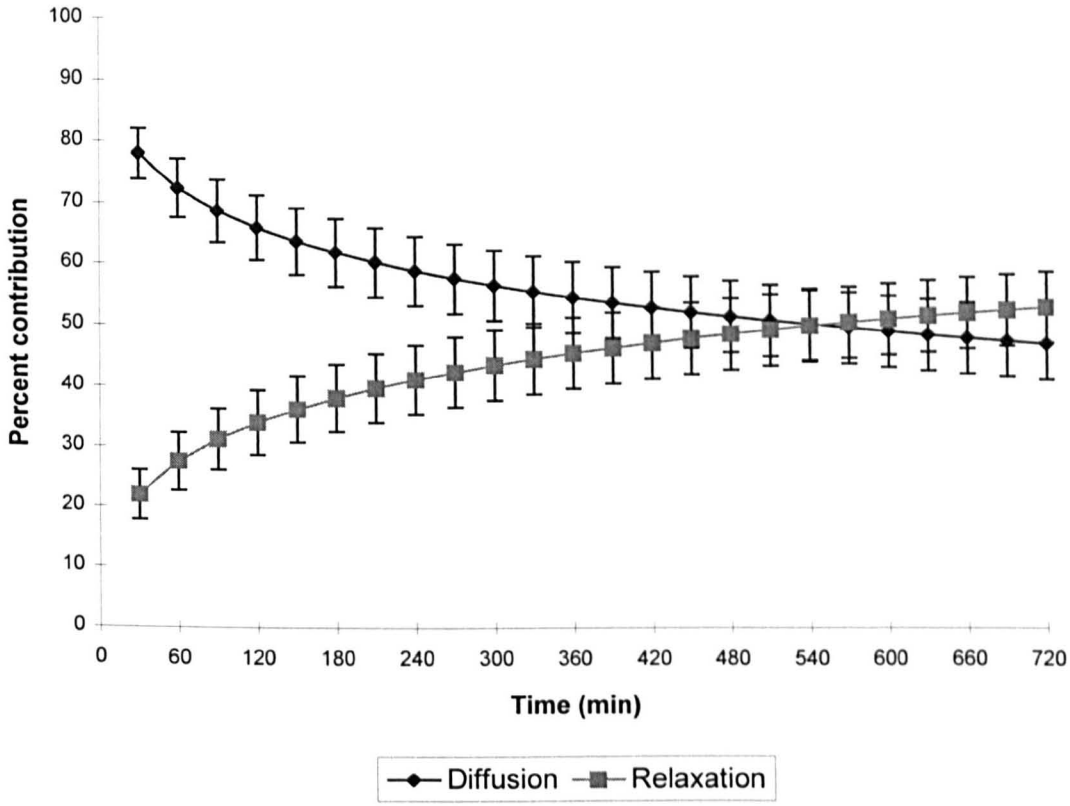


Figure 4.2a. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and xanthan gum (mean values±SD, n=3).

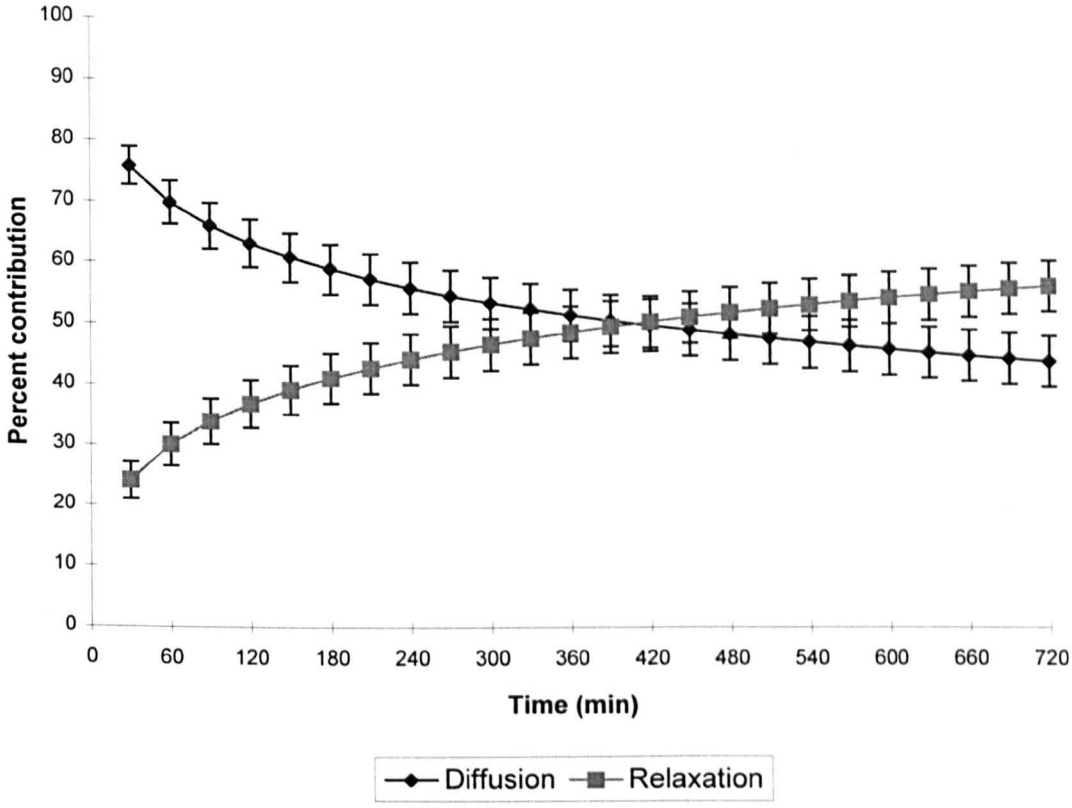


Figure 4.2b. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and karaya gum (mean values±SD, n=3).

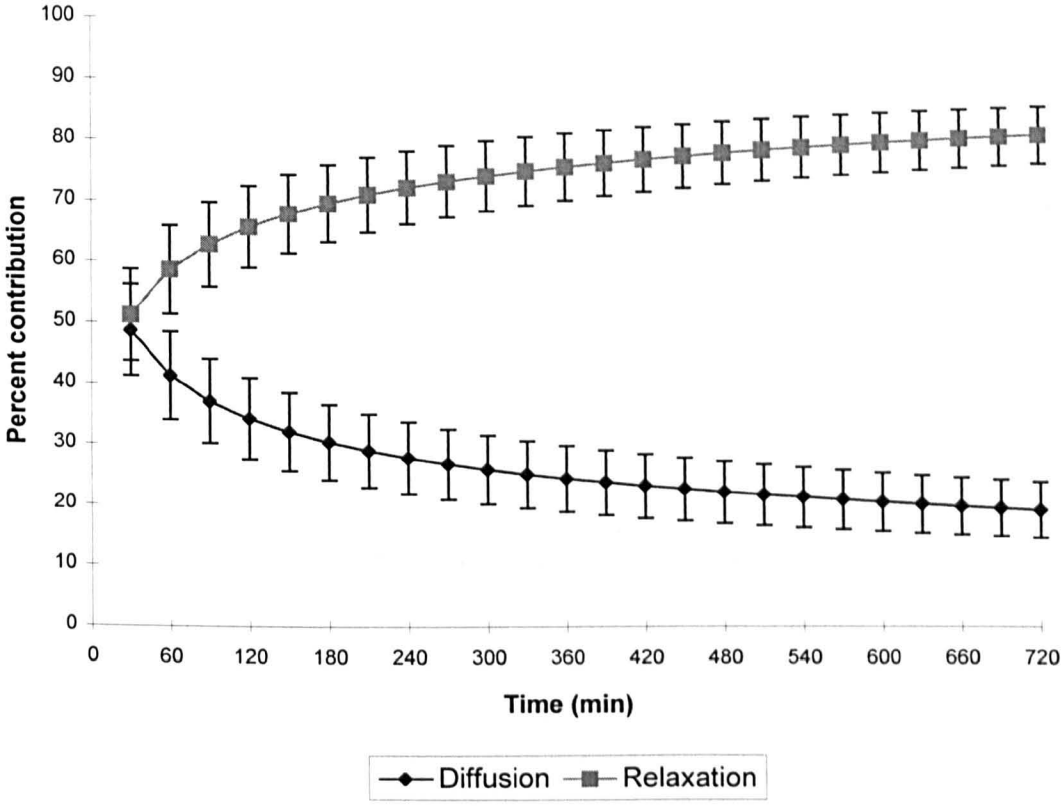


Figure 4.2c. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and locust bean gum (mean values±SD, n=3).

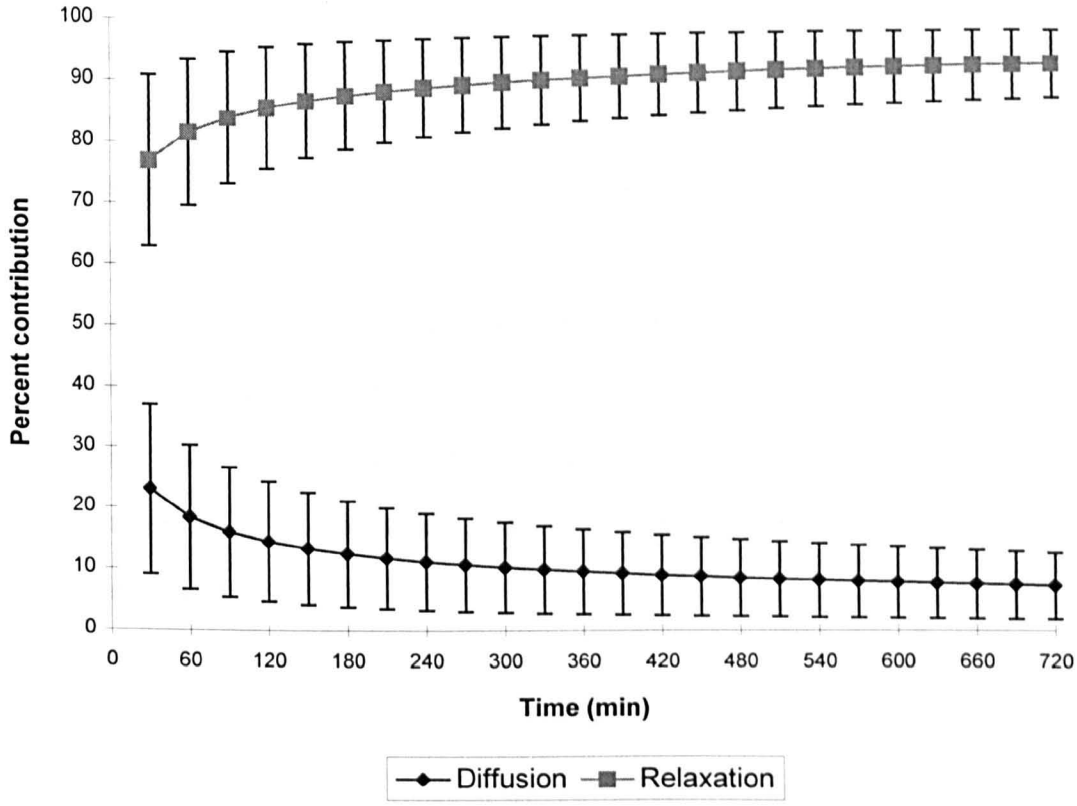


Figure 4.2d. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and HPMC (mean values±SD, n=3).

4.4.2 Effect of quantity of gum on release characteristics

Xanthan gum was selected for this study because approximately 50% of the drug was released after almost half of the dissolution time period. Drug: xanthan gum ratios of 2:1, 1:1, 2:3 and 1:2 were used with compositions as shown in Table 4.1 (Formulations 7,1,8 and 9 respectively). Figure 4.3 clearly shows that the drug release rate is greatly influenced by the diclofenac sodium: xanthan gum ratio of the matrix. As the proportion of xanthan gum increases, there is a progressive decline in the release rate. This can also be shown by plotting the release rates (% $min^{-½}$) for diclofenac sodium against the percentage of xanthan gum in each capsule (Figure 4.4). This

curve could be used to allow predictions of the release rate to be made for diclofenac sodium: xanthan gum ratios not experimentally determined provided that no drug/gum interactions are encountered which will complicate the calculations. Values for n and k (±SD; n=3) are shown in Table 4.3 and these also show anomalous (non-Fickian) release behaviour for drug: xanthan gum ratios of 1:1, 2:3 and 1:2. Although the drug release rate decreased with increasing gum content, the mechanism of release nevertheless remained the same. However, for drug: gum ratio of 2:1, the n value is 0.906 (Super Case II transport). This would be due to the greater drug concentration which would enhance the dissolution mechanism and compensate for the decrease in release due to gum swelling.

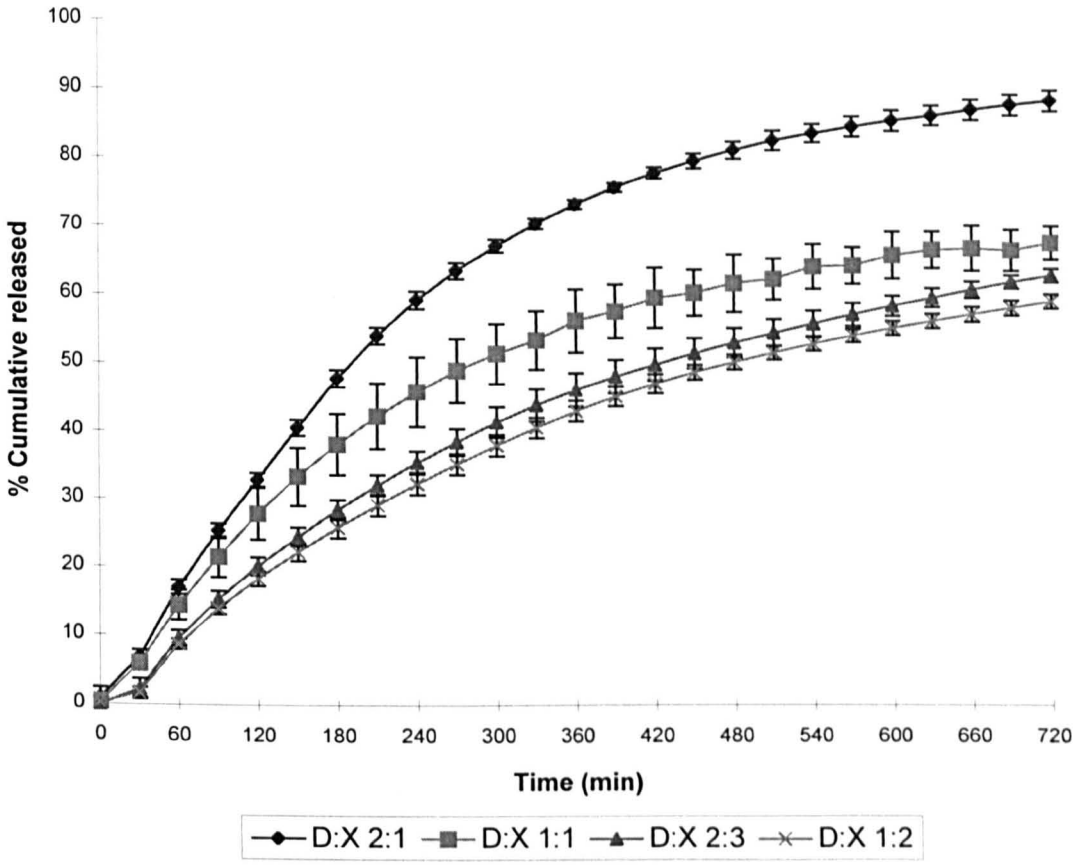


Figure 4.3. Percentage of diclofenac sodium released against time from 6 mini-matrices (4.5 mm diameter) containing diclofenac sodium (D) and xanthan gum (X) in various proportions enclosed in a hard gelatin capsule (mean values±SD, n=3).

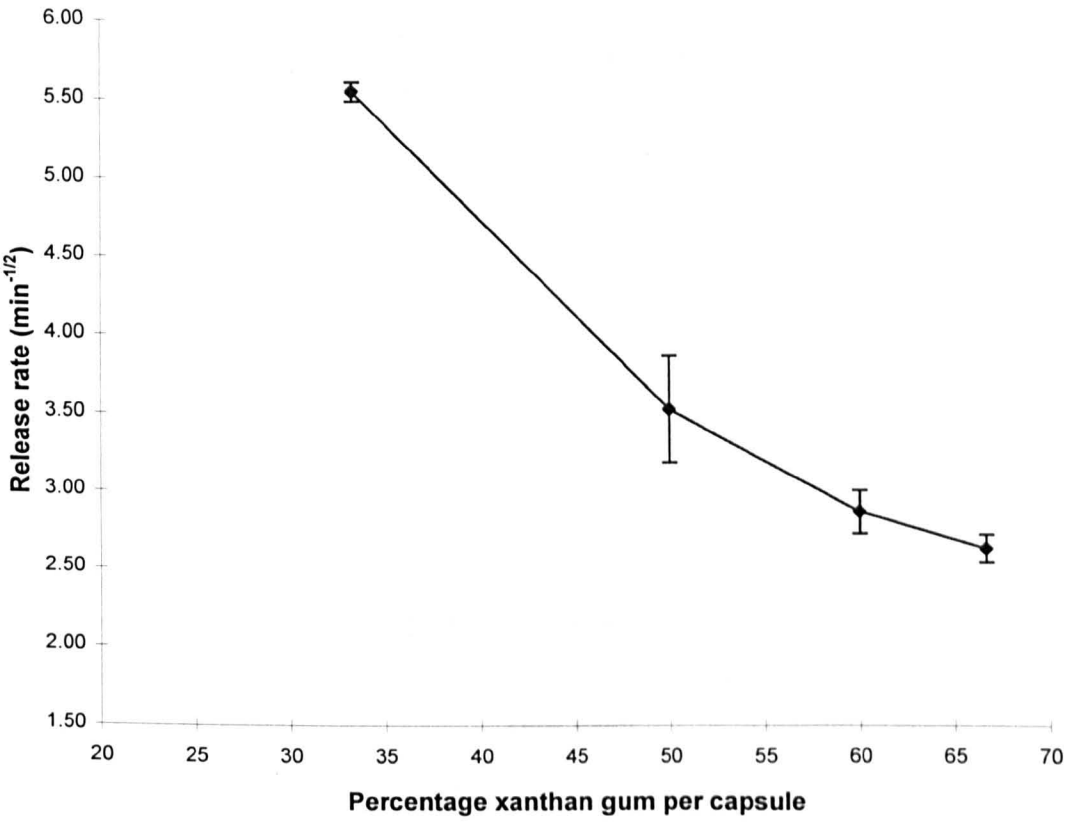


Figure 4.4. Relationship between release rate of diclofenac sodium (%$min^{-1/2}$) and the percentage of xanthan gum contained in each capsule (mean values±SD, n=3).

The percentage contributions of Fickian diffusion and Relaxation over the first 60% of drug release for diclofenac sodium and xanthan gum in the ratios of 2:1, 2:3 and 1.2 are shown graphically in Figures 4.5a, b and c. The Fickian diffusion contribution to the release process decreases as the proportion of xanthan gum decreases, with a corresponding increase in the Relaxation contribution as the drug content increases. This relationship is especially dramatic between the diclofenac sodium: xanthan gum 1:1 and 2:1 ratios. It can be concluded therefore that the xanthan gum is mainly responsible for the Fickian diffusion mechanism, whereas the drug contributes mainly to the dissolution or erosion mechanism.

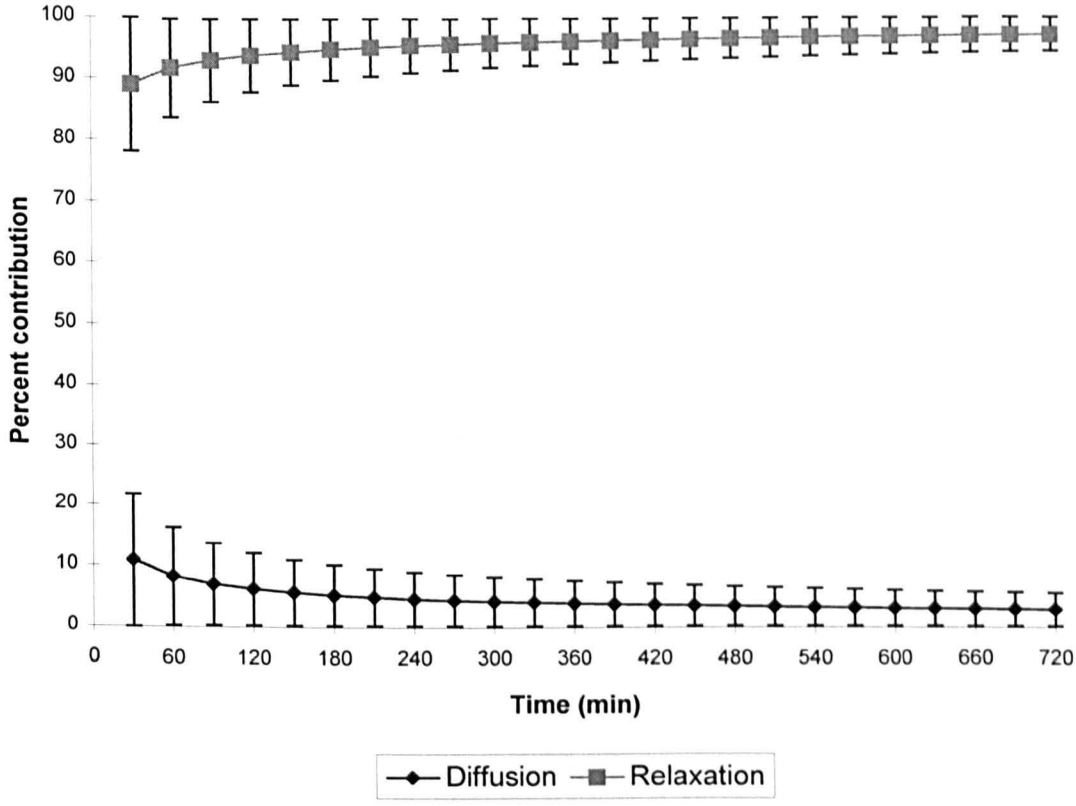


Figure 4.5a. The percentage contributions of the Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and xanthan gum in the ratio of 2:1 (mean values±SD, n=3).

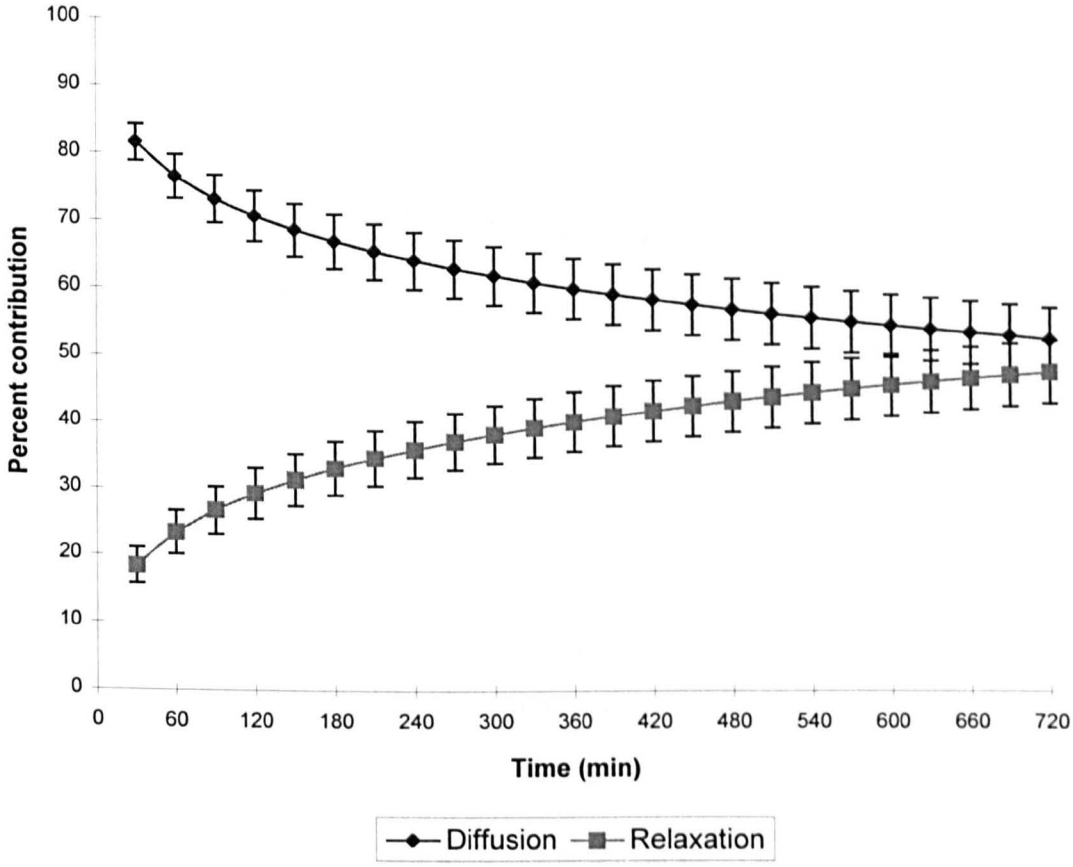


Figure 4.5b. The percentage contributions of the Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and xanthan gum in the ratio of 2:3 (mean values±SD, n=3).

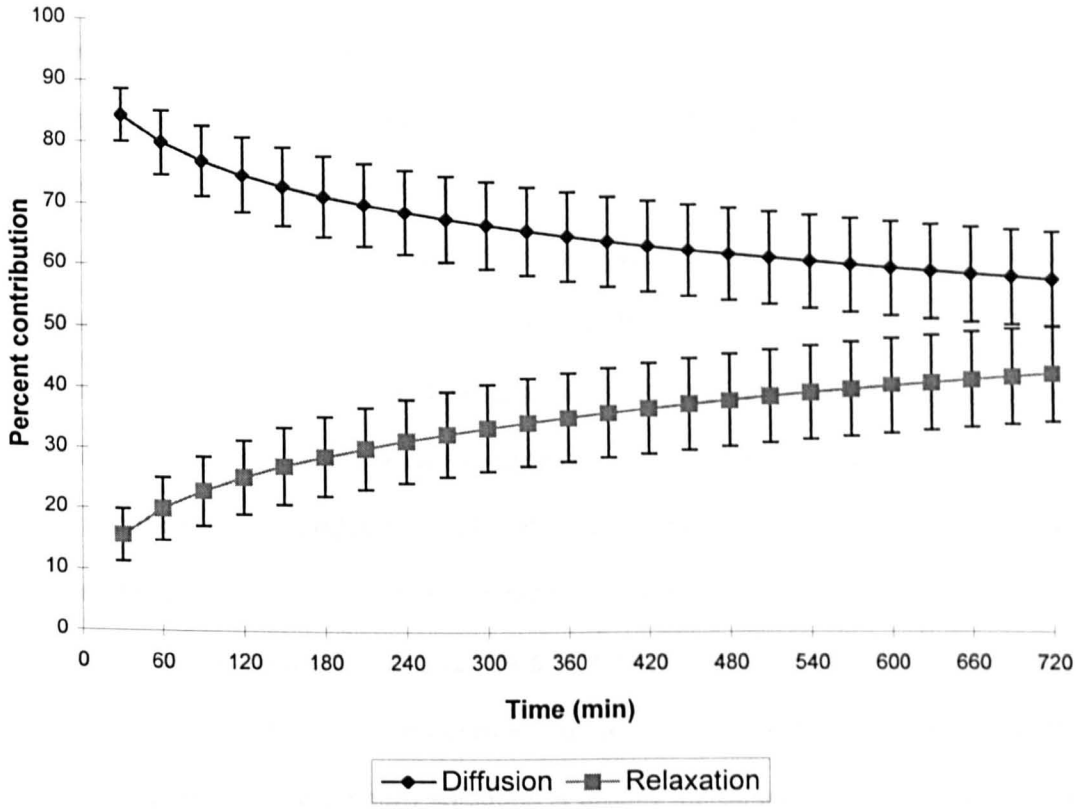


Figure 4.5c. The percentage contributions of the Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing diclofenac sodium and xanthan gum in the ratio of 1:2 (mean values±SD, n=3).

4.4.3 Effect of excipients on release characteristics

4.4.3.1 Rational for selection of excipients

Lactose (freely water-soluble), dicalcium phosphate (Encompress®, water-insoluble), cellulose acetate phthalate (CAP; soluble in USP buffer solutions pH ≥ 6.2) and magnesium aluminium silicate (Veegum F®; practically insoluble in water, but swells to form a colloidal dispersion) were used as excipients in various proportions. Lactose and Encompress® are commonly used as diluents in tablet formulations.

Having opposite solubility characteristics, it is reasonable to expect that lactose and Encompress® would exhibit significant differences in drug release from hydrated gum matrices. It has been reported that lactose produced increased release rates of various drugs from polymeric matrices (Marín Boscá et al. 1995; Talukdar and Kinget 1995). Lactose diffuses outwards through the gel layer, increasing the porosity and decreasing the tortuosity of the diffusion path of drug. On the other hand, Encompress® forms a porous, insoluble and nonswellable matrix which has been used to control the release of some water-soluble drugs (Mulye and Turco 1994). Cellulose acetate phthalate was blended with gum in order to maintain the integrity of the mini-matrix in the acid contents of the stomach. On reaching the intestine (pH>6), the cellulose acetate phthalate would dissolve and then possibly act in a similar manner to lactose in regulating the drug release rate. Furthermore, it has been reported that the viscosity of aqueous xanthan gum solutions is greatly increased, or gelation occurs, by combination with Veegum F® due to synergistic effects (Kovacs 1973). Veegum F® was therefore combined with xanthan gum to investigate whether such synergism would produce any significant effect on drug release from the solid mini-matrices.

The dissolution studies were carried out on Formulations 10A-D - 14A-D (Table 4.2) and consisted of six mini-matrices (4.5 mm diameter, 30.2±1.1 mg weight) enclosed in a hard gelatin capsule.

4.4.3.2 Effect of excipients on release characteristics

In spite of the widely varying physico-chemical characteristics of the excipients, the drug dissolution profiles displayed similar tendencies. The drug release rate increased with increasing proportions of excipient (corresponding decrease in xanthan gum content) irrespective of the solubility characteristics of the excipient. The release profiles of diclofenac sodium, xanthan gum and various excipients; lactose,

Encompress®, CAP and Veegum®, at different ratios are shown in Figures 4.6-4.9 respectively. The values for release exponent (n), kinetic constant (k), $t_{50\%}$ and release rate together with the correlation coefficient (r) of these mini-matrices are shown in Tables 4.4 - 4.7. The release exponent for some formulations containing drug, xanthan gum and excipients in the ratio of 3:1:2 and 3:0.5:2.5 are not shown because there were insufficient data points on the release profiles between 10 and 60% release to provide accurate values. The tabulated data show that the release mechanism changes from anomalous (non-Fickian) transport ($0.45<n<0.89$) to Case II transport ($n=0.89$) and Super Case II transport ($n>0.89$) when xanthan gum was increasingly substituted with excipients. It is evident that dissolution or erosion of the excipient would account for the increasing values of n as the excipient content increased. The $t_{50\%}$ values for mini-matrices containing Veegum F®/xanthan gum and cellulose acetate phthalate/xanthan gum mixtures were on average 10-15% longer than those containing lactose and Encompress® as excipients (Tables 4.4-4.7). These relatively small differences in $t_{50\%}$ values suggest that the nature of the excipient used appeared to play a minor role in regulating release, while the xanthan gum content was the dominating factor. A lower gum content would result in reduced swelling with corresponding decrease in diffusional path length. Moreover the excipients would enhance either the dissolution or erosion mechanism, depending on the solubility of the excipient, which compensates for the slowing diffusion rate through the gradually increasing gel layer by creating greater porosity for the drug pathway.

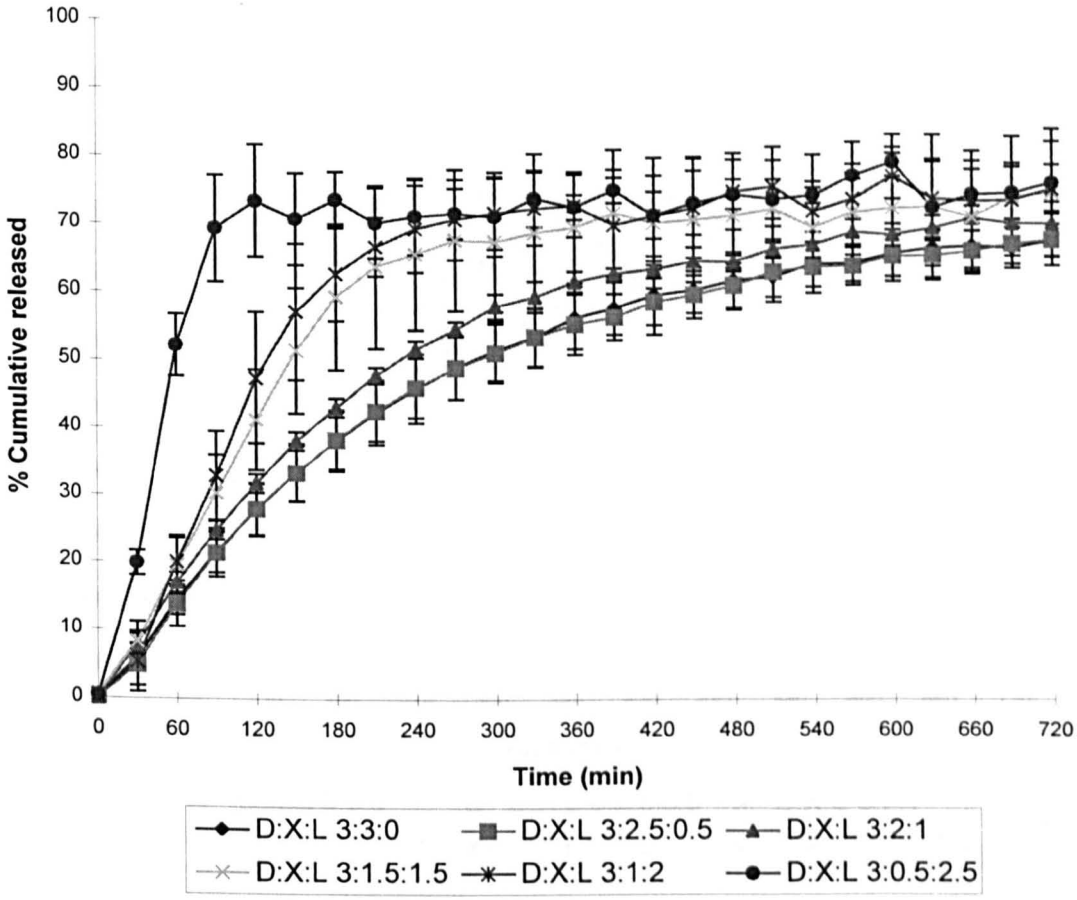


Figure 4.6. Percentage of diclofenac sodium release against time from 6 mini-matrices containing diclofenac sodium (D), xanthan gum (X) and lactose (L) enclosed in a hard gelatin capsule (mean values±SD, n=3). Each mini-matrix contains 15 mg of diclofenac sodium and variable ratio of xanthan gum and lactose.

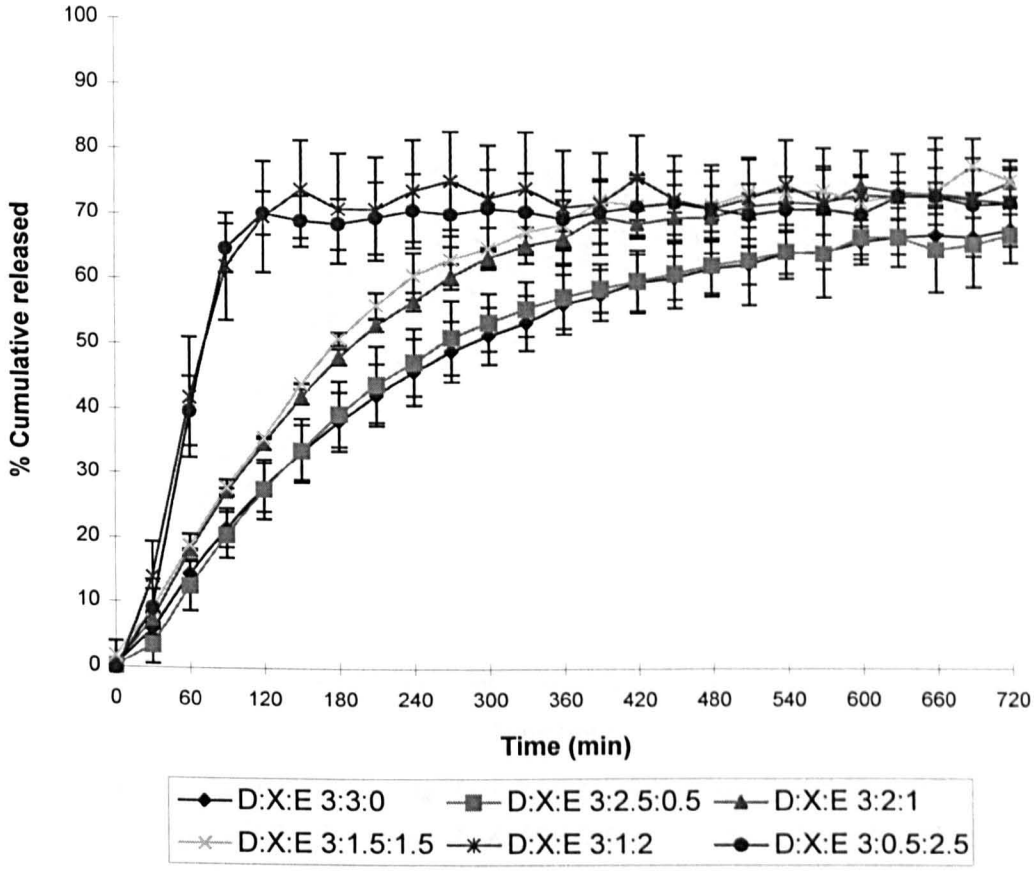


Figure 4.7. Percentage of diclofenac sodium release against time from 6 mini-matrices containing diclofenac sodium (D), xanthan gum (X) and Encompress® (E) enclosed in a hard gelatin capsule (mean values±SD, n=3). Each mini-matrix contains 15 mg of diclofenac sodium and variable ratio of xanthan gum and Encompress®.

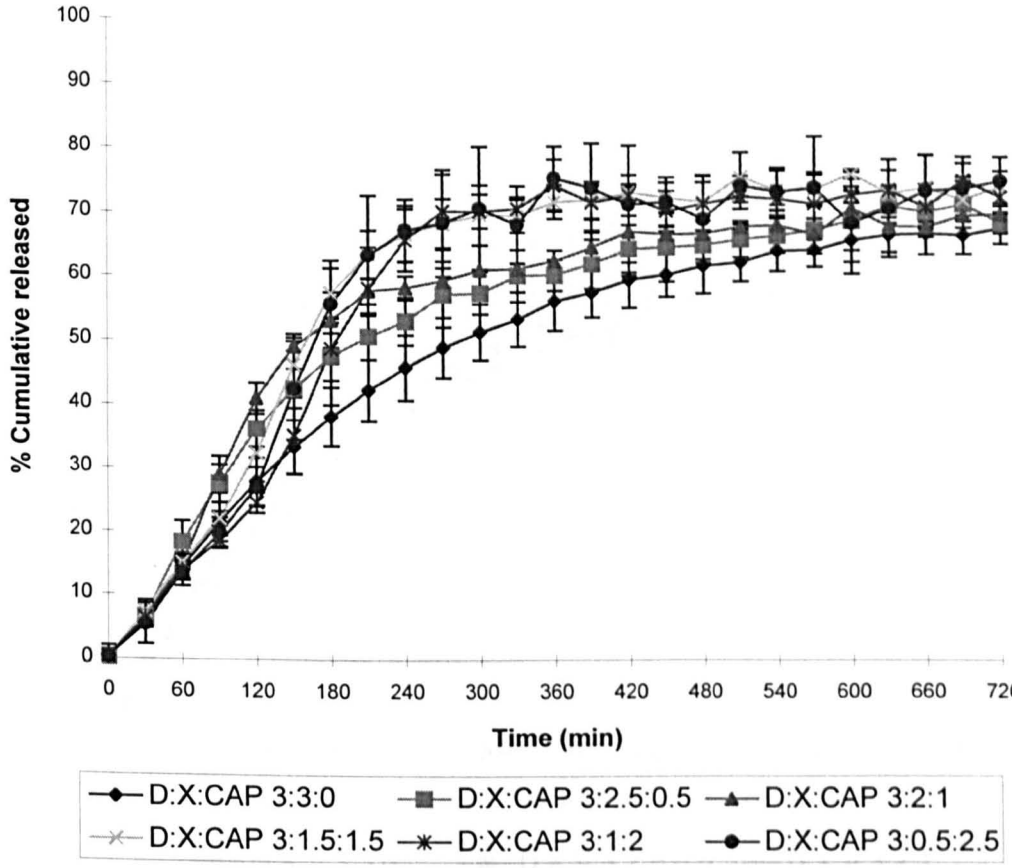


Figure 4.8. Percentage of diclofenac sodium release against time from 6 mini-matrices containing diclofenac sodium (D), xanthan gum (X) and cellulose acetate phthalate (CAP) enclosed in a hard gelatin capsule (mean values±SD, n=3). Each mini-matrix contains 15 mg of diclofenac sodium and variable ratio of xanthan gum and CAP.

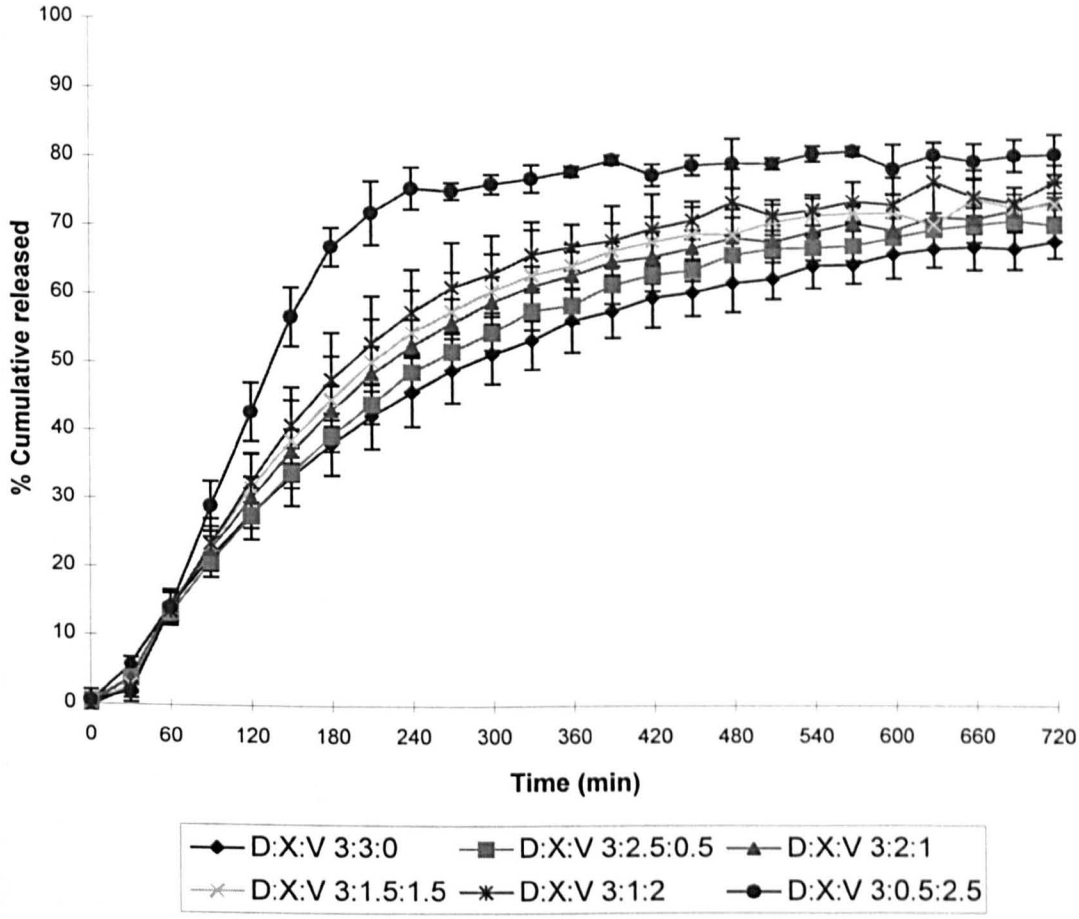


Figure 4.9. Percentage of diclofenac sodium release against time from 6 mini-matrices containing diclofenac sodium (D), xanthan gum (X) and Veegum F® (V) enclosed in a hard gelatin capsule (mean values±SD, n=3). Each mini-matrix contains 15 mg of diclofenac sodium and variable ratio of xanthan gum and Veegum F®.

Table 4.4. Release parameters from the encapsulated mini-matrices (4.5 mm diameter) containing diclofenac sodium (D), xanthan gum (X) and lactose (L) using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values±SD, n=3).

Mini-matrices composition	Release exponent (n)	Kinetic constant (k) (min^{-n}) $\times 10^{-3}$	Correlation coefficient (r)	$t_{50\%}$ value (min)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X:L 3:3:0	0.703±0.017	9.27±1.63	0.988	280	3.53±0.34	0.994
D:X:L 3:2.5:0.5	0.695±0.048	9.78±2.81	0.983	280	3.44±0.43	0.991
D:X:L 3:2:1	0.727±0.047	9.66±2.52	0.991	229	4.15±0.18	0.995
D:X:L 3:1.5:1.5	0.985±0.136	3.83±1.89	0.991	145	6.85±0.78	0.993
D:X:L 3:1:2	1.123±0.216	3.06±3.29	0.989	127	8.74±1.60	0.996
D:X:L 3:0.5:2.5	-	-	-	57	-	-

Table 4.5. Release parameters from the encapsulated mini-matrices (4.5 mm diameter) containing diclofenac sodium (D), xanthan gum (X) and Emcompress® (E) using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values±SD, n=3).

Mini-matrices composition	Release exponent (n)	Kinetic constant (k) (min^{-n}) $\times 10^{-3}$	Correlation coefficient (r)	$t_{50\%}$ value (min)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X:E 3:3:0	0.703±0.017	9.27±1.63	0.988	280	3.53±0.34	0.994
D:X:E 3:2.5:0.5	0.727±0.044	8.25±0.90	0.980	261	3.67±0.62	0.985
D:X:E 3:2:1	0.795±0.036	7.75±1.66	0.995	190	5.01±0.17	0.998
D:X:E 3:1.5:1.5	0.887±0.104	5.41±2.57	0.998	174	5.36±0.76	0.998
D:X:E 3:1:2	1.122±0.180	4.19±2.91	0.978	72	-	-
D:X:E 3:0.5:2.5	-	-	-	72	-	-

Table 4.6. Release parameters from the encapsulated mini-matrices (4.5 mm diameter) containing diclofenac sodium (D), xanthan gum (X) and cellulose acetate phthalate (CAP) using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values±SD, n=3).

Mini-matrices composition	Release exponent (n)	Kinetic constant (k) (min^{-n}) $\times 10^{-3}$	Correlation coefficient (r)	$t_{50\%}$ value (min)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X:CAP 3:3:0	0.703±0.017	9.27±1.63	0.988	280	3.53±0.34	0.994
D:X:CAP 3:2.5:0.5	0.745±0.099	9.76±4.30	0.976	204	4.14±1.34	0.984
D:X:CAP 3:2:1	0.839±0.064	6.35±1.85	0.940	156	5.85±0.91	0.977
D:X:CAP 3:1.5:1.5	1.199±0.121	1.28±0.94	0.991	160	7.27±0.82	0.975
D:X:CAP 3:1:2	1.181±0.093	1.04±0.36	0.979	184	6.75±0.71	0.959
D:X:CAP 3:0.5:2.5	1.240±0.120	0.85±0.34	0.983	167	-	-

Table 4.7. Release parameters from the encapsulated mini-matrices (4.5 mm diameter) containing diclofenac sodium (D), xanthan gum (X) and Veegum F® (V) using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values±SD, n=3).

Mini-matrices composition	Release exponent (n)	Kinetic constant (k) (min^{-n}) $\times 10^{-3}$	Correlation coefficient (r)	$t_{50\%}$ value (min)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X:V 3:3:0	0.703±0.017	9.27±1.63	0.988	280	3.53±0.34	0.994
D:X:V 3:2.5:0.5	0.816±0.041	5.45±0.82	0.989	250	4.22±0.38	0.995
D:X:V 3:2:1	0.861±0.066	4.85±1.90	0.991	219	4.74±0.40	0.997
D:X:V 3:1.5:1.5	0.930±0.076	3.51±1.04	0.989	208	5.12±0.90	0.997
D:X:V 3:1:2	1.016±0.130	2.59±1.09	0.990	193	5.82±1.20	0.998
D:X:V 3:0.5:2.5	-	-	-	134	9.35±0.49	0.999

The plots of release rate (% $min^{-½}$) versus the percentage of excipients; lactose, Encompress®, CAP and Veegum F®, contained in the mini-matrices are shown in Figure 4.10. It is seen from this graph that there is a linear increase in release rate until the percentage of Veegum F® reaches about 33%. Higher percentages of Veegum F® result in a sudden marked increase in release rate. The percentage of lactose in the range of 0-17% only slightly affected the release rate of diclofenac sodium from the mini-matrices. Higher concentration of lactose resulted in a greater increased release rate until about 33% lactose. At higher concentration than 33%, the release of diclofenac sodium from the mini-matrices was very fast, hence the accurate release rate cannot be provided as mentioned earlier. Encompress® and CAP also showed a linear increase in release rate with percentage increase in Encompress® and CAP until the percentage of them were about 25%. The release rate seemed to be constant at the percentage of CAP from 25 to 33%. At higher concentration than 25% for Encompress®, and 33% for CAP the release rates of the drug from the mini-matrices were too fast to obtain an accurate release rate. These results indicated that the added excipients similarly affected the release rates of diclofenac sodium from mini-matrices but to different extents. There is an amount which each excipient must not exceed in order to maintain the sustaining performance of the mini-matrices. These plots (Figure 4.10) can be used to predict release rates for amounts of excipient not experimentally determined. From these results there is no evidence to show that the synergistic viscosity effects between Veegum F® and xanthan gum had any noticeable affect on the rate of drug release from solid mini-matrices.

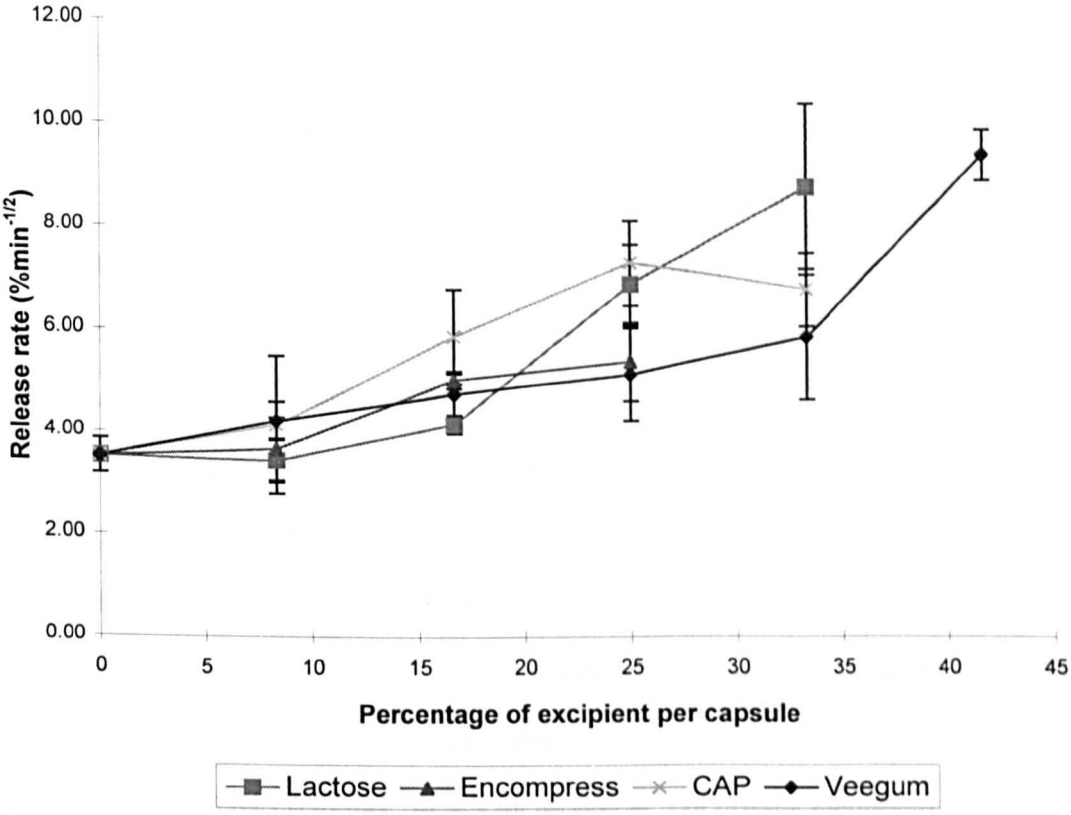


Figure 4.10. Relationship between release rate of diclofenac sodium ($\%min^{-1/2}$) and the percentage of excipients; lactose, Encompress®, CAP and Veegum F®, contained in each capsule (mean values±SD, n=3).

4.4.4 Effect of dissolution medium on release characteristics

The dissolution profiles of diclofenac sodium mini-matrices (Formulations 1 and 2, Table 4.1) encapsulated in hard gelatin capsules were carried out in 0.1 M HCl pH 1.5; in order to simulate the pH of the stomach. The amount of diclofenac sodium released was very little (<1% after 10 hours). Negligible swelling of the mini-matrices were observed after 10 hours contact with 0.1 M HCl pH 1.5. Since the swelling is not evident, it was expected that the drug release should be very rapid due to the short diffusional path length. However, the pH solubility profile carried out on diclofenac sodium showed that diclofenac sodium was practically insoluble in the dissolution

medium at pH ≤ 2 (3.8 mg/l) and at pH 5 the drug was still practically insoluble (43.8 mg/l). It is reasonable to say that the dissolution medium has an influence on the solubility of the drug consequently affecting the release profile of the mini-matrices. Since the solubility of the drug in the acid gastric fluid would be so poor it is doubtful whether there is a need to enteric coat oral sustained release dosage forms of diclofenac sodium (which are based on the matrix principle) to protect the gastric membrane from its irritant effects.

The release profiles of commercial sustained-release diclofenac sodium products; Diclomax® and Motifene®, in citrate-phosphate buffer pH 3, 4, 5 and 5.5, and 0.05 M phosphate buffer pH 6, 6.5, 7, 7.4 and 8 are shown in Figures 4.11a and b respectively. The release of diclofenac sodium from these two products depended greatly on the dissolution medium pH. The amount of drug released is very small (<20%) at pH ≤ 5.5 for Diclomax® or ≤ 5 for Motifene® but greatly increased at pH > 5.5 or >5 for these two products respectively. The release profiles at pH ≥ 7 for Diclomax® and ≥ 6.5 for Motifene® were very similar. This implied that there was a certain solubility of diclofenac sodium in phosphate buffer. These profiles were consistent with the pH solubility profile of diclofenac sodium which was practically insoluble at pH<5.2, solubility gradually increased from pH 5.2 to 6.5, greatly increased at pH 6.5 to 7.8 after which the solubility remained the same.

It is noticeable that, in the dissolution medium pH 7.0, 90% of diclofenac sodium released from Diclomax® within 120 minutes and from Motifene® within 90 minutes. These release rates were much faster than the release rates of mini-matrices containing xanthan gum, karaya gum or locust bean gum (Figure 4.1).

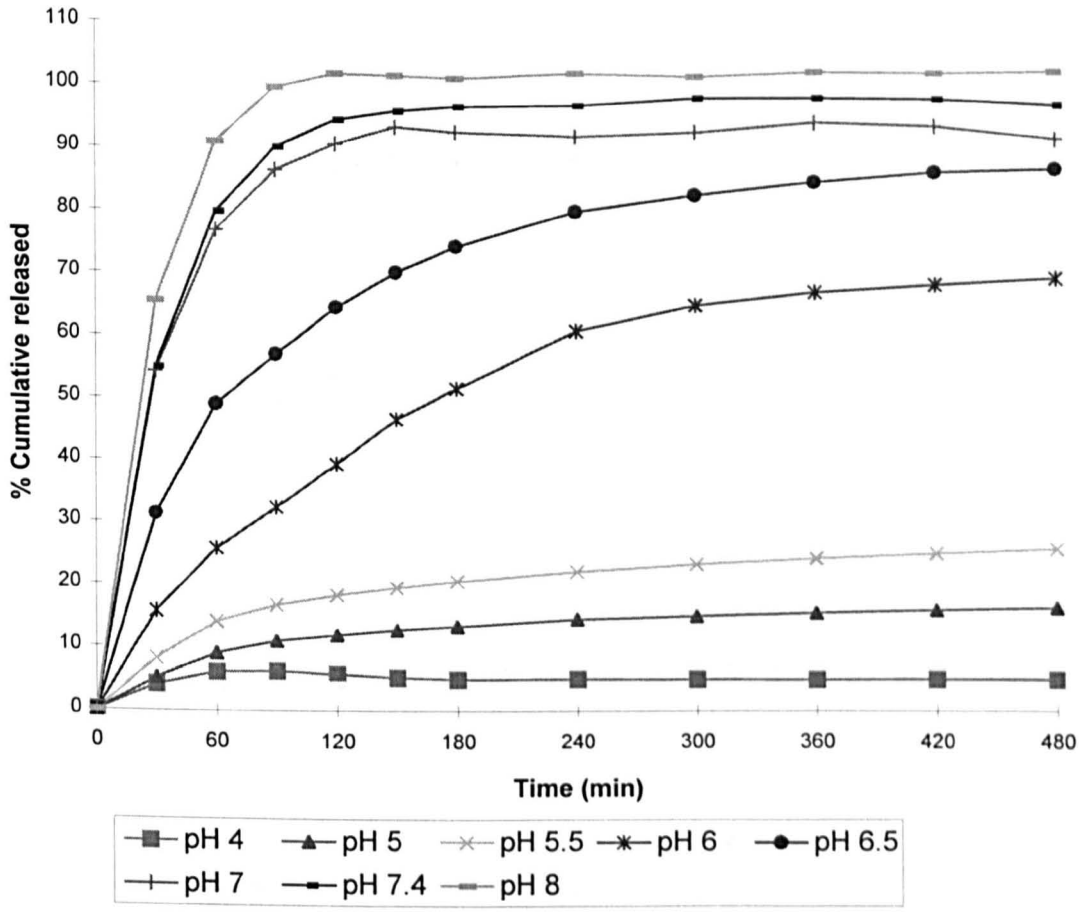


Figure 4.11a. Percentage of diclofenac sodium release against time from Diclomax Retard® in various dissolution medium.

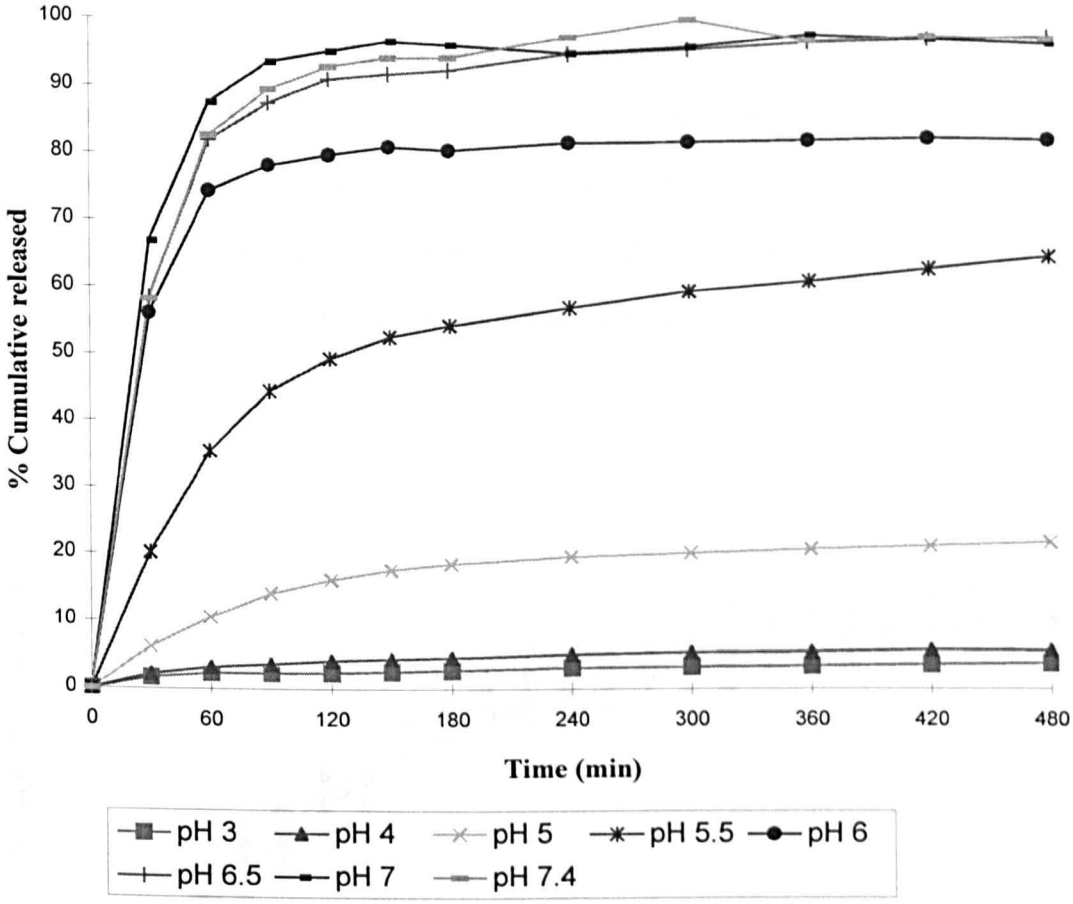


Figure 4.11b. Percentage of diclofenac sodium release against time from Motifene® in various dissolution medium.

4.4.5 Effect of stirring speed on release characteristics

The release profiles of mini-matrices containing diclofenac sodium and xanthan, karaya, locust bean and carrageenan gums in the ratio of 1:1 were monitored in 0.05 M phosphate buffer pH 7.0 at stirring speeds of 50, 100 and 150 rpm. The release profiles showed that the release of diclofenac sodium was only slightly increased (<10%) when the stirring speed increased from 50 to 150 rpm (Figures 4.12a-d). When the stirring speed increased, the increased hydrodynamic flow would have the potential to increase the erosion or dissolution of the mini-matrix material and

consequently produce faster drug release. If erosion is the sole factor controlling the release of the drug, increasing the stirring speed of the basket should have a great effect on the release rate. The result implied that erosion is not the only factor controlling the release of the drug from mini-matrices. This lends support to the previous findings which demonstrated that both diffusion and erosion play a part in drug release (n values indicate anomalous mechanisms).

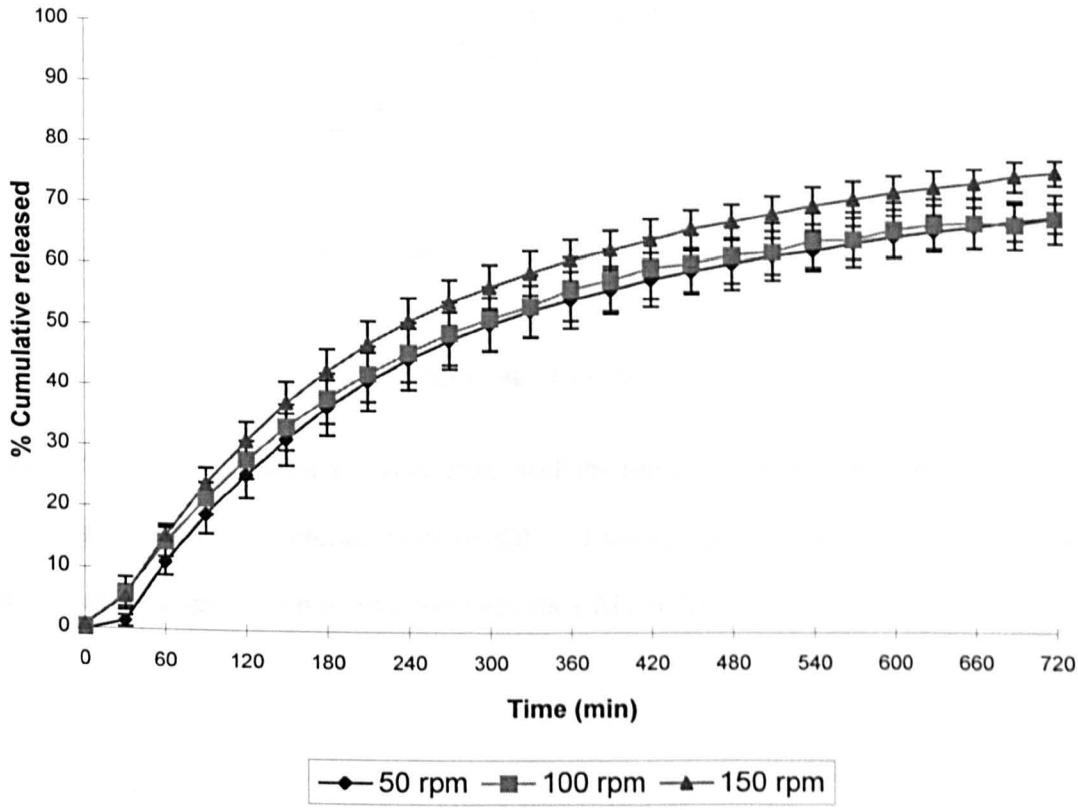


Figure 4.12a. Percentage of diclofenac sodium release against time from six mini-matrices containing diclofenac sodium (D) and xanthan gum (X) in the ratio of 1:1 at various stirring speed of basket (mean values ± SD, n=3).

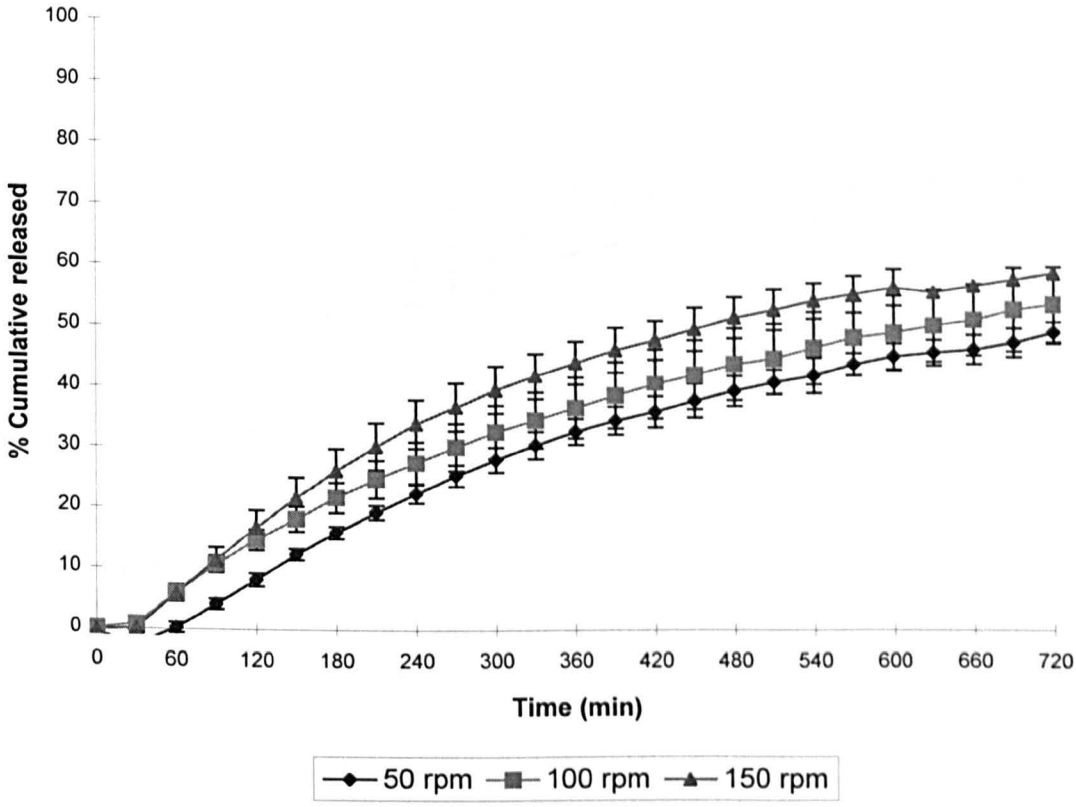


Figure 4.12b. Percentage of diclofenac sodium release against time from six mini-matrices containing diclofenac sodium (D) and karaya gum (K) in the ratio of 1:1 at various stirring speed of basket (mean values ± SD, n=3).

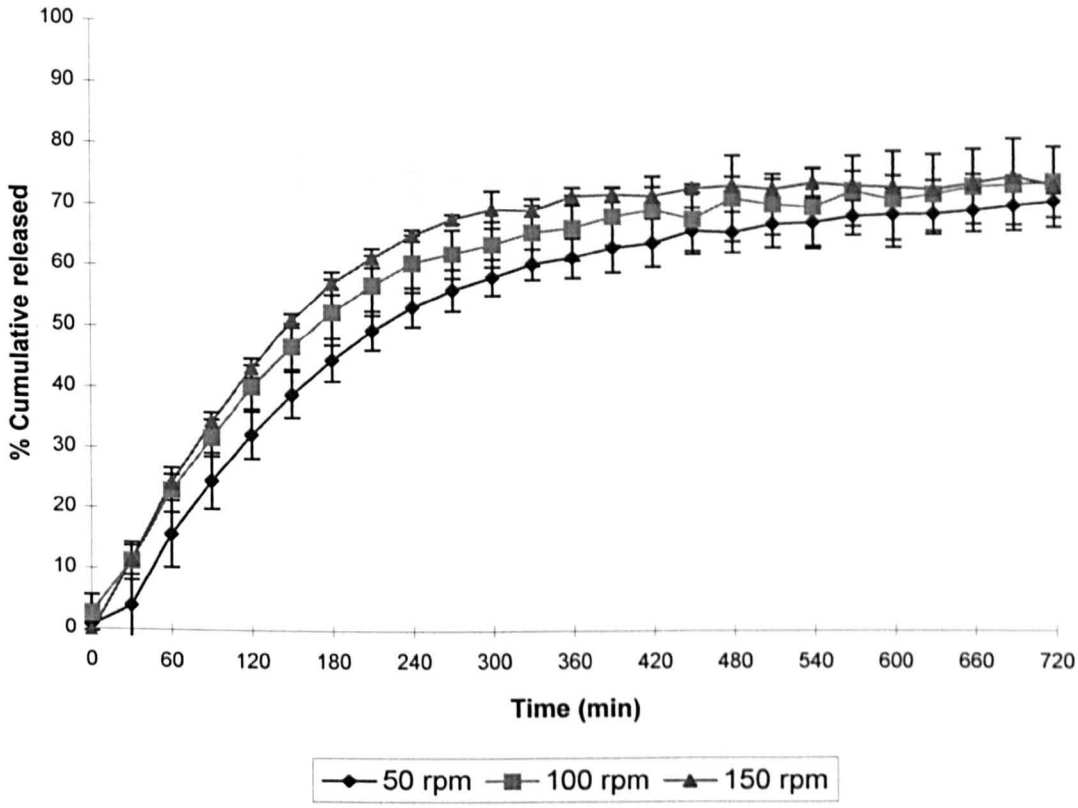


Figure 4.12c. Percentage of diclofenac sodium release against time from six mini-matrices containing diclofenac sodium (D) and locust bean gum (LB) in the ratio of 1:1 at various stirring speed of basket (mean values ± SD, n=3).

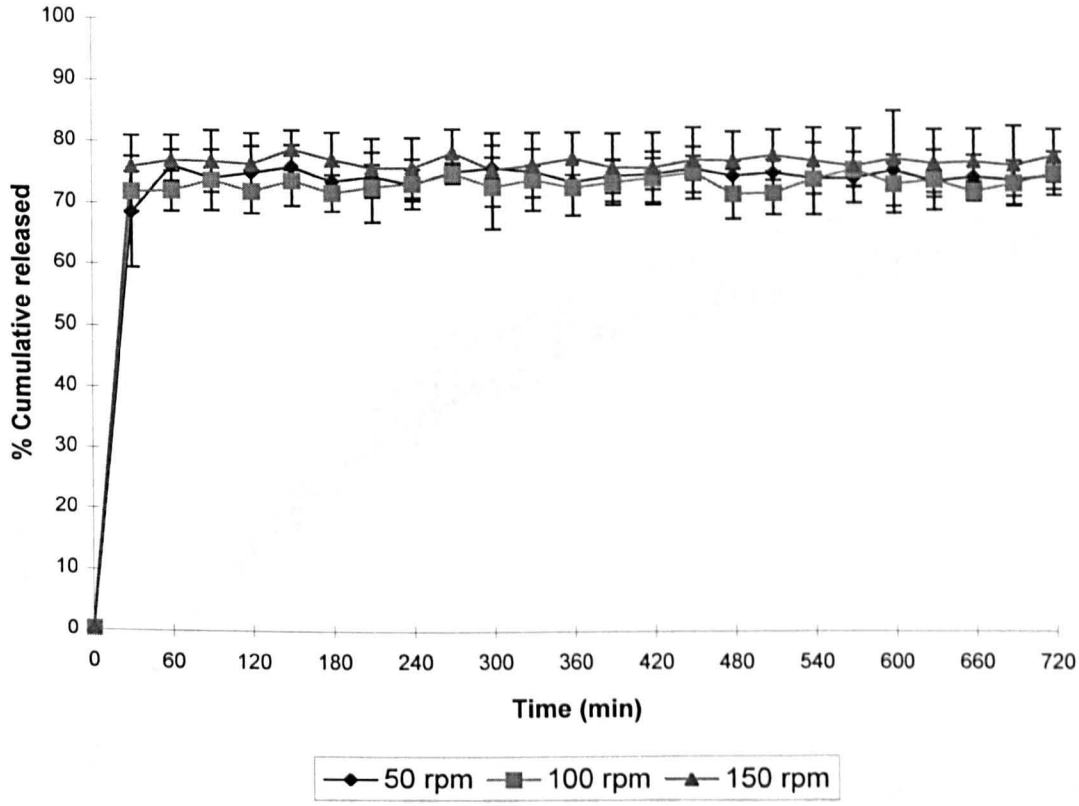


Figure 4.12d. Percentage of diclofenac sodium release against time from six mini-matrices containing diclofenac sodium (D) and carrageenan gum (C) in the ratio of 1:1 at various stirring speed of basket (mean values ± SD, n=3).

4.4.6 Effect of tablet volume on release characteristics

In order to establish the effect of matrix volume on drug release rate, mini-matrices of diameters 3, 4.5, and 5.5 mm were produced with the same composition (drug: xanthan gum ratio 1:1). The calculated volumes of the 3, 4.5 and 5.5 mm mini-matrices were 15.1, 22.35 and 31.12 mm^3 respectively. Dissolution studies were carried out on a single mini-matrix of each volume and the profiles show that more than 90% of drug was released (Figure 4.13). There was < 10% difference in the average cumulative release between the smallest and largest volume matrices after 10 hours. Compared with the substantial differences in volume, the differences in

cumulative release are relatively small and provide evidence that gum concentration is the main retarding factor.

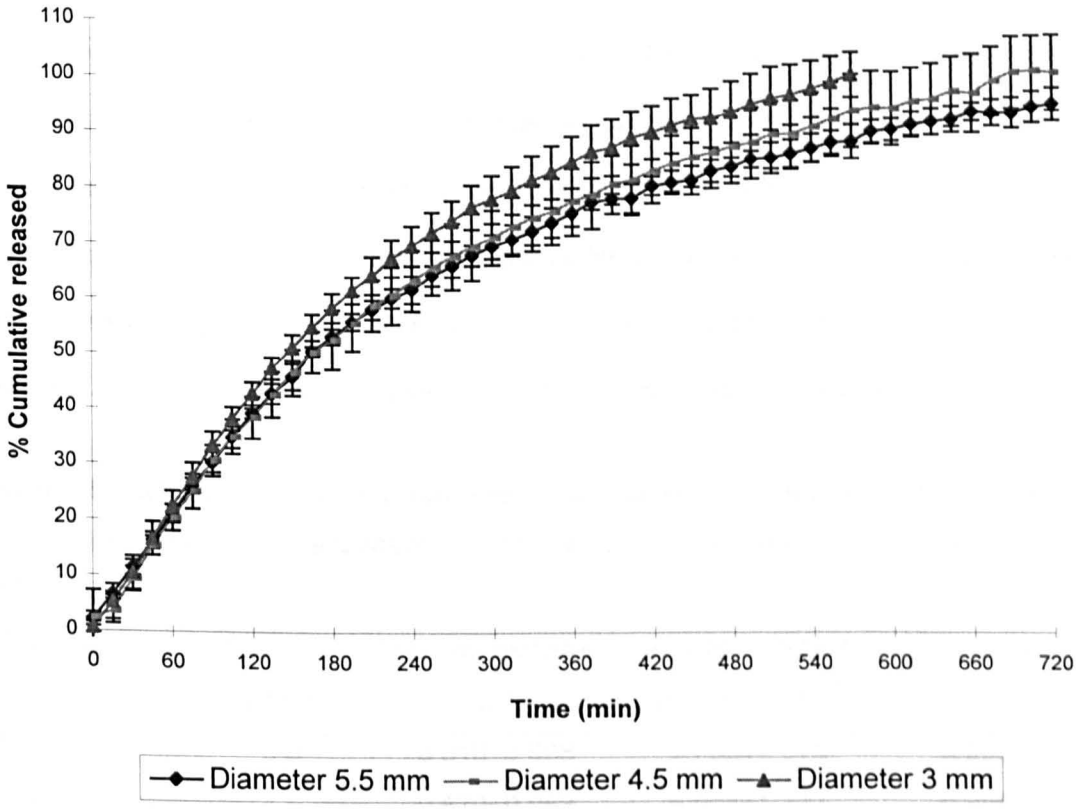


Figure 4.13. Percentage of diclofenac sodium released against time from single mini-matrices of varying diameter containing diclofenac sodium (D) and xanthan gum (X) in the ratio of 1:1 (mean values±SD, n=3).

The release exponents (n values) calculated from the first 60% of drug released from the **individual** mini-matrices were 0.910, 0.870 and 0.825 for the 3, 4.5 and 5.5 mm diameters respectively (Table 4.8). Phenomenologically therefore the single mini-matrices behave as near Case II and Super Case II transport regardless of the specific molecular mechanisms of drug transport. The larger surface area to volume ratio of the individual mini-matrices provides a suitable balance between swelling and dissolution of the matrix to achieve Case II transport. As noted earlier, the

maximum release after 12 hours from six encapsulated mini-matrices contained in the dissolution basket was lower (71%) than that from individual mini-matrices (>90%). This is probably due to the fact that in the former case the mini-matrices are confined to the area of the base of the basket (±3.14 cm^2). These matrices tend to aggregate forming a gel-like mass which is much larger in volume than an individual mini-matrix. Therefore complete release of the drug from the centre of the collective gel is very slow. The surface area to volume ratio is smaller and dissolution is suppressed. The main release mechanism through this larger swollen gel is diffusion, while dissolution is reduced. Hence the release mechanism tends towards Case I (Fickian) transport.

Table 4.8. Release parameters from the encapsulated mini-matrices using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k) (mean values±SD, n=3).

Mini-matrices Composition*	Diameter (mm)	Release exponent (n)	Kinetic constant (k) $(min^{-n})\times10^{-3}$	Correlation coefficient (r)
D:X 1:1	3.0	0.910±0.068	5.755±2.375	0.997
D:X 1:1	4.5	0.870±0.053	5.917±1.133	0.996
D:X 1:1	5.5	0.825±0.022	7.344±1.066	0.998

*D, Diclofenac sodium; X, Xanthan gum.

4.5 CONCLUSION

Diclofenac sodium sustained-release mini-matrices can be produced from xanthan gum, karaya gum, locust bean gum and HPMC while carrageenan gum does not produce sufficient sustained release. The degree of sustaining the release of diclofenac sodium is much different for each gum. Karaya gum can sustain the release of diclofenac sodium to a greater degree than xanthan gum, locust bean gum and HPMC, with the maximum amount of accumulated drug released 54%, 66%, 75% and 86% at 12 hours, respectively. The mechanisms of diclofenac sodium release from

three natural gums were anomalous diffusion with n values of 0.703, 0.731, 0.777 for xanthan gum, karaya gum and locust bean gum, respectively, while HPMC exhibits Super Case II transport with a n value of 0.913. There is no synergistic effect between xanthan gum and locust bean gum on the release of diclofenac sodium from solid mini-matrices.

The effect of quantity of gum on release characteristics was carried out using xanthan gum. The drug release rate declined linearly with a progressive increase in gum content. The mechanisms of drug release are still anomalous diffusion for diclofenac sodium and xanthan gum in the ratios of 1:1, 2:3 and 1:2 while at the ratio of 2:1, the mechanism is changed to Super Case II transport as a result of dissolution of the drug. From the contribution of Fickian diffusion and Relaxation, xanthan gum is mainly responsible for the Fickian diffusion mechanism and diclofenac sodium contributes mainly to the dissolution or erosion mechanism.

In spite of the widely varying physico-chemical characteristics of the excipients, the drug dissolution profiles display similar tendencies. The drug release rate increased with increasing proportions of excipient and corresponding decrease in xanthan gum content. The mechanisms of drug release were anomalous (non - Fickian) diffusion at low proportion of excipient which gradually changed to Case II and Super Case II transport at higher proportion of excipient.

The pH of the dissolution medium greatly affected the release of diclofenac sodium. The higher the pH of the dissolution medium, the faster the release rate. These results are consistent with the pH solubility profile of diclofenac sodium.

The stirring speed (from 50 to 150 rpm) and the tablet volume have a relatively small effect on drug release.

It can be concluded that the release profile of diclofenac sodium is greatly dependent on the proportion of xanthan gum in the formulation, and the pH of the dissolution medium.

CHAPTER 5

HYDROPHILIC MINI-MATRICES CONTAINING DICLOFENAC SODIUM AND NATURAL GUMS: INVESTIGATION OF THE SWELLING, SOLVENT PENETRATION AND EROSION PROPERTIES

5.1 INTRODUCTION

The mechanism of drug release from hydrophilic matrices is controlled by two factors; drug diffusion and polymer relaxation (Calanchi et al. 1987) (see also Chapter 1). The diffusion of the drug throughout the gel layer into the dissolution medium is directly influenced by the swelling behaviour of the system. Hence, the swelling behaviour, the solvent penetration profile (a factor that would affect the swelling behaviour) and the erosion profile of the mini-matrices are the important factors in the release characteristics of hydrophilic matrices. The swelling behaviours, both axial and radial, and the solvent penetration profiles were studied using photographic techniques. The erosion profiles were studied using the method applied from the dissolution study. The compatibility between model drug and excipients (from the most satisfactory formulation) was also studied using differential scanning calorimetry (DSC).

5.2 MATERIALS

Diclofenac sodium mini-matrices (formulations 1-3, Table 4.1 and formulations 10-14D, Table 4.2).

Buffers, liquids and solutions: sodium hydroxide and potassium dihydrogen orthophosphate were used to prepare phosphate buffer solution pH 7.0 (USP XXIII 1994).

5.3 METHODS

5.3.1 Swelling properties of mini-matrices

5.3.1.1 Axial swelling test

A single mini-matrix tablet was placed on a glass slide in a petri dish (6 cm in diameter) containing 30 ml of 0.0001% w/v methylene blue solution in 0.05 M phosphate buffer pH 7.0 (USP XXIII 1994). Methylene blue was added in the buffer solution in order to ensure that the swelling was easily observed. The temperature was controlled at 37±0.5°C in a thermostatic water bath. The lateral edge of the mini-matrix was photographed (Olympus OM-2n camera with Zuiko MC Auto-S lens, focal length 50 mm, maximum aperture 1.4, fitted with multiple extension tubes up to 65 mm) at regular time intervals for 360 minutes. The axial swelling distances were measured directly from the photographs using the thickness of the glass slide as a reference. All determinations were performed in triplicate and the mean axial swelling index (%; ±SD) was plotted against time.

5.3.1.2 Radial swelling test

A mini-matrix tablet was placed in identical conditions as described under axial swelling, but with a standard scale (in mm) placed underneath the petri dish. Visual measurements of the diameter were taken at regular time intervals for 360 minutes. All determinations were performed in triplicate and the mean radial swelling index (%; ±SD) was plotted against time.

5.3.2 Solvent penetration study

The penetration of the solvent front was monitored as a function of time using a simple method to allow solvent to penetrate only from the lateral edge of the mini-matrices. Both flat surfaces of the matrices were coated with a silicone high vacuum grease to prevent solvent penetration from these surfaces. Each mini-matrix was then sandwiched between two glass cover slips and then placed in a petri dish (6 cm in diameter). To ensure that the penetration front was easily distinguishable, a 0.0001% w/v solution of methylene blue in 0.05 M phosphate buffer (pH 7.0) was poured into the petri dish just sufficient to reach the level of the top cover slip. The penetration of the solvent was easily visible as a sharp front and this solvent front was photographed (Olympus OM-2n camera with Zuiko MC Auto-S lens, focal length 50 mm, maximum aperture 1.4, fitted with multiple extension tubes up to 65 mm) at regular time intervals for 360 minutes. From the photographs the penetration distance of the solvent (in mm) was measured using the scale on micrometer disc as a reference. All determinations were performed in triplicate and the mean solvent front penetration distance (in mm; ±SD) was plotted against time.

5.3.3 Data analysis

The axial and radial swelling indices (*SI*) were calculated according to Equation 5.1:

$$SI = \left(\frac{s-a}{a}\right) \times 100 \quad \text{.....(5.1)}$$

For axial swelling; *a* is the original thickness, while for radial swelling *a* is the original diameter of the dry mini-matrix. In the case of the swollen mini-matrix, *s* is the thickness and diameter for axial and radial swelling respectively. Swelling profiles were obtained by plotting the swelling index against time (*t*). The kinetics of the swelling and

the solvent front penetration processes were calculated according to Equations 5.2a and b respectively:

$$\delta_s = C_s t^{n_s} \quad \text{.....(5.2a)}$$

$$\delta_p = C_p t^{n_p} \quad \text{.....(5.2b)}$$

where δ_s is the swelling index, δ_p is the solvent front penetration distance, n_s is the exponent describing the swelling mechanism, n_p is the exponent describing the solvent front penetration mechanism, and C_s and C_p are constants for swelling and penetration fronts respectively. The values for n_s and n_p = 0.45 for Case I or Fickian diffusion, 0.45 < n_s and n_p < 0.89 for anomalous (non-Fickian) diffusion, n_s and n_p = 0.89 for Case II transport and n_s and n_p > 0.89 for Super Case II transport.

5.3.4 Erosion study

The method used was similar to the method of determining the *in vitro* dissolution profile as described in Chapter 4. However, single mini-matrices were placed in thoroughly clean wire mesh baskets and then weighed accurately. During the dissolution process at 60 minute time intervals a basket containing the remnants of a mini-matrix was removed and dried at 60°C for 24 hours. After cooling in a desiccator to room temperature these were weighed accurately and the percentage weight loss (% erosion) was calculated and plotted against time.

5.3.5 Compatibility of model drug and excipients

Only the diclofenac sodium mini-matrices that produced satisfactory release profiles were considered for this test. Physical mixtures of binary systems containing either diclofenac sodium, natural hydrophilic gums and/or excipients in a ratio of 1:1 were prepared with a mortar and pestle. The individual substances and physical

mixtures were thermally characterised by using a differential scanning calorimeter (Pyris1, Perkin Elmer, USA). The samples (1.5-5 mg) were weighed directly into flat bottomed aluminium sample pans. The pans were crimped with the lid on top of the sample. These samples were heated in a nitrogen atmosphere. The heat flow rate of 20°C/min was monitored as a function of temperature from 30 to 400°C. The thermograms were recorded.

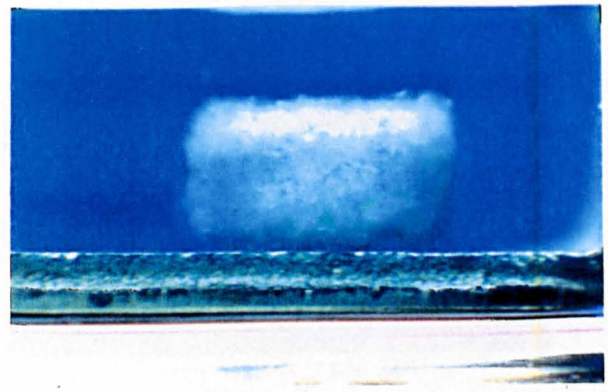
5.4 RESULTS AND DISCUSSION

5.4.1 Swelling study of mini-matrices

5.4.1.1 Effect of gum type

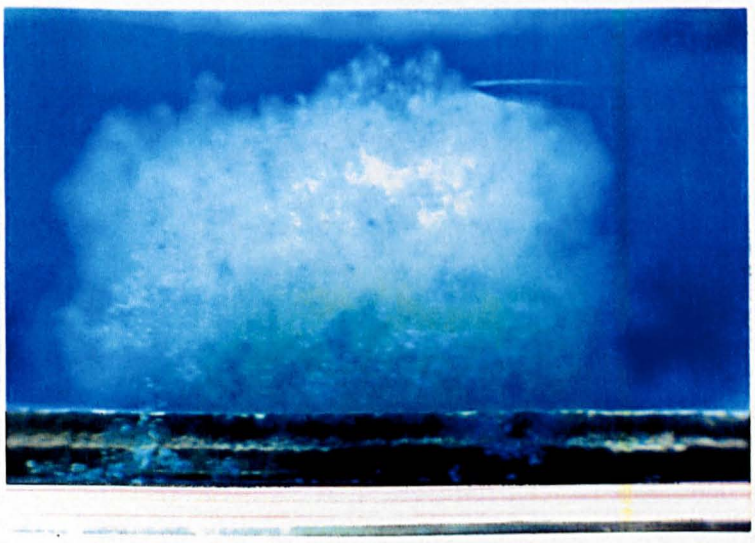
When the mini-matrix was placed in the 0.0001% methylene blue solution in 0.05 M phosphate buffer, liquid penetrates into the matrix and a gel is formed due to uncoiling of the structure of the gum molecules and the formation of hydrogen bonds with water molecules. As a result, the thickness and diameter of the matrix increase progressively and a distinct gel-sol boundary develops.

The photographs of the lateral edge of a mini-matrix containing diclofenac sodium and hydrophilic gums; xanthan gum, karaya gum or locust bean gum, in a ratio of 1:1 at 0, 60 and 360 minutes after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 are shown in Figures 5.1a-c, 5.2a-c and 5.3a-c respectively.



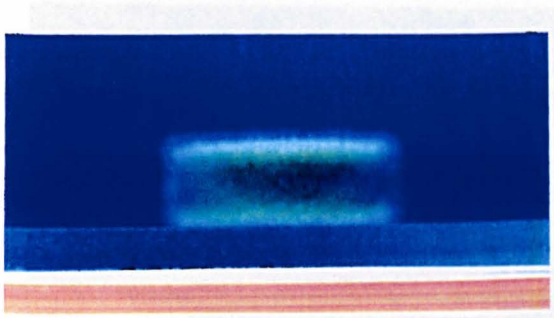
(a)

(b)

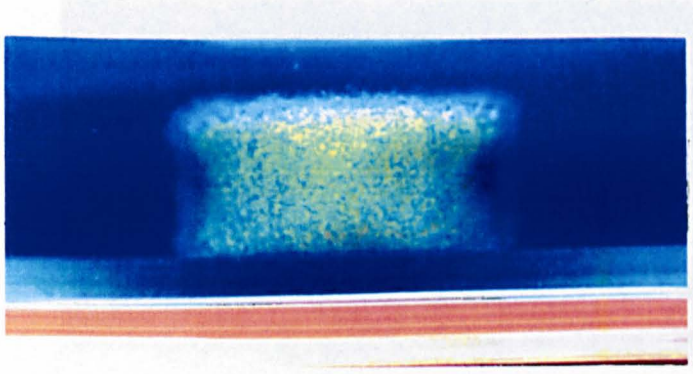


(c)

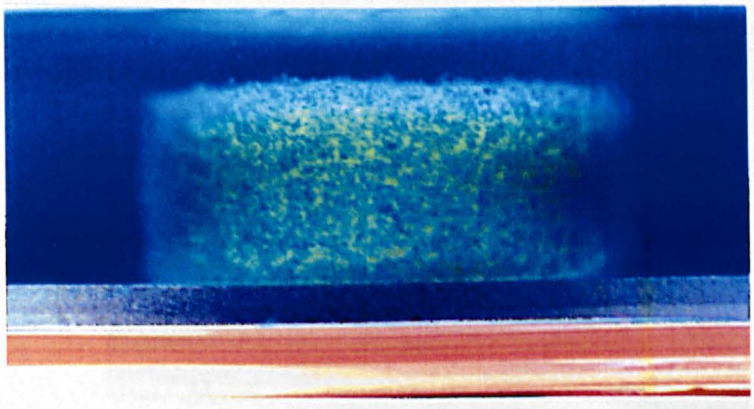
Figure 5.1a-c. The photographs of the lateral edge of a mini-matrix containing diclofenac sodium and xanthan gum in a ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.



(a)

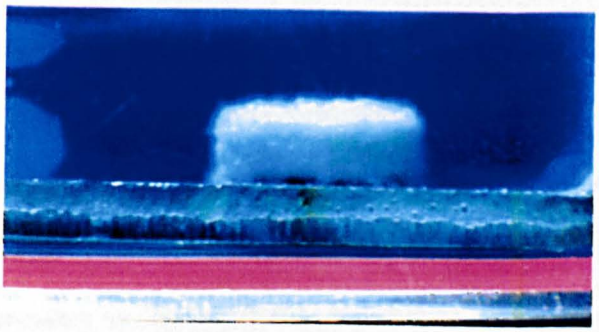


(b)

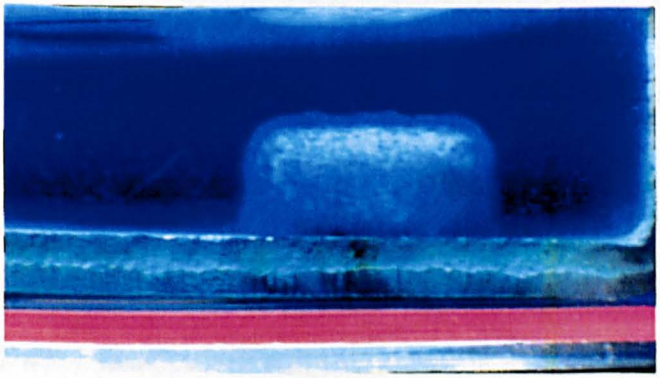


(c)

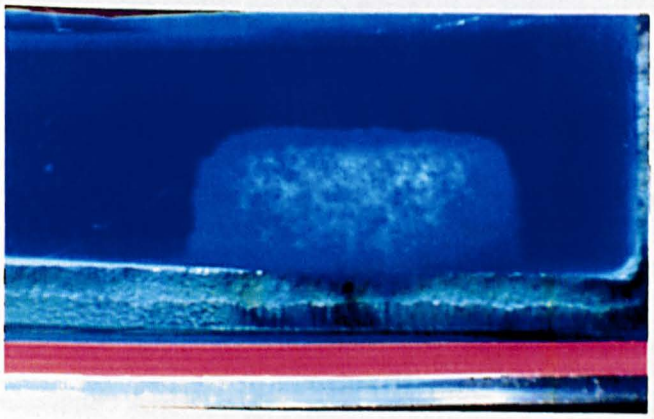
Figure 5.2a-c. The photograph of the lateral edge of a mini-matrix containing diclofenac sodium and karaya gum in a ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.



(a)



(b)



(c)

Figure 5.3a-c. The photograph of the lateral edge of a mini-matrix containing diclofenac sodium and locust bean gum in a ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.

The axial and radial swelling profiles (SI against time) of mini-matrix formulations of each gum (xanthan gum, karaya gum and locust bean gum) combined with diclofenac sodium in a ratio of 1:1 are shown respectively in Figures 5.4a and b. Diclofenac sodium and carrageenan gum in a ratio of 1:1 disintegrated within 10 minutes after contact with the medium, so the experiment with carrageenan gum was discontinued. The xanthan gum mini-matrices showed the greatest swelling indices in both the axial and radial dimensions when in contact with the phosphate buffer (0.05 M) at pH 7.0, being 254.7±10.5% and 178.3±4.1% respectively after 360 minutes. Karaya gum displayed an intermediate swelling index (153.7±6.9% and 166.9±2.8% respectively), while the lowest indices were for locust bean gum (69.6±7.2% and 91.3±1.4% respectively) after 360 minutes. The swelling rates, calculated from the slopes of the plots of swelling index versus square root of time (Figures 5.5a and b), for xanthan gum, karaya gum and locust bean gum were 12.44, 7.30 and 2.68 % $min^{-1/2}$ for axial dimension and 9.73, 9.44 and 4.29 % $min^{-1/2}$ for radial dimension respectively (Tables 5.1 and 5.2). This order would indicate the rates at which the gums are able to absorb water and swell. Thus xanthan gum has the ability to hydrate more rapidly than the other two gums used. The resulting drug diffusional path length for xanthan gum was therefore the longest. Provided the gums have nearly similar diffusion coefficients, it would follow that the drug release rate from the xanthan gum matrices would be the slowest. However, the drug dissolution profiles (see Figure 4.1) actually show that the order of decreasing drug release was locust bean gum>xanthan gum>karaya gum, with mean dissolution times (MDT) of 180±36, 329±60 and 655±120 minutes respectively. It is obvious therefore that Fickian drug diffusion through the gradually expanding hydrated matrix with increasing diffusional path length was not the only mechanism accounting for drug release. The release behaviour of each of the three gums was anomalous (non-Fickian) having release exponent (*n*) values of 0.703±0.014, 0.731±0.008 and 0.777±0.080 for xanthan, karaya

and locust bean gums respectively. On the other hand, when the results of the swelling index studies are processed in accordance with Equation 5.2a, the resulting swelling exponents (n_s) in both dimensions (Tables 5.1 and 5.2) represent almost Fickian swelling behaviour. This swelling mechanism can be explained as a result of the rapid hydration of gum molecules on the surface of the mini-matrices, which results in a gel or a highly viscous solution surrounding the mini-matrices that restricts water penetration into the centre. Swelling occurs rapidly both axially and radially in the first 30 minutes and thereafter the swelling rate gradually declines with time. The diclofenac sodium: locust bean gum 1:1 formulation showed little axial swelling behaviour (n_s= 0.299±0.054). This could be due in part to the poor swellability of the locust bean gum. Figure 5.5a shows plots of axial swelling index versus square root of time which are linear (r = 0.994, 0.993 and 0.982 for diclofenac sodium: xanthan gum 1:1, diclofenac sodium: karaya gum 1:1 and diclofenac sodium: locust bean gum 1:1 respectively). Figure 5.5b also shows the similar results for radial swelling (r = 0.990, 0.980 and 0.984 respectively). The swelling rates in both dimensions are calculated from the slope of these plots and shown in Tables 5.1 and 5.2.

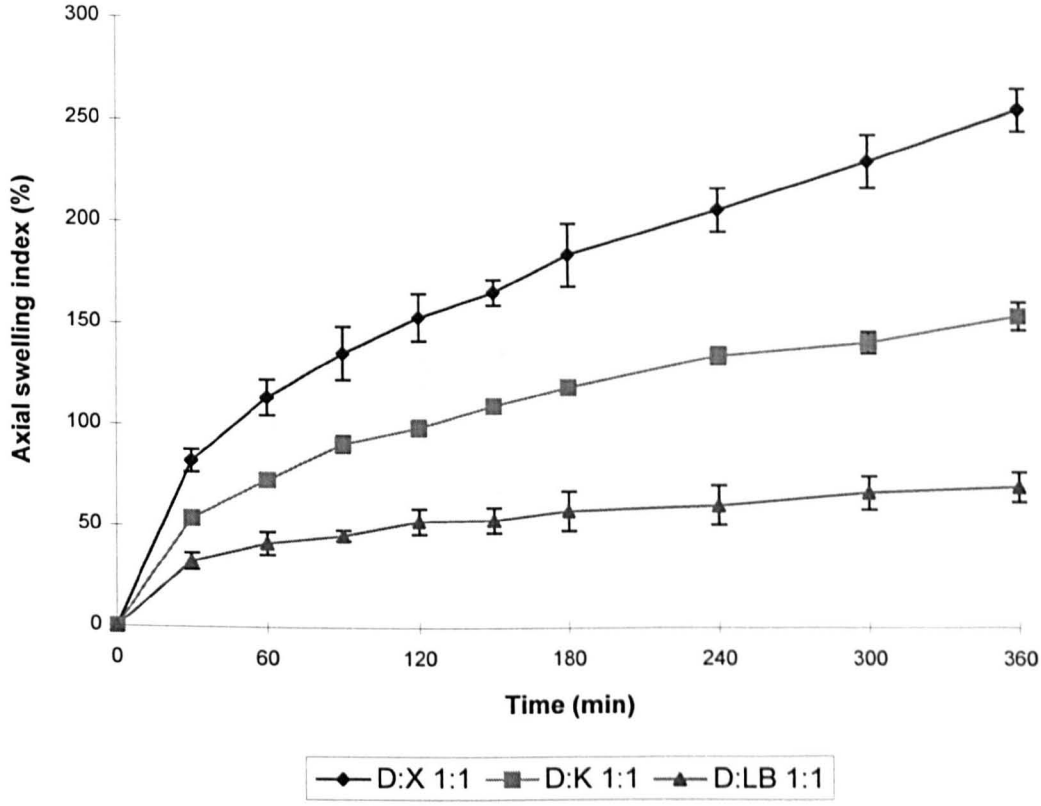


Figure 5.4a. Axial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing 1:1 mixtures of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

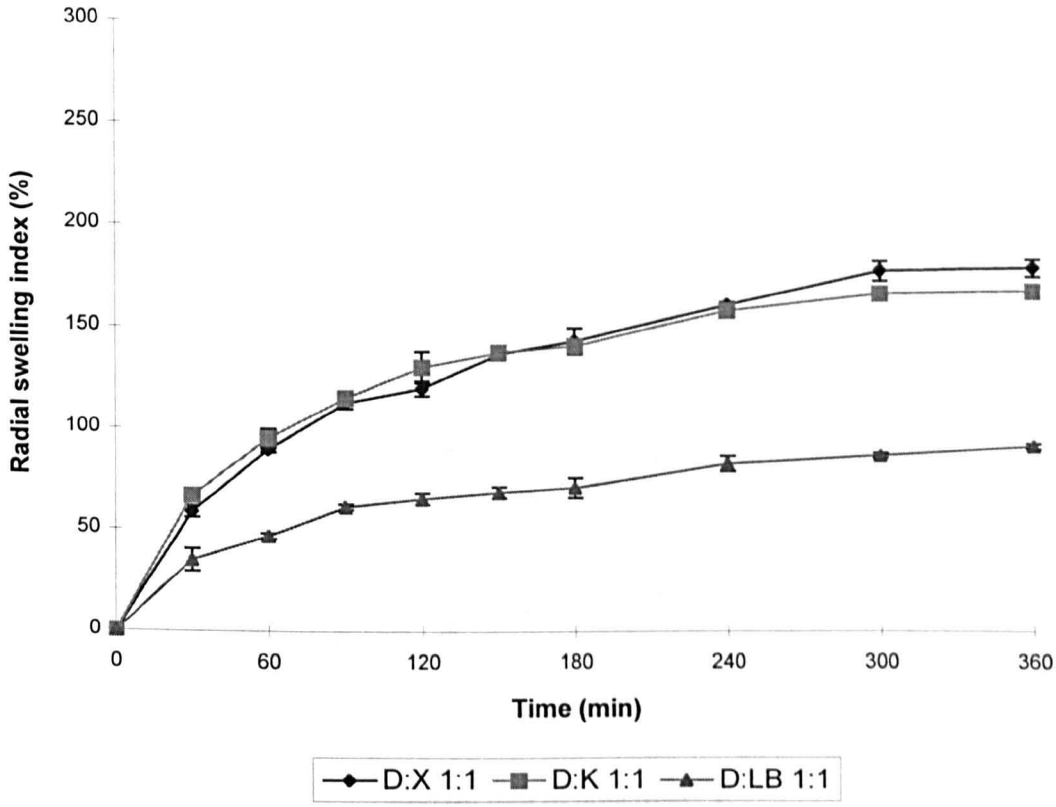


Figure 5.4b. Radial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing 1:1 mixtures of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

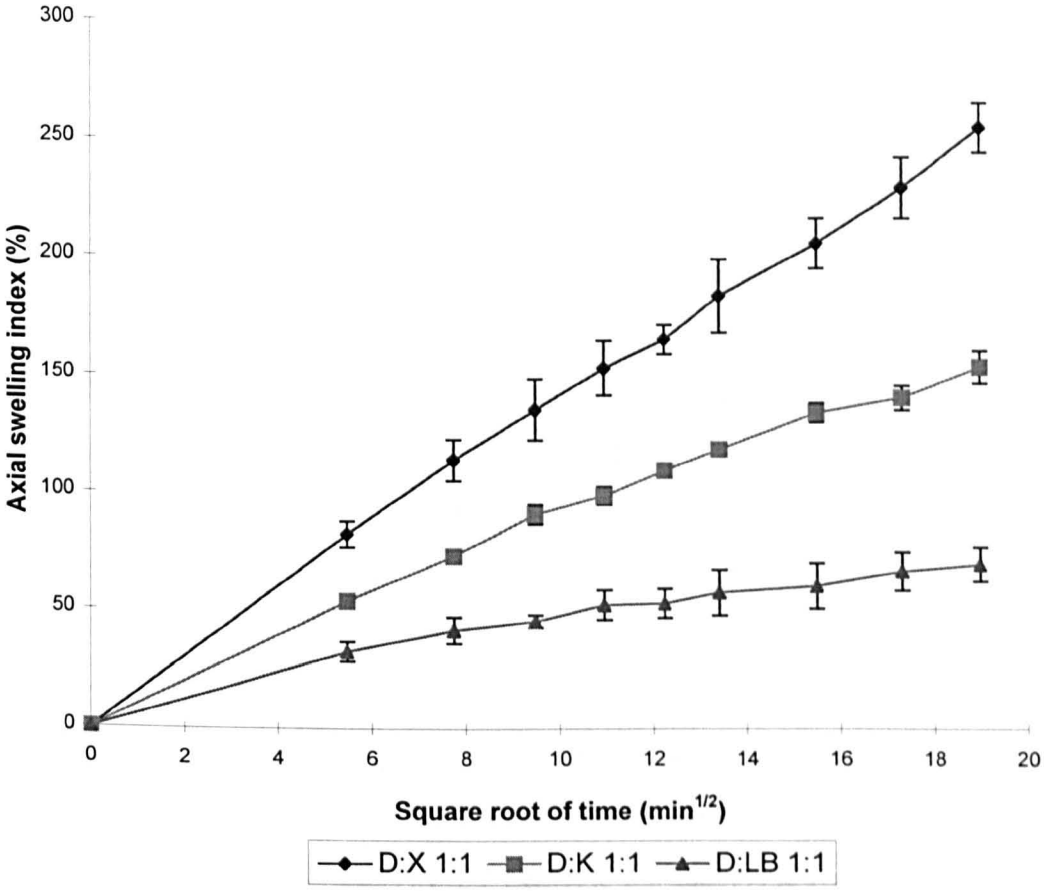


Figure 5.5a. Plot of mean axial swelling index (%) against the square root of time ($min^{1/2}$) of single mini-matrices containing 1:1 mixtures of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3). [If straight lines were drawn the correlation coefficients (r) would be 0.994 (xanthan gum), 0.993 (karaya gum) and 0.982 (locust bean gum)].

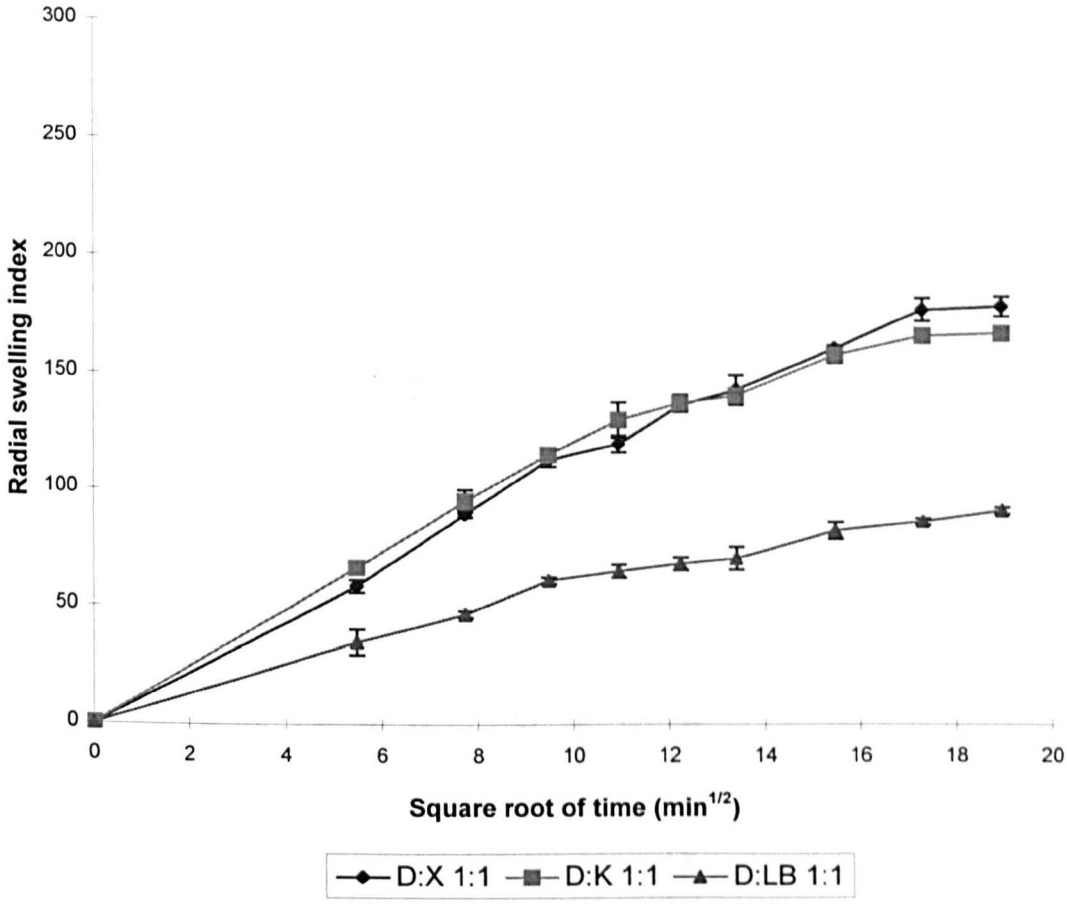


Figure 5.5b. Plot of mean radial swelling index (%) against the square root of time ($min^{1/2}$) of single mini-matrices containing 1:1 mixtures of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3). [If straight lines were drawn the correlation coefficients (r) would be 0.990 (xanthan gum), 0.980 (karaya gum) and 0.984 (locust bean gum)].

Table 5.1. ***Axial*** *swelling parameters and correlation coefficients from single mini-matrices using Equation 5.2a to derive the swelling exponent (n_s) and the kinetic constant (C_s). The swelling rate (% $min^{-1/2}$) was calculated from the slopes of the plots of axial swelling index versus square root of time (mean values±SD; n=3).*

Mini-matrices composition*	Swelling exponent (n_s)	Kinetic constant (C_s) (min^{-n})	Correlation coefficient (r)	Swelling rate (% $min^{-1/2}$)	Correlation coefficient (r)
D:X 1:1	0.460±0.056	17.46±4.83	0.993	12.44±1.52	0.994
D:K 1:1	0.414±0.029	13.63±1.79	0.996	7.30±0.61	0.993
D:LB 1:1	0.299±0.054	12.16±3.00	0.987	2.68±0.54	0.982
D:X 2:1	0.462±0.029	22.43±1.75	0.992	17.65±1.29	0.991
D:X 2:3	0.423±0.025	18.16±3.67	0.990	11.80±1.51	0.994
D:X 1:2	0.441±0.069	15.52±4.05	0.987	11.67±2.32	0.983

*D, Diclofenac sodium; X, Xanthan gum; K, Karaya gum; LB, Locust bean gum.

Table 5.2. **Radial** swelling parameters and correlation coefficients from single mini-matrices using Equation 5.2a to derive the swelling exponent (n_s) and the kinetic constant (C_s). The swelling rate (% $min^{-1/2}$) was calculated from the slopes of the plots of radial swelling index versus square root of time (mean values±SD; n=3).

Mini-matrices composition*	Swelling exponent (n_s)	Kinetic constant (C_s) (min^{-n})	Correlation coefficient (r)	Swelling rate (% $min^{-1/2}$)	Correlation coefficient (r)
D:X 1:1	0.460±0.019	13.24±1.18	0.990	9.73±0.43	0.990
D:K 1:1	0.432±0.020	15.91±1.67	0.988	9.44±0.79	0.980
D:LB 1:1	0.384±0.052	10.17±2.70	0.986	4.29±0.53	0.984
D:X 2:1	0.706±0.023	3.96±0.40	0.998	13.88±0.31	0.995
D:X 2:3	0.421±0.010	13.63±0.52	0.994	7.65±0.81	0.989
D:X 1:2	0.395±0.003	16.52±0.27	0.995	7.61±0.09	0.991

*D, Diclofenac sodium; X, Xanthan gum; K, Karaya gum; LB, Locust bean gum.

5.4.1.2 Effect of drug: xanthan gum ratio

The axial and radial swelling profiles for various mixtures of diclofenac sodium with xanthan gum are shown in Figure 5.6a and b respectively, while the respective swelling exponents (n_s) and swelling rates are shown in Tables 5.1 and 5.2. The mini-matrix containing the lowest proportion of xanthan gum (drug: gum 2:1) produced profiles with the highest rate of axial and radial swelling over the 6 hour period. The axial swelling index decreased in the order of drug: gum ratios of 2:1, 1:1, 2:3 and 1:2. A similar, but less pronounced, trend was observed for the radial swelling index. Initially this order of decreasing swelling index profiles was not expected since, as pointed out in Chapter 4, the drug release rate decreased in the order of increasing proportion of xanthan gum. It was reasoned that as the amount of xanthan gum in the matrix increased there would be a greater degree of gum hydration with simultaneous swelling. This would result in a corresponding lengthening of the drug diffusion pathway and reduction in drug release rate. The increased drug release that occurred with increased swelling rate could, however, be explained on the basis of a change in the integrity of the matrix. Mini-matrices with a drug: gum ratio of 2:1 actually showed a disintegration of the matrix structure as seen in Figure 5.6a which shows a sudden surge in the axial swelling index after 3 hours. The phosphate buffer medium will permeate through the gum matrix dissolving the drug which passes by diffusion outwards into the medium and the volume occupied by the drug molecules will be replaced with water molecules. If drug diffusion outwards through the hydrated gel is slower than the permeation of water inwards, then the swelling effect would be more pronounced.

Swelling studies carried out concurrently using mini-matrices of xanthan gum only (no drug present) showed that the mini-matrices maintained their integrity and reached a radial swelling index of 233% after 24 hours (compared to a maximum radial swelling index at 6 hours of 178% for a 1:1 drug: gum ratio as seen in Figure 5.6b). Hydration and

swelling of matrices with a high gum content may be slower, but eventually they swell to greater maximum values compared to matrices with a low gum content, which would swell more rapidly but reach a lower maximum swelling index, or disintegrate, in a relatively shorter time period.

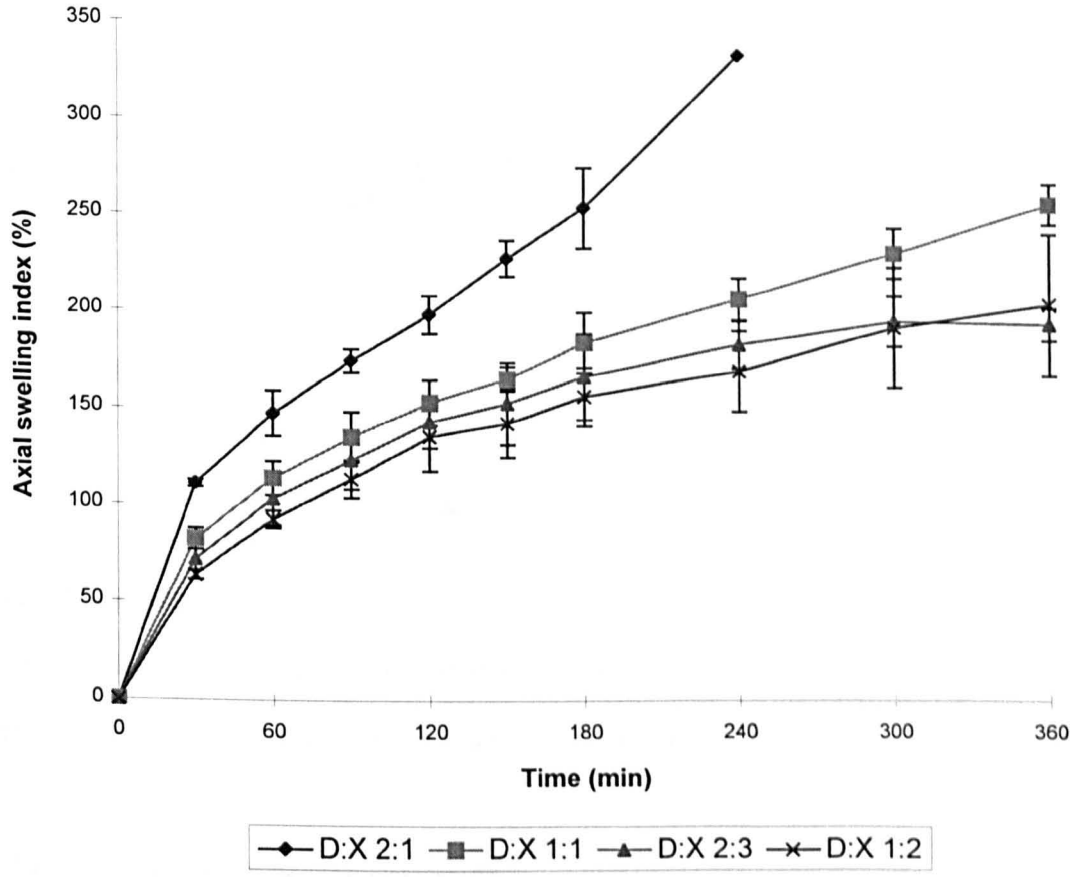


Figure 5.6a. Axial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing various mixtures of xanthan gum (X) with diclofenac sodium (D) in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

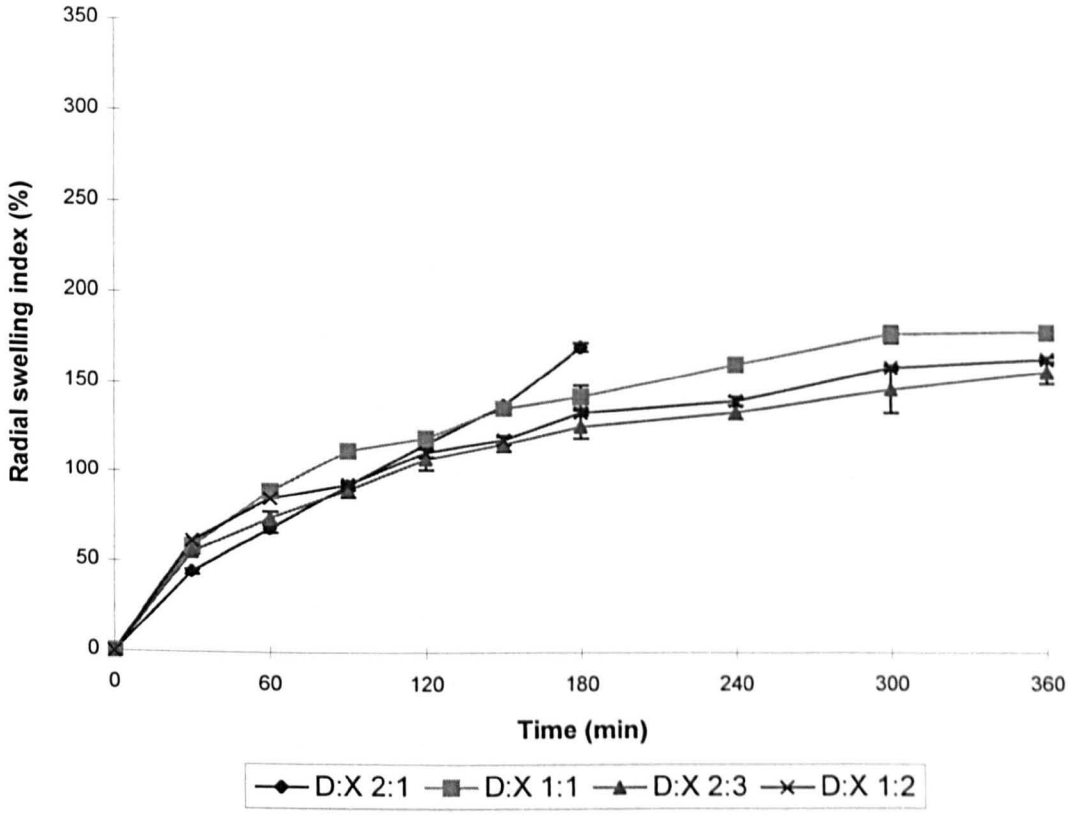


Figure 5.6b. Radial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing various mixtures of xanthan gum (X) with diclofenac sodium (D) in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

5.4.1.3 Effect of excipient concentration

The mini-matrices containing diclofenac sodium, xanthan gum and Veegum® at various ratios were carried through the swelling study because they showed the most discriminating drug release profiles between each ratio (see Figure 4.9). The axial and radial swelling profiles of these mini-matrices are shown in Figures 5.7a and b respectively. The swelling exponents (n_s) and swelling rates for both dimensions are also shown in Tables 5.3 and 5.4. The axial swelling profiles tend to decline when the amount of Veegum® increases, corresponding to a decrease in the amount of xanthan gum

(Figure 5.7a). This decline is very little at the low proportion of Veegum® (drug: xanthan gum: Veegum® 3:3:0 to 3:1.5:1.5), until the ratio of drug: xanthan gum: Veegum® was 3:1:2, the profile is greatly declined. When the mini-matrices contacted with 0.05 M phosphate buffer pH 7.0, xanthan gum and Veegum® absorbed water, they swelled and formed a viscous gel layer around the mini-matrices. The profiles from Figure 5.7a indicated that Veegum® swells to a smaller extent than xanthan gum at equal time, resulting in less swelling of the mini-matrices at low proportions of Veegum®. In addition, Veegum® also has a disintegration property, therefore the mini-matrices containing a high proportion of Veegum®, drug: xanthan gum: Veegum® in a ratio of 3:0.5:2.5, exhibited initial high swelling and disintegrated within 60-120 minutes after contact with phosphate buffer solution. The swelling rate and swelling exponent of this ratio (3:0.5:2.5) were unobtainable because there were not sufficient data points to provide accurate values. The swelling exhibited Fickian and anomalous mechanisms with a n_s value range of 0.333-0.470 (Table 5.3).

The radial swelling profiles exhibited similar but less pronounced trends (Figure 5.7b). The swelling exhibited an anomalous mechanism with a n_s value range of 0.452-0.564 and swelling rate range between 7.51-10.33 $\%min^{-1/2}$ (Table 5.4).

It can be concluded that Veegum® did not affect the swelling of the mini-matrices consisting of diclofenac sodium and xanthan gum. The decline in swelling at high proportions of Veegum® should be due to the lowering of xanthan gum proportion. As the xanthan gum proportion decreases there would be a lesser degree of gum hydration with simultaneous swelling. This would result in a corresponding shortening of the drug diffusional path length and an increase in drug release rate. This result is consistent with the release profiles of the mini-matrices which exhibited the higher drug release rate at lower xanthan gum proportion (see also Figure 4.9).

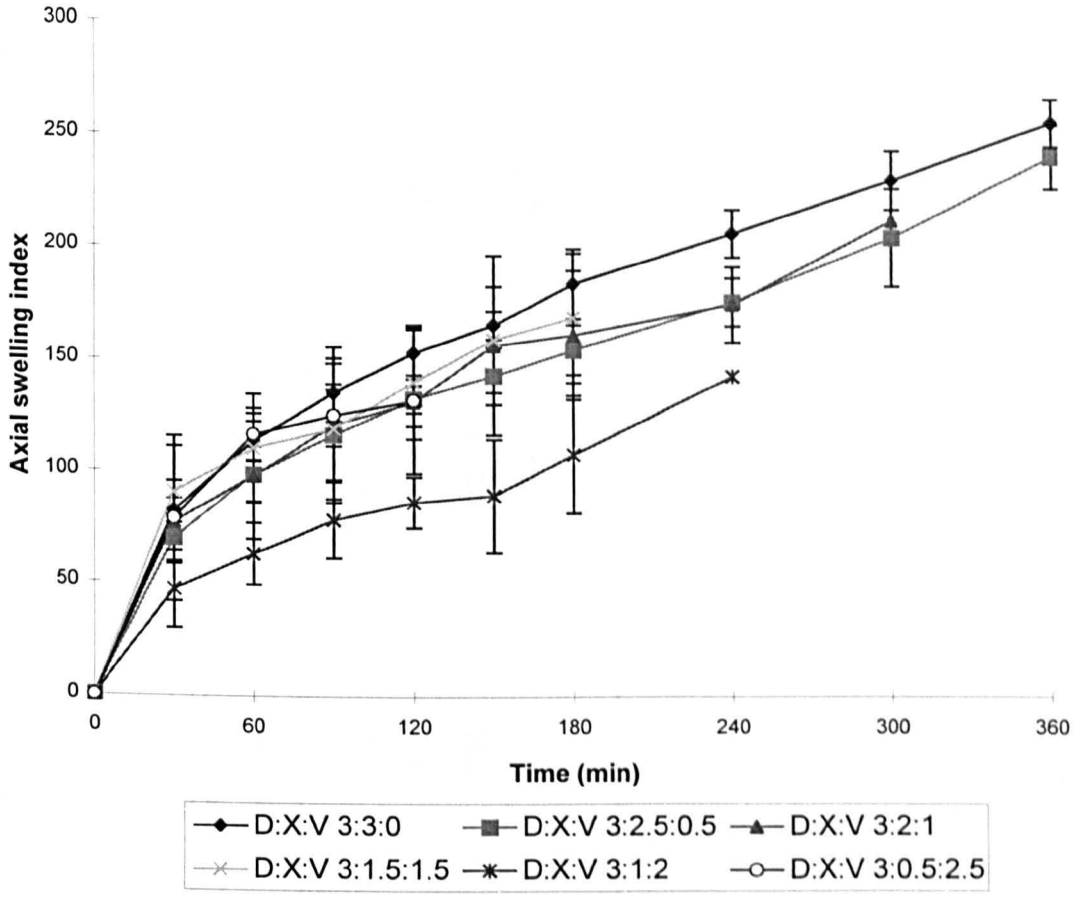


Figure 5.7a. Axial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing diclofenac sodium (D), xanthan gum (X) and Veegum® (V) at various ratios in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

Table 5.3. **Axial** swelling parameters and correlation coefficients from single mini-matrices using Equation 5.2a to derive the swelling exponent (n_s) and the kinetic constant (C_s). The swelling rate (% $min^{-1/2}$) was calculated from the slopes of the plots of axial swelling index versus square root of time (mean values±SD; n=3).

Mini-matrices composition*	Swelling exponent (n_s)	Kinetic constant (C_s) (min^{-n})	Correlation coefficient (r)	Swelling rate (% $min^{-1/2}$)	Correlation coefficient (r)
D:X:V 3:3:0	0.460±0.056	17.46±4.83	0.993	12.44±1.52	0.994
D:X:V 3:2.5:0.5	0.470±0.058	14.47±5.20	0.987	11.36±1.83	0.988
D:X:V 3:2:1	0.467±0.116	14.70±9.23	0.976	10.16±1.78	0.973
D:X:V 3:1.5:1.5	0.333±0.042	32.92±11.27	0.976	10.41±0.73	0.980
D:X:V 3:1:2	0.436±0.039	12.55±4.42	0.970	8.40±1.56	0.970
D:X:V 3:0.5:2.5	-	-	-	-	-

*D, Diclofenac sodium; X, Xanthan gum; V, Veegum®.

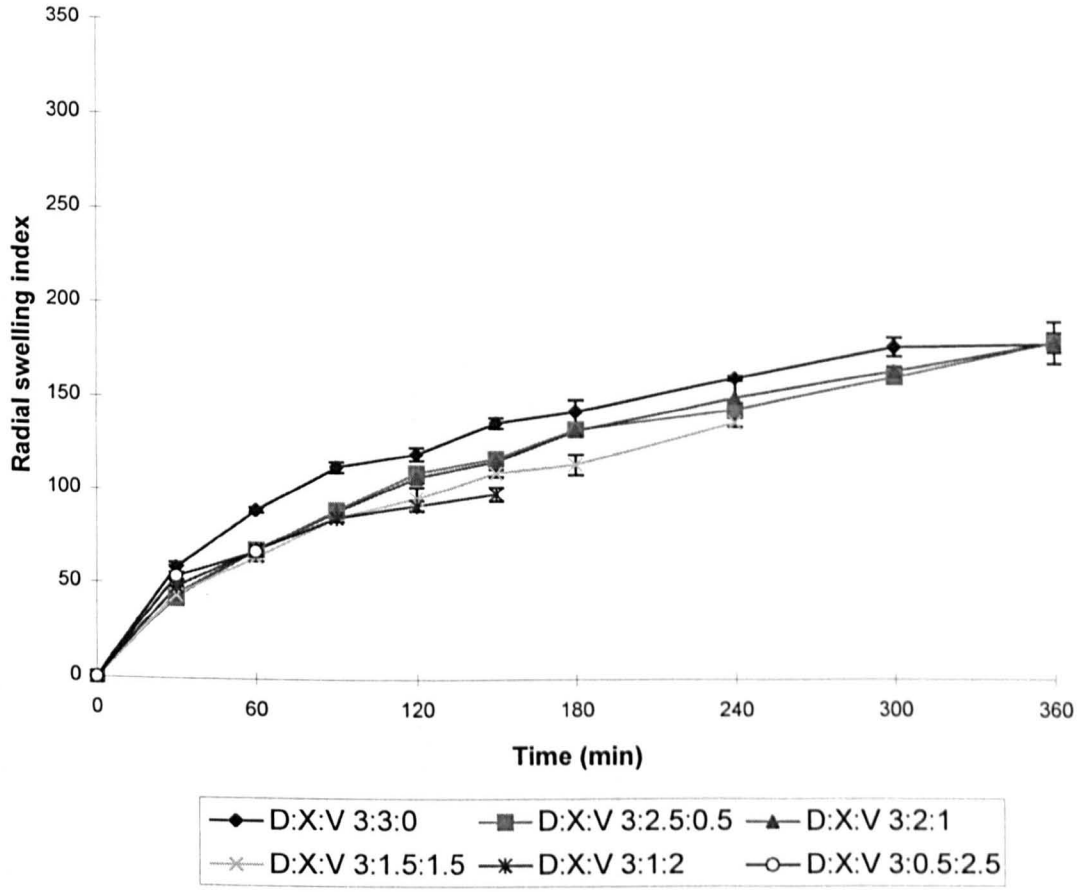


Figure 5.7b. Radial swelling profiles showing the swelling indices (%) against time (min) of single mini-matrices containing diclofenac sodium (D), xanthan gum (X) and Veegum® (V) at various ratios in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

Table 5.4. **Radial** *swelling parameters and correlation coefficients from single mini-matrices using Equation 5.2a to derive the swelling exponent (n_s) and the kinetic constant (C_s). The swelling rate (% $min^{-1/2}$) was calculated from the slopes of the plots of radial swelling index versus square root of time (mean values±SD; n=3).*

Mini-matrices composition*	Swelling exponent (n_s)	Kinetic constant (C_s) (min^{-n})	Correlation coefficient (r)	Swelling rate (%$min^{-1/2}$)	Correlation coefficient (r)
D:X:V 3:3:0	0.460±0.019	13.24±1.18	0.990	9.73±0.43	0.990
D:X:V 3:2.5:0.5	0.564±0.039	6.85±1.32	0.992	9.84±0.44	0.994
D:X:V 3:2:1	0.562±0.017	6.91±0.71	0.994	10.33±0.32	0.996
D:X:V 3:1.5:1.5	0.555±0.008	6.69±0.28	0.994	9.38±0.22	0.992
D:X:V 3:1:2	0.452±0.054	10.87±2.72	0.990	7.51±0.77	0.984
D:X:V 3:0.5:2.5	-	-	-	-	-

*D, Diclofenac sodium; X, Xanthan gum; V, Veegum®.

5.4.2 Solvent penetration study

5.4.2.1 Effect of gum type

The photographs of solvent front penetration of mini-matrices containing diclofenac sodium and hydrophilic gums; xanthan gum, karaya gum and locust bean gum, in a ratio of 1:1 at 0, 60 and 360 minutes after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 are shown in Figures 5.8a-c, 5.9a-c and 5.10a-c respectively.

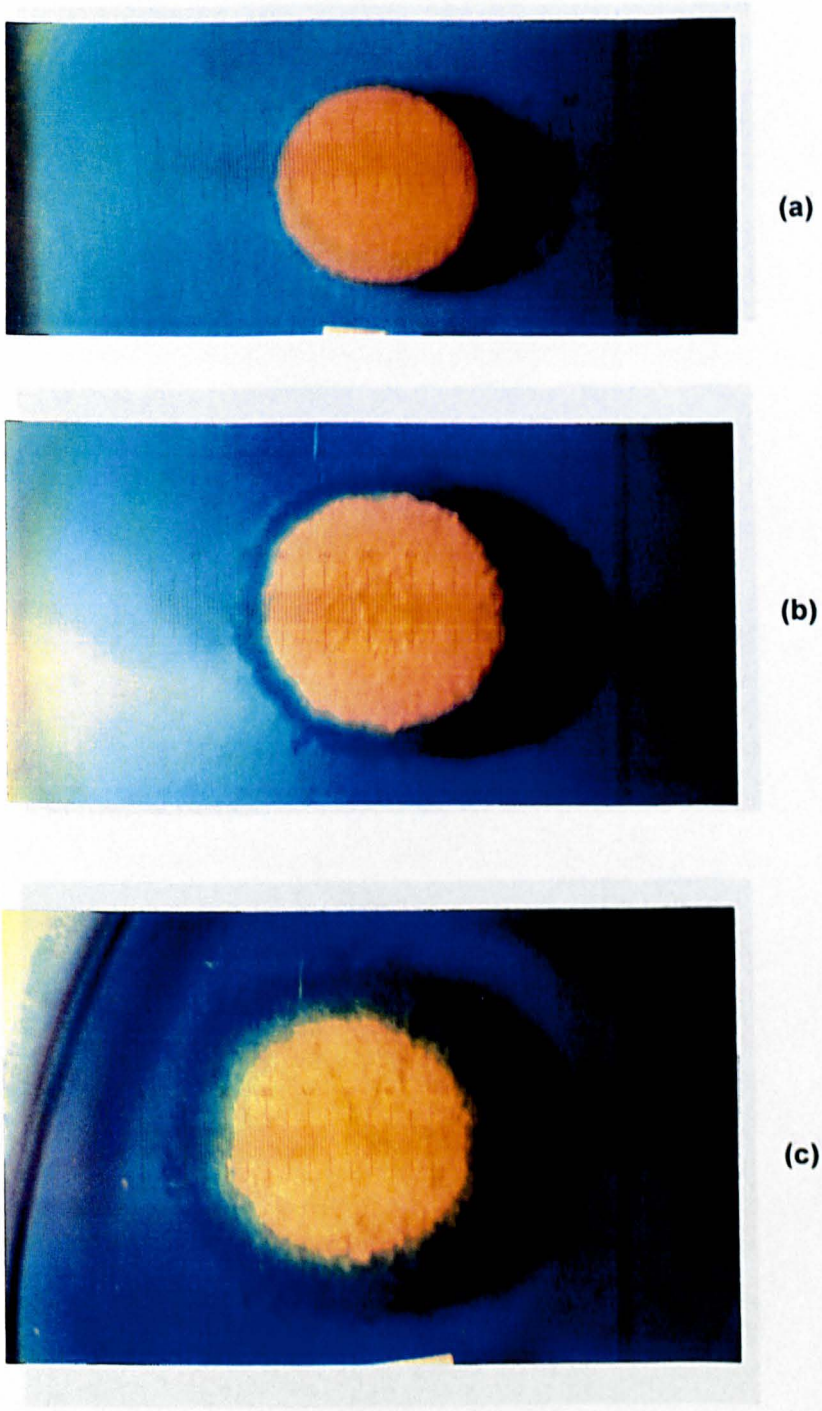


Figure 5.8a-c. The photograph of solvent front penetration of mini-matrix containing diclofenac sodium: xanthan gum in the ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.

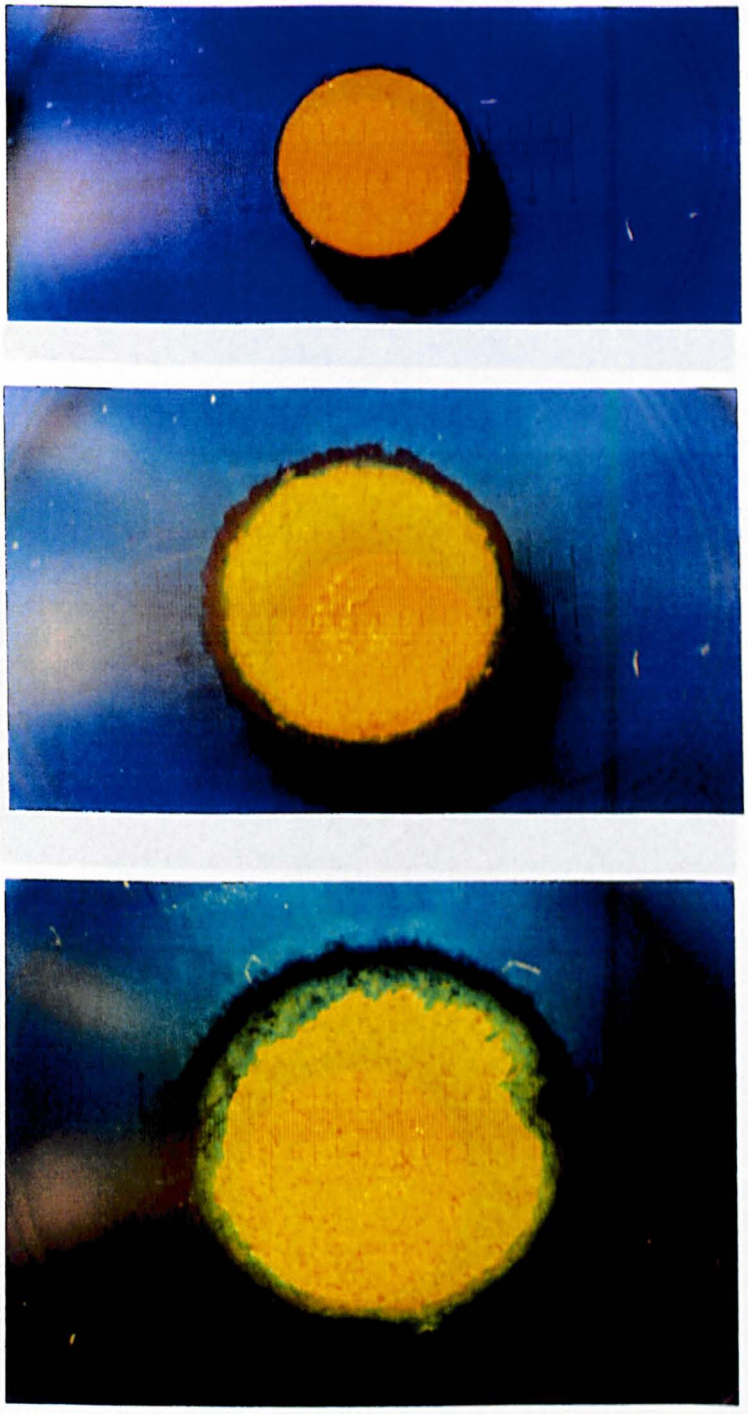


Figure 5.9a-c. The photograph of solvent front penetration of mini-matrix containing diclofenac sodium: karaya gum in the ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.

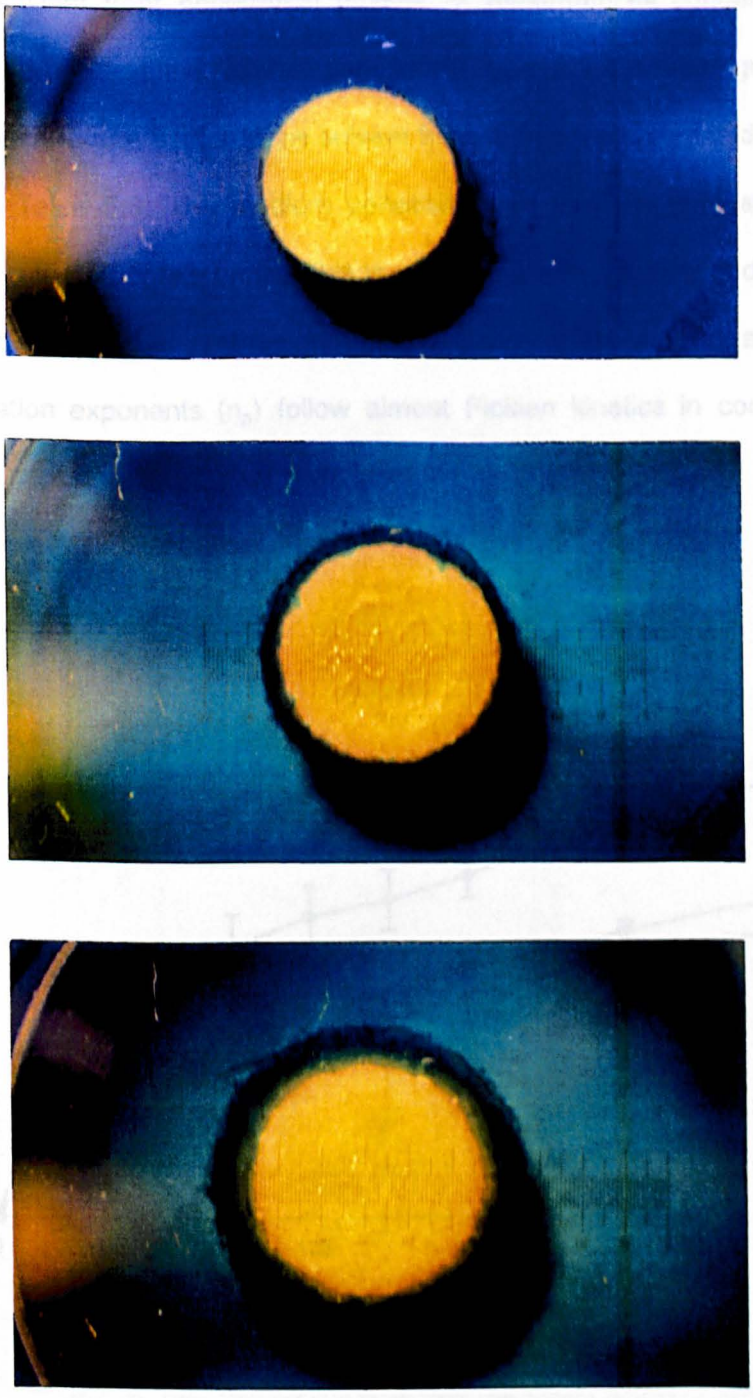


Figure 5.10a-c. The photograph of solvent front penetration of mini-matrix containing diclofenac sodium: locust bean gum in the ratio of 1:1, at time zero (a), 60 (b) and 360 minutes (c) after contact with 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0.

The solvent front penetration profiles of mini-matrices containing diclofenac sodium and hydrophilic gums; xanthan gum, karaya gum or locust bean gum, in a ratio of 1:1 are shown in Figure 5.11 and the solvent front penetration rates and exponents are presented in Table 5.5. The medium penetrates the xanthan gum at a faster rate compared with the other two gums. This is consistent with the axial and radial swelling studies which showed that xanthan gum also had the fastest swelling rate. The solvent front penetration exponents (n_p) follow almost Fickian kinetics in common with the swelling exponents.

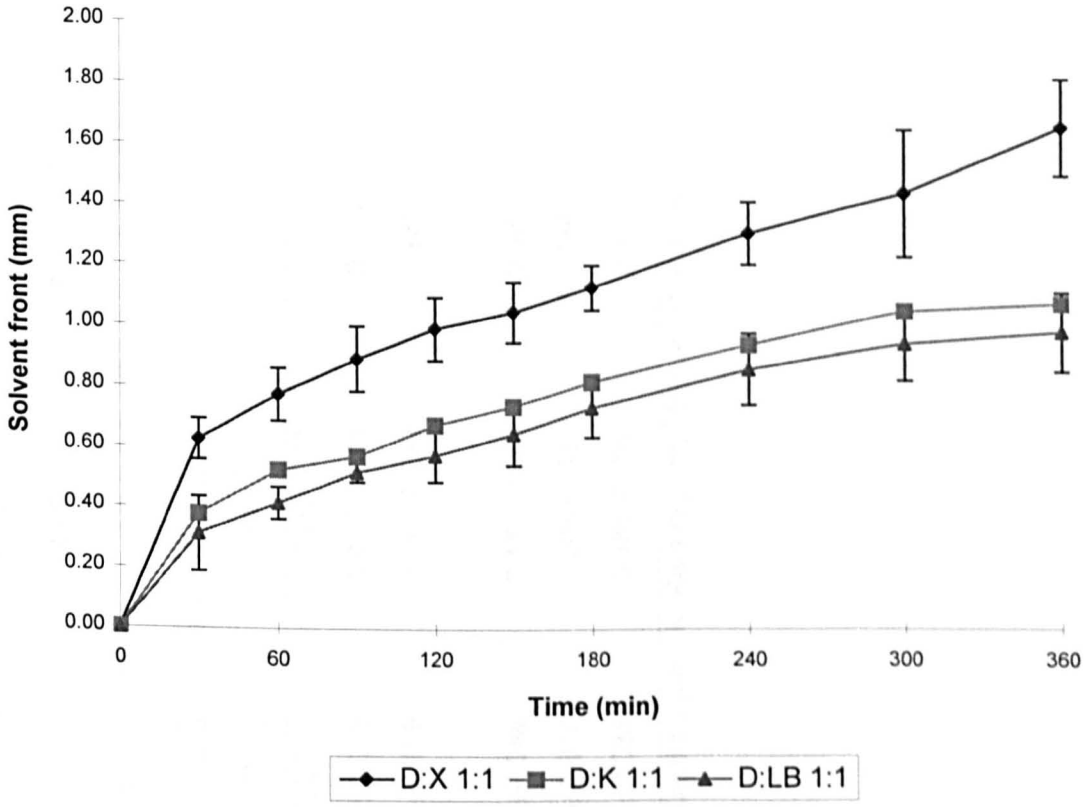


Figure 5.11. Solvent front penetration profiles showing the degree of solvent front penetration (mm) against time (min) in single mini-matrices containing 1:1 mixture of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

Table 5.5. Solvent front penetration parameters using Equation 5.2b to calculate the solvent front penetration exponent (n_p) and the kinetic constant (C_p). The solvent front penetration rate was calculated from the slopes of the linear portion of the plot of penetration front versus square root of time (mean values±SD; n=3).

Mini-matrices composition*	Solvent penetration exponent (n_p)	Kinetic constant (C_p) (min^{-n})	Correlation coefficient (r)	Solvent front penetration rate (mm $sec^{-1/2}$)×10^{-3}	Correlation coefficient (r)
D:X 1:1	0.396±0.051	0.155±0.041	0.989	9.02±2.02	0.992
D:K 1:1	0.430±0.052	0.087±0.011	0.995	7.70±1.40	0.985
D:LB 1:1	0.592±0.119	0.045±0.029	0.989	6.71±1.32	0.992
D:X 2:1	0.361±0.048	0.172±0.045	0.982	8.39±0.75	0.987
D:X 2:3	0.366±0.010	0.208±0.021	0.990	10.64±0.98	0.994
D:X 1:2	0.426±0.035	0.188±0.029	0.993	15.04±2.06	0.994

*D, Diclofenac sodium; X, Xanthan gum; K, Karaya gum; LB, Locust bean gum.

5.4.2.2 Effect of drug: xanthan gum ratio

The solvent front penetration profiles of diclofenac sodium: xanthan gum at various ratios (Figure 5.12) show that medium penetration is impeded in the matrices with the highest drug content (drug: gum 2:1). The solvent front penetration rates of the mini-matrices containing various proportions of drug and xanthan gum are shown in Table 5.5. The penetration rate is lowest in the matrices containing the highest drug content. Other workers (Mitchell et al. 1991; Vandelli and Cameroni 1993; Panomsuk et al. 1995a) have reported similar findings using other polymers and drugs. The solvent molecules bombard the polymer chains in a random fashion, therefore the presence of solid particles of drug embedded in the polymer network will further impede the movement of water molecules through the hydrated material. Although water penetration into highly drug-loaded matrices is relatively slow, these hydrated regions would be much more porous as a result of dissolution of the drug. The degree of porosity and swelling would be directly related to the drug content of the matrix. The dissolved drug does not inhibit the swelling process, but rather bonding between the polymer network chains is reduced as they become separated with consequent loss of matrix integrity.

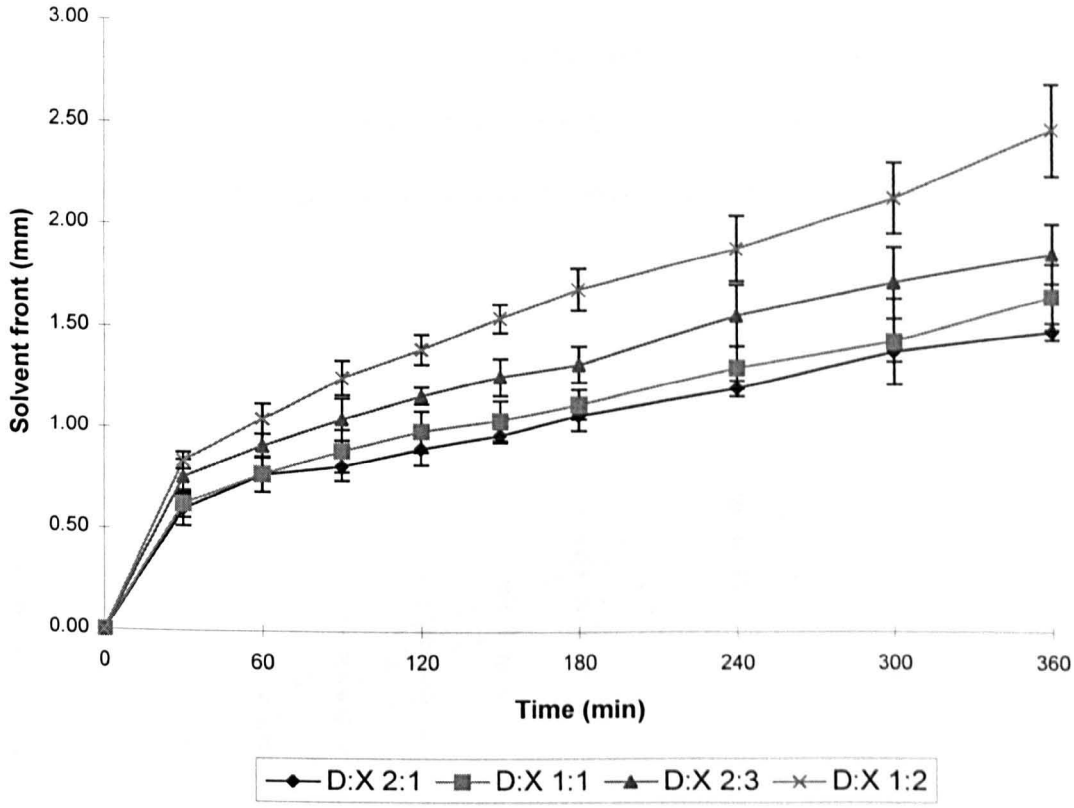


Figure 5.12. Solvent front penetration profiles showing the degree of solvent front penetration (mm) against time (min) in single mini-matrices containing various mixtures of xanthan gum (X) with diclofenac sodium (D) in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

5.4.2.3 Effect of excipient concentration

The solvent front penetration profiles of diclofenac sodium, xanthan gum and Veegum® at various ratios are shown in Figure 5.13. The solvent front penetration profiles were insignificantly different; ≤ 0.3 mm difference between the maximum and minimum front at 360 minutes after contact with the medium. All the profiles exhibited Fickian kinetics with the n_p value range between 0.384-0.447 and the penetration rate range between 8.55-11.29×10^{-3} mm $sec^{-1/2}$ (Table 5.6). These results implied that

Veegum® neither impeded nor enhanced the penetration of the medium into the matrices. It might have similar performance to xanthan gum when in contact with the medium. These results are consistent with the axial and radial swelling which showed that Veegum® had an insignificant effect on the swelling profiles.

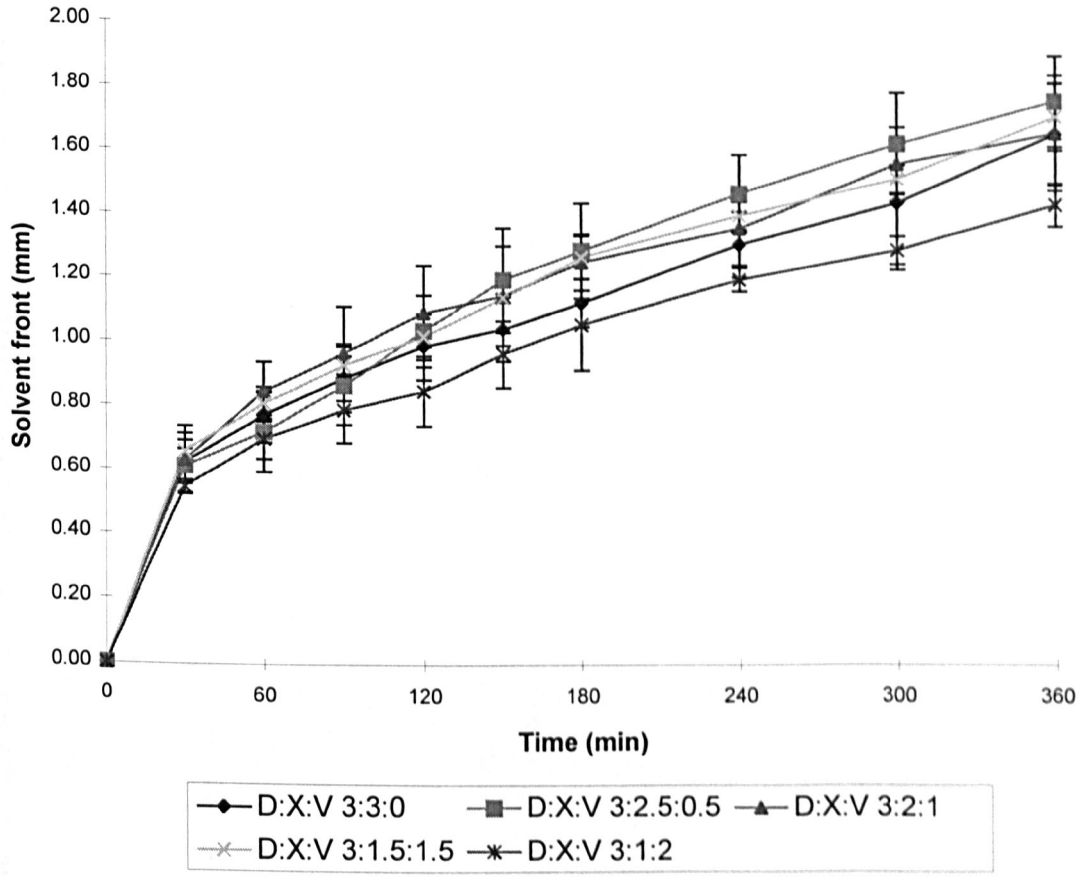


Figure 5.13. Solvent front penetration profiles showing the degree of solvent front penetration (mm) against time (min) in single mini-matrices containing diclofenac sodium (D), xanthan gum (X) and Veegum® (V) at various ratios in 0.0001% methylene blue solution in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

Table 5.6. Solvent front penetration parameters using Equation 5.2b to calculate the solvent front penetration exponent (n_p) and the kinetic constant (C_p). The solvent front penetration rate was calculated from the slopes of the linear portion of the plot of penetration front versus square root of time (mean values±SD; n=3).

Mini-matrices composition*	Solvent penetration exponent (n_p)	Kinetic constant (C_p) (min^{-n})	Correlation coefficient (r)	Solvent front penetration rate ($mm\ sec^{-1/2}$)$\times 10^{-3}$	Correlation coefficient (r)
D:X:V 3:3:0	0.396±0.051	0.16±0.04	0.989	9.02±2.02	0.992
D:X:V 3:2.5:0.5	0.447±0.084	0.14±0.05	0.989	11.29±2.07	0.989
D:X:V 3:2:1	0.384±0.036	0.18±0.03	0.983	10.04±0.99	0.983
D:X:V 3:1.5:1.5	0.393±0.017	0.16±0.02	0.988	10.12±0.70	0.990
D:X:V 3:1:2	0.394±0.017	0.14±0.02	0.980	8.55±0.40	0.986
D:X:V 3:0.5:2.5	-	-	-	-	-

*D, Diclofenac sodium; X, Xanthan gum; V. Veegum®.

5.4.3 Erosion study

Results of the erosion studies on diclofenac sodium: gum ratios of 1:1 are provided in Figure 5.14. These studies reflect both the amounts of drug dissolved and the relaxation of the gum from the mini-matrices during the dissolution study. The matrix consisting of diclofenac sodium: locust bean gum 1:1 showed the greatest degree of erosion after 6 hours (63%), followed by diclofenac sodium: xanthan gum (43%) and diclofenac sodium: karaya gum (24%).

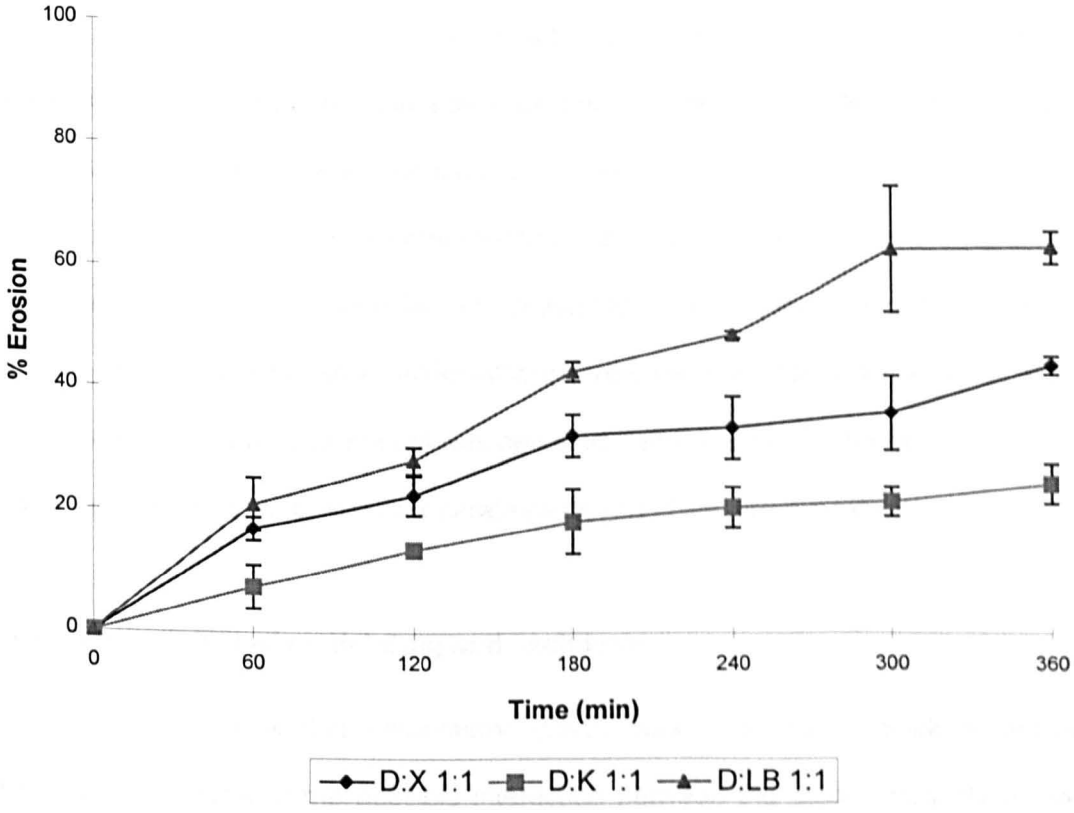


Figure 5.14. The percentage of erosion against time (min) from single mini-matrices containing 1:1 mixtures of various hydrophilic gums; xanthan gum (X), karaya gum (K) and locust bean gum (LB), and diclofenac sodium (D) in 0.05 M phosphate buffer pH 7.0 (mean values±SD, n=3).

The fact that xanthan gum does not yield the slowest drug dissolution rate can be explained by its moderate erosion rate. There are two competing mechanisms of drug release. Swelling and erosion of the material are occurring simultaneously resulting in moving boundary conditions which continuously modify the effective diffusivity of the drug. Erosion increases the drug dissolution rate thus compensating to some extent for the high swelling index and the consequent slowing of drug diffusion by the increasing diffusional path length.

With locust bean, on the other hand, the high erosion rate coupled with the low axial and radial swelling index and consequent shorter diffusional path length, account for the high drug release rate. As would be expected, the penetration rate of the dissolution medium was also low, which is characteristic of a material with a low swelling index.

Karaya gum shows moderate swelling and solvent penetration rates, but has a very slow rate of erosion. These factors combine to result in a low rate of drug release. Karaya gum did not demonstrate an initial "burst" release, but in fact there was a brief lag time before any measurable amount was detected (see Figure 4.1). This lag period could also be explained on the basis of moderate swelling and low erosion rate.

5.4.4 Compatibility of model drug and excipients

Differential scanning calorimetry (DSC) was used as a quick screening technique for assessing the possible interaction between the model drug, diclofenac sodium, and the substances used in the formulation. Interaction in the samples are derived or deduced from DSC by changes in the thermal events such as elimination of an endotherm or exotherm peak or appearance of a new endotherm or exotherm peak. Changes in peak shape, peak onset or peak maximum temperature and relative peak heights are changes which might also be considered. However, it should be cautioned that some broadening of peaks leading to changes in area, onset or peak

temperatures are simply due to mixing the components without indicating an interaction. Provided that all thermal features more or less remain in the sample, compatibility can be accepted. The thermal characteristics of all the substances and mixtures studied were tabulated in Table 5.6.

The thermogram of diclofenac sodium showed an endotherm with an onset temperature of 280.4°C followed by the broad exotherm in the range of 310-335°C. This result indicated melting and decomposition of diclofenac sodium respectively. The thermogram of xanthan gum showed a broad exotherm at the range of 254-316°C. It indicated decomposition of the gum. The physical mixture of diclofenac sodium and xanthan gum 1:1 showed the endotherm of diclofenac sodium and the combination of exotherm of diclofenac sodium and xanthan gum with the endotherm onset of 281.4°C and the exotherm range of 288-310°C. The transitions of diclofenac sodium and xanthan gum might overlap each other resulting in slightly changed transition temperatures.

The thermogram of lactose exhibited two endotherms with onset temperatures of 146.7 and 212.3°C. Lactose exists in several forms which vary in their response to water. α-Lactose is an unstable anhydrate which absorbs one water molecule to form α-lactose monohydrate. Therefore, the first endotherm referred to loss of water of crystallisation and the second shows the melting of α-lactose. A physical mixture of xanthan gum and lactose 1:1 exhibited two endotherms of lactose with onset temperature of 145.8 and 210.5°C and one exotherm of xanthan gum at the range of 281-303°C (Table 5.6). The physical mixture of diclofenac sodium and lactose 1:1 exhibited the two endotherms of lactose and an irregular exotherm at the range of 240 to 300°C (Table 5.6). Diclofenac sodium and lactose might be dissolving in each other resulting in lowering of the second endotherm onset (lower melting point) and no endotherm of diclofenac sodium. However, the broad irregular exotherm resulting from

decomposition of diclofenac sodium still remained. There was no evidence of any new thermal events. In addition, this test was performed at elevated temperature but the production and administration of this product would be at room temperature. Hence lactose was unlikely to cause any interaction in the preparation of diclofenac sodium, xanthan gum and lactose mini-matrices.

The thermogram of Encompress® exhibited no transition over the temperature range of 30-400°C. The physical mixture of diclofenac sodium and Encompress® 1:1 exhibited the endotherm of diclofenac sodium at an onset temperature of 258.3°C. The physical mixture of xanthan gum and Encompress® 1:1 exhibited the exotherm of xanthan gum at the range of 254-316°C. Encompress® is reported to decompose below 100°C (Parikh 1994) but from this experiment there was no exotherm of decomposition of Encompress®. However, the thermal characteristics of diclofenac sodium and xanthan gum still remained in the mixtures of these substances and Encompress®. These results indicated no interaction between diclofenac sodium, xanthan gum and Encompress®.

The thermogram of cellulose acetate phthalate (CAP) and physical mixture of either diclofenac sodium or xanthan gum and CAP 1:1 exhibited no transition over the temperature range of 30-400°C. The melting point of CAP was reported to be 192°C (Sakellariou et al. 1985). The thermal characteristics of diclofenac sodium and xanthan gum were eliminated from the mixture of these substances and CAP. This might indicate some interaction between diclofenac sodium and xanthan gum with CAP.

Table 5.6. The onset and range of transition (°C) of diclofenac sodium, xanthan gum, excipients and 1:1 physical mixtures of each of these substances from DSC thermograms.

Substance*	Endotherm onset (°C)	Exotherm range (°C)	Endotherm onset (°C)	Endotherm onset (°C)	Exotherm range (°C)
D	280.4	310-335	-	-	-
X	-	-	-	-	254-316
L	-	-	146.7	212.3	-
D:X	281.4	-	-	-	288-310
D:L	-	240-300	147.0	176. 7	-
X:L	-	-	145.8	210.5	281-303
E	-	-	-	-	-
D:E	258.3	-	-	-	-
X:E	-	-	-	-	254-316
CAP	-	-	-	-	-
D:CAP	-	-	-	-	-
X:CAP	-	-	-	-	-
V	-	-	-	-	-
D:V	287.9	295-315	-	-	-
X:V	-	-	-	-	289-317
MgSt	-	-	-	106.3	-
D:MgSt	-	-	-	104.6	-

*D; Diclofenac sodium, X; Xanthan gum, L; Lactose, E; Encompress®, CAP; Cellulose acetate phthalate, V; Veegum F® and MgSt; Magnesium Stearate.

The thermogram of Veegum® also exhibited no transition over the temperature range of 30-400°C. The physical mixture of diclofenac sodium and Veegum® 1:1 exhibited the endotherm of diclofenac sodium at the onset temperature of 287.9°C

followed by the exotherm in the range of 295-315°C. The physical mixture of xanthan gum and Veegum® 1:1 exhibited the exotherm of xanthan gum in the range of 289-317°C. The thermal characteristics of diclofenac sodium and xanthan gum in the mixtures of these substances with Veegum® indicated no interaction between diclofenac sodium, xanthan gum and Veegum®.

The thermogram of magnesium stearate exhibited one endotherm with an onset temperature of 106.3°C. The physical mixture of diclofenac sodium and magnesium stearate 1:1 exhibited one endotherm of magnesium stearate at an onset temperature of 104.6°C. The endotherm of diclofenac sodium was eliminated indicating that diclofenac sodium had possibly dissolved in the melted magnesium stearate. However, in the real situation this phenomenum was unlikely to happen because of the fact that this test was performed at elevated temperature but the production and administration of this product would be at room temperature. Furthermore, the amount of magnesium stearate used in the formulation was very little, 1% in the matrix, compared with 50% in this experiment. In addition, there are many reports using magnesium stearate in diclofenac sodium sustained-release preparation without the evidence of any incompatibility problem (Malamataris and Ganderton 1991; Bain et al. 1991; Naggar et al. 1992; Sarisuta and Mahahpunt 1994; Navarro and Ballesteros 1994; Conte et al. 1994; Chetty et al. 1994; Lin et al. 1995; Chattaraj and Das 1996).

5.5 CONCLUSION

The xanthan gum mini-matrices showed the greatest swelling in both the axial and radial dimensions. The medium penetration profiles presented the same order; xanthan gum> karaya gum> locust bean gum but the degree of erosion was somewhat different; locust bean gum> xanthan gum> karaya gum. The drug release from these

mini-matrices depended on both swelling and erosion of the gum. These results supported the findings on the Fickian diffusion and relaxation contributions shown in Chapter 4.

For diclofenac sodium and xanthan gum at various ratios, the higher the xanthan gum content the slower the swelling rate. However, high xanthan gum content mini-matrices eventually swell to a greater maximum extent compared to low xanthan gum content mini-matrices. The solvent penetration profiles of diclofenac sodium and xanthan gum mini-matrices in the ratio of 1:2 is higher than 2:3, 1:1 and 2:1 respectively. The presence of solid particles of drug embedded in the polymer network impede the movement of water molecules through the hydrated material. Although water penetration into highly drug loaded matrices is relatively slow, these hydrated regions would be much more porous as a result of dissolution of the drug.

Veegum® has insignificant effect on the swelling and solvent penetration of mini-matrices consisting of diclofenac sodium and xanthan gum. The slight lowering of the swelling rate at high proportion of Veegum® was due to the corresponding lowering of the xanthan gum proportion.

Diclofenac sodium, xanthan gum and excipients used in this formulation (lactose, Encompress® and Veegum®), except for CAP, were unlikely to have any interaction with each other due to the screening by DSC.

CHAPTER 6

APPLICATION OF THE HYDROPHILIC MINI-MATRIX PRINCIPLE TO THE DEVELOPMENT AND EVALUATION OF A MULTIPLE-UNIT ORAL SUSTAINED RELEASE DOSAGE FORM FOR S(+)IBUPROFEN

6.1 INTRODUCTION

Ibuprofen (2-(4-isobutylphenyl) propionic acid) is a non-steroidal anti-inflammatory drug (NSAID) widely used in rheumatoid arthritis, osteoarthritis and a number of other painful conditions. It has a chiral carbon atom on the propionic side-chain and therefore exists in two enantiomeric forms. S(+) ibuprofen is the pharmacologically active form and 160 times more potent than R(-) ibuprofen (Adams et al. 1976). R(-) ibuprofen is inverted to S(+) ibuprofen (Hutt and Caldwell 1983) to the extent of 57-69% for oral doses (Cheng et al. 1994; Lee et al. 1985) and 69% for intravenous doses (Cheng et al. 1994). A large inter-individual variability in the ratio of S(+) to R(-) ibuprofen average concentration at steady-state was observed and probably accounts for the known lack of correlation between racemic ibuprofen concentration and therapeutic efficacy (Oliary et al. 1992; Evans et al. 1990). In addition, previous studies in the rat revealed that R(-) ibuprofen formed potentially toxic hybrid triglycerides that slowly eliminated from adipose tissue (Williams et al. 1986). S(+) ibuprofen is therefore a better choice of drug than racemic ibuprofen. Not only the dose of drug but also the metabolic inversion in the body will be reduced. The toxicity resulting from R(-) ibuprofen administration will consequently be eliminated.

The purpose of this study is to prepare S(+) ibuprofen mini-matrix MUDFs. The knowledge gained from the preparation of diclofenac sodium mini-matrix MUDFs will

be applied to S(+) ibuprofen. Xanthan gum and karaya gum will be the principle materials used to form the matrix because they produced satisfactory release profiles of diclofenac sodium from mini-matrix MUDFs (see also Chapter 4). HPMC will also be used for comparative purposes. The most satisfactory formulation will be subjected to stability studies at elevated temperatures and relative humidities.

6.2 MATERIALS

Natural hydrophilic gums: xanthan gum (X) and karaya gum (K).

Synthetic hydrophilic polymer: HPMC.

Model drug: S(+) ibuprofen (I).

Excipients: lactose (L), dicalcium phosphate (Encompress®, E) and microcrystalline cellulose (Avicel® PH101, A).

Lubricant: talc and hydrogenated cottonseed oil (Lubritab®).

Buffers, liquids and solutions: sodium hydroxide and potassium dihydrogen orthophosphate were used to prepare phosphate buffer solutions pH 6.5, 7.0 and 7.2 (USP XXIII 1994), hydrochloric acid and potassium chloride were used to prepare hydrochloric acid buffer solution pH 1.5 (USP XXIII 1994), sodium phosphate and citric acid were used to prepare citrate-phosphate buffer solution pH 5.0 (Wade 1980), and potassium hydroxide, magnesium chloride and sodium chloride were used to prepare saturated solutions for use in the humidity chamber (Wade 1980).

6.3 METHODS

6.3.1 Preparation of mini-matrices

All materials were passed through a mesh sieve with an aperture of 250 μm before use. Matrix tablets were prepared by the wet granulation method. The

composition of the formulations are given in Table 6.1. All materials, with the exception of lubricants (talc or Lubritab®), were thoroughly mixed in a tumbling mixer for 5 minutes and then wetted in a mortar with 50% v/v ethanol. The wet mass was then passed through a 500 μm mesh sieve and dried at a temperature not greater than 40°C (well below the melting point of S(+) ibuprofen) for 18 hours. The dried granules were then rescreened through a 300 μm mesh sieve, lubricated with talc 2% w/w or Lubritab® 1% w/w and compressed into flat-faced mini-matrices of diameters 4.5 mm each weighing 30.61±1.0 mg and containing 10±0.33 mg of S(+)ibuprofen. An instrumented Manesty F3 single punch tablet machine (Manesty Machines Ltd., Liverpool, England) was used to compress the mini-matrices. The crushing strength of 10 matrices was individually measured using an Erweka hardness tester (Erweka TBH 28, Germany). The mean crushing strength and standard deviation were calculated. Eight mini-matrices were encapsulated in size 1 hard gelatin capsules to produce a multiple unit dosage form (MUDF), with a total dose of 80 mg of S(+) ibuprofen.

Table 6.1. Composition (%) of the mini-matrices containing S(+)ibuprofen, hydrophilic gums (xanthan gum, karaya gum) or HPMC, and various excipients.

	Formulations			
	15A-C*	16A-C*	17A*	18A*
S(+) ibuprofen	32.67	32.67	32.67	33
Xanthan gum	32.67	-	-	33
Karaya gum	-	32.67	-	-
HPMC K4M	-	-	32.67	
Excipients (lactose, Encompress® and Avicel® PH101)	32.67	32.67	32.67	33
Talc	2	2	2	-
Lubritab®	-	-	-	1

*A, B and C series for each formulation number contain lactose, Encompress®, and Avicel® PH101, respectively.

6.3.2 Compression study

They have been reports in the literature that compression force has a negligible influence on the drug release rate from compressed hydrophilic matrices (Hogan 1989; Huber and Christenson 1968; Lapidus and Lordi 1968; Ford et al. 1985a; Talukdar and Plaizier-Vercammen 1993). However, these studies were conducted using active ingredients with much higher melting points than S(+) ibuprofen. Due to the low melting point of S(+) ibuprofen (53-55°C) there is a greater tendency for capping to occur. Mini-matrices containing S(+) ibuprofen, xanthan gum or karaya gum and lactose in a ratio of 1:1:1 (Formulations 15A and 16A, Table 6.1) were produced using a compression force in the range of 11-26 kN (F3 Compression Cycle Analysis System, BWI Manesty, England). The 5.5 mm diameter punches and die were used for easy observation. The weight of the mini-matrices was increased to 54.93±1.12 mg to suit their size. The crushing strength of these mini-matrices was investigated by the method mentioned earlier. The mean crushing strength and standard deviation were calculated and plotted against compression forces (Figure 6.1).

6.3.3 Mini-matrix dissolution study

The USP XXIII basket method (Copley Dissolution System and Drive Control, Copley Instruments, Nottingham, England) was used with a constant temperature water bath at 37±0.5°C. The dissolution medium used was 0.05 M phosphate buffer (pH 7.0). The speed of rotation was 100±1 rpm. The dissolution apparatus was connected to a flow-through UV spectrophotometer (Ultrospec II, LKB Biochrom Ltd., England) via a peristaltic pump. The absorbance was measured automatically at 231 nm in a 10 mm cell at 30 minute intervals over a 12 hour period.

In addition to the new formulations produced, the release profile of commercially available ibuprofen sustained release products; Brufen Retard® (Boots, 800 mg/tablet) and Fenbid Spansule® (Goldshield, 300 mg/capsule), were also studied.

The studies were carried out in triplicate. The cumulative percentage of S(+) ibuprofen released was calculated and plotted against time. The release rates were calculated from a Higuchi plot (Equation 1.8). The values of n and k were calculated from a plot of log fraction of drug release against log time (Equation 1.1). The Fickian and relaxational contributions were calculated according to Equation 1.2.

The pH change dissolution method (changing the pH of the dissolution medium while running the dissolution test) was also used with mini-matrices formulations 15A and 17A in order to simulate the environment of the gastro-intestinal tract. The dissolution media used were 0.05 M hydrochloric acid buffer pH 1.5 for the first hour, citrate-phosphate buffer pH 5 for the second hour, 0.05 M phosphate buffer pH 6.5 for the next 3 hours and finally 0.05 M phosphate buffer pH 7.2 for 3 hours. Each medium was warmed to 37±0.5°C. At defined time intervals, the dissolution medium was removed and fresh medium added. The amount of drug released in the dissolution medium at pH 1.5 was analysed by the first order derivative spectrophotometric method because of the broad absorbance spectrum. For the other media, the simple UV absorption at wavelength 231 nm was used.

6.3.4 Compatibility of model drug and excipients

Only the S(+) ibuprofen mini-matrices that produced satisfactory release profiles were considered for this test. Physical mixtures of binary systems containing either S(+) ibuprofen, natural hydrophilic gums and/or excipients in a ratio of 1:1 were prepared with a mortar and pestle. The individual substances and physical mixtures

were thermally characterised using a differential scanning calorimeter (Pyris1, Perkin Elmer, USA). The samples (1.5-5 mg) were weighed directly into flat bottomed aluminium sample pans. The pans were crimped with the lid on top of the sample. These samples were heated in a nitrogen atmosphere. The heat flow rate of 20°C/min was monitored as a function of temperature from 30 to 400°C. The thermograms were recorded.

6.3.5 Stability study of S(+) ibuprofen mini-matrices

Only the S(+) ibuprofen mini-matrices that produced the most satisfactory release profiles were considered for this test. They were stored in open amber bottles at 10, 33 and 75% relative humidity. The 10 and 75% relative humidity chambers were kept at 22 and 37°C and the 33% relative humidity chambers were kept at 5, 22 and 37°C for 2 months. The mini-matrices were sampled after 2 weeks and then at 2 months for investigation of the physical characteristics; weight, crushing strength and friability, and the release characteristics compared with mini-matrices within 24 hours after preparation. In addition, this production batch was also investigated for uniformity of content and weight.

6.3.5.1 Uniformity of weight

The weight of 20 tablets were individually measured. The average weight and standard deviation were calculated. For the tablets that weigh ≤ 80 mg, the requirements are met if not more than two of the individual weights deviate from the average weight by more than 10% and none deviates by more than 20% (BP 1993). For uncoated tablets that are required to comply with the test for uniformity of content for all active ingredients, the test for uniformity of weight is not required.

6.3.5.2 *Uniformity of content*

In general, the tablets that contain more than 2 mg or more than 2% w/w of active ingredient are not required to pass the uniformity of content test (BP 1993). But in this experiment, both the uniformity of weight and the uniformity of content were studied for the new product.

The requirements for dose uniformity are met if the amount of the active drug in each of the 10 dosage units lies within the range of 85.0% to 115.0% of the stated amount. If one unit is outside the range of 85.0 to 115.0% of the stated amount and no unit is outside the range of 75.0% to 125.0% of the stated amount, test 20 additional units. The requirements are met if not more than one unit of the 30 is outside the range of 85.0% to 115.0% of the stated amount and no unit is outside the range of 75.0% to 125.0% of the stated amount (BP 1993).

For this study, 10 tablets were individually weighed and dissolved in 10 ml of 0.05 M phosphate buffer pH 7.0. They were left in the mechanical shaker overnight for complete dissolution of the active drug. The solutions were filtered using Whatman® filter paper number 1 with cotton as a filter aid, diluted and the absorbance measured using a UV-spectrophotometer (Shimadzu, UV 160A, Japan) at wavelength 221 nm. The percent labelled amount of active ingredient of each tablet was calculated.

6.3.5.3 *Friability measurement*

Twenty tablets were brushed to remove loose dust and weighed. They were placed in the drum of the friabilator (Erweka TA, Germany) and tumbled with a speed of 25 rpm for 4 minutes. The loose dust was removed and the tablets were weighed again. The percentage weight loss was calculated.

If the weight loss is greater than 1%, the test should be repeated twice and the mean of the three tests determined. A maximum weight loss of not more than 1% of the weight of the tablets being tested is considered acceptable for most products (USP XXIII 1994).

6.4 RESULTS AND DISCUSSION

6.4.1 Preparation of mini-matrices

Initially, the production of mini-matrices containing S(+) ibuprofen and xanthan gum or karaya gum in a ratio of 1:1 was attempted. Both these matrices produced serious capping problems, i.e., the partial or complete separation of the top or bottom crowns of the tablet from its main body. Compaction of cooled granules (5°C) or an increase in the diameter of punches to 5.5 mm were also tried, unsuccessfully, to solve this problem. Therefore the excipients; lactose, Encompress® and Avicel®, which are commonly used and have good compressibility properties, were added to the formulations to improve the compression characteristics.

The S(+) ibuprofen granules became moist when magnesium stearate was added, indicating the incompatibility of magnesium stearate and S(+) ibuprofen. This interaction between magnesium stearate and racemic ibuprofen was also reported by Gordon and co-worker (1984). The lubricant was then changed to talc. The mini-matrices containing S(+) ibuprofen, gum and excipient 1:1:1 were well formed and no capping problems were experienced.

6.4.2 Compression study

Compression forces in the range of 11-26 kN were suitable for the production of mini-matrices containing S(+) ibuprofen, xanthan gum or karaya gum and lactose in

a ratio of 1:1:1 (Formulations 15A and 16A, Table 6.1). At compression forces ≥26 kN, the capping problem was amplified for both formulations. For S(+) ibuprofen mini-matrices containing xanthan gum, a compression force as small as 2.3 kN could be used while for karaya gum the smallest compression force acceptable was 11.3 kN. This implied that xanthan gum had better adhesion properties than karaya gum.

Compression forces in the range 11-26 kN had little effect on crushing strength (Figure 6.1). The crushing strengths of mini-matrices containing xanthan gum varied from 25.1 to 28.0 N while the one containing karaya gum varied from 23.3 to 27.6 N. Hence the crushing strengths of these two formulations were not very different.

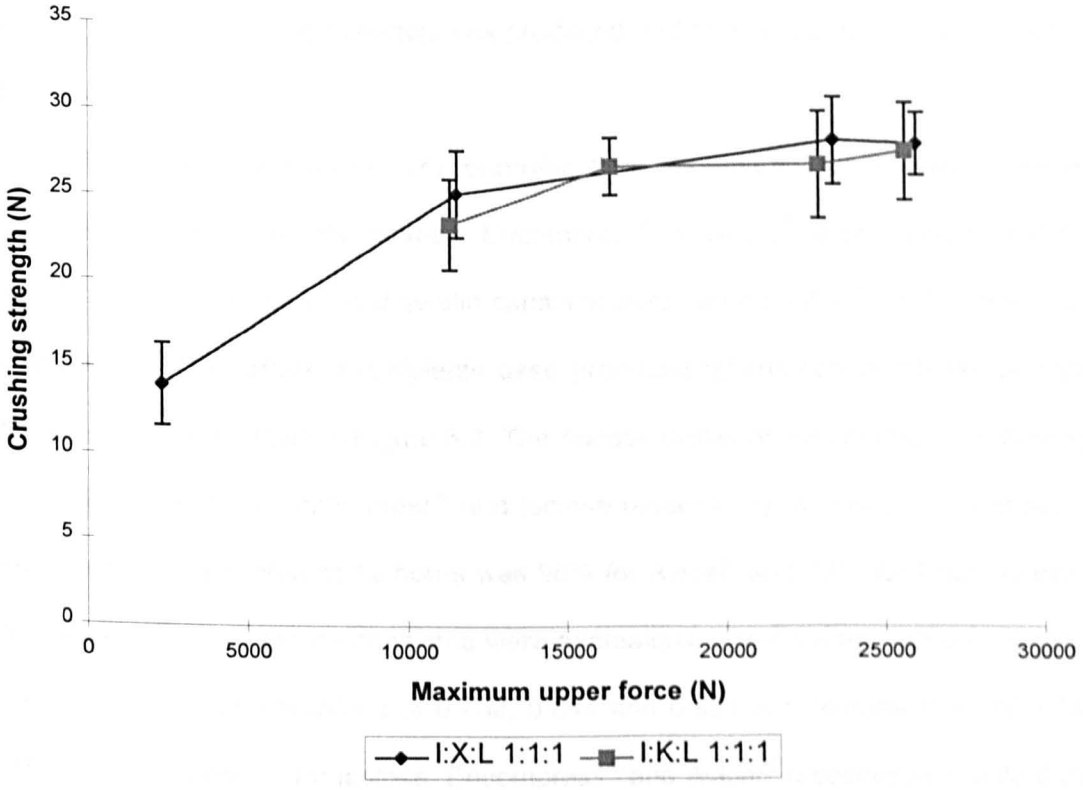


Figure 6.1. The crushing strength of mini-matrices containing S(+) ibuprofen (I), xanthan gum (X) or karaya gum (K), and lactose (L) in a ratio of 1:1:1 against compression force (mean values ± SD; n =10).

6.4.3 Mini-matrices dissolution study

6.4.3.1 Effect of excipients and type of gum on release characteristics

Xanthan gum and karaya gum were used to sustain the release of S(+) ibuprofen from mini-matrices because they presented a satisfactory release profile for diclofenac sodium mini-matrices (see Chapter 4). The excipients were included in the formulations not only to overcome the capping problem but also to regulate the release rate of the drug. Lactose (freely water soluble), dicalcium phosphate (Encompress®, water insoluble) and microcrystalline cellulose (Avicel®, water insoluble) were used in a ratio of drug: gum: excipient 1:1:1. All three excipients are commonly used as diluents in tablet formulations. The mini-matrices produced had crushing strengths in the range of 13-19 N.

The release studies of S(+) ibuprofen from mini-matrices containing xanthan gum and various excipients; lactose, Encompress® or Avicel® (Formulations 15A-C, Table 6.1) encapsulated in hard gelatin capsules were carried out in 0.05 M phosphate buffer pH 7.0. The different excipients used produced differences in release profiles and the results are shown in Figure 6.2. The release profile of mini-matrices containing Avicel® is higher than Encompress® and lactose respectively. Maximum accumulated release of S(+) ibuprofen at 12 hours was 98% for Avicel® and 82% for Encompress® and lactose. The release mechanisms were anomalous (non-Fickian), but approached Case II transport with n values of 0.732, 0.644 and 0.881 and release rates of 3.74, 3.69 and 5.56 % $min^{-1/2}$ for lactose, Encompress® and Avicel® respectively (Table 6.2). There was little difference in release from the formulations containing Encompress® and lactose. Although Avicel® and Encompress® are water insoluble excipients, their drug release profiles were different. The mini-matrices containing Avicel® exhibited a higher drug release rate than those containing Encompress® after the first 2 hours.

This could result from the disintegration property of Avicel®. When in contact with the dissolution medium, xanthan gum absorbs water, swells and becomes a hydrated gel. At the same time Avicel®, having disintegration properties, promoted the disintegration of the mini-matrices. The mini-matrices were therefore easier to erode, compared with Encompress®, resulting in a higher release profile. A similar result, i.e., a slightly higher dissolution rate of acetylsalicylic acid from Eudragit® S-100 matrix containing Avicel® PH101 than that containing Encompress®, was also observed (Jovanovic et al. 1997). In addition, studies have been carried out showing that tablets produced with Encompress® do not disintegrate readily (Rubinstein and Bodey 1976; Koparkar et al. 1990; Fischer 1992), so mini-matrices containing Encompress® would have less tendency to erode, compared with Avicel®, consequently showing a slower release profile.

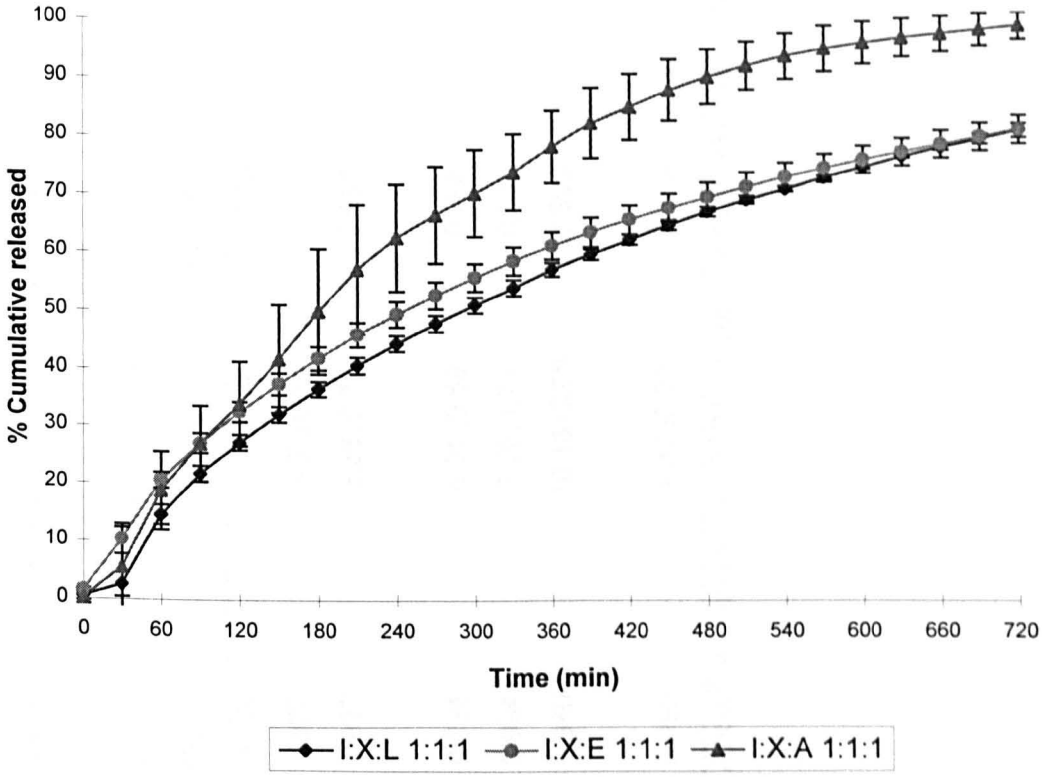


Figure 6.2. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen (I), xanthan gum (X) and lactose (L), Encompress® (E) or Avicel® (A) enclosed in a hard gelatin capsule (mean values ± SD; n =3).

Table 6.2. Release parameters from the encapsulated mini-matrices using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k). The release rate (% $min^{-1/2}$) was calculated from the slopes of the plots of fraction of drug released versus square root of time (Equation 1.8) (mean values ±SD; n=3).

Mini-matrices composition*	Release exponent (n)	Kinetic constant (k) (min^{-n})×10^{-3}	Correlation coefficient (r)	Release rate (% $min^{-1/2}$)	Correlation coefficient (r)
I:X:L 1:1:1	0.732±0.043	8.19±2.34	0.996	3.74±0.06	1.000
I:X:E 1:1:1	0.644±0.012	14.53±1.33	0.997	3.69±0.13	1.000
I:X:A 1:1:1	0.881±0.144	7.21±6.27	0.997	5.56±0.77	0.993
I:K:L 1:1:1	1.143±0.062	1.48±0.39	0.994	6.91±0.69	0.998
I:K:E 1:1:1	1.248±0.261	2.02±2.21	0.994	7.79±1.71	0.997
I:K:A 1:1:1	1.620±0.181	0.30±0.28	0.980	10.18±0.68	0.990
I:HPMC:L 1:1:1	0.763±0.030	8.88±1.81	0.999	4.80±0.22	0.999

*I, S(+) ibuprofen; X, Xanthan gum; L, Lactose; E, Encompress®; A, Avicel®; K, Karaya gum; HPMC, Hydroxypropyl methylcellulose.

The percentage contributions of Fickian diffusion (F) and Relaxation (R) over the first 60% of drug release from mini-matrices containing xanthan gum and lactose or Encompress® are shown graphically in Figure 6.3a and 6.3b respectively. For mini-matrices containing Encompress®, the contribution of Fickian diffusion predominated for the first 8.5 hours of the dissolution period, and gradually decreased until polymer relaxation become predominant at the end (Figure 6.3b). Whereas with mini-matrices containing lactose, the contribution of Fickian diffusion predominated during the first 2 hours, gradually decreasing until polymer relaxation became predominant (Figure 6.3a). On the other hand, with Avicel® the contribution of polymer relaxation occurs almost exclusively throughout the entire dissolution time period, and therefore the graph for this is not shown. This is also apparent from the n value of 0.881 which approaches Case II transport.

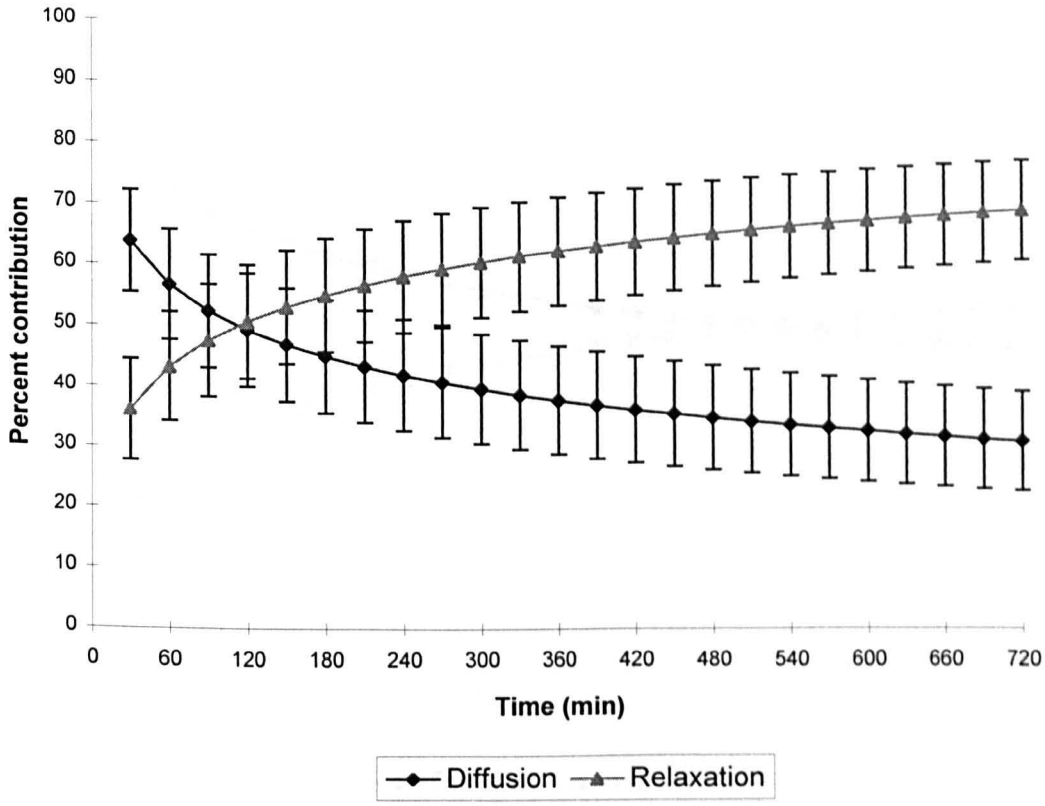


Figure 6.3a. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing S(+) ibuprofen, xanthan gum and lactose (mean values ± SD; n = 3).

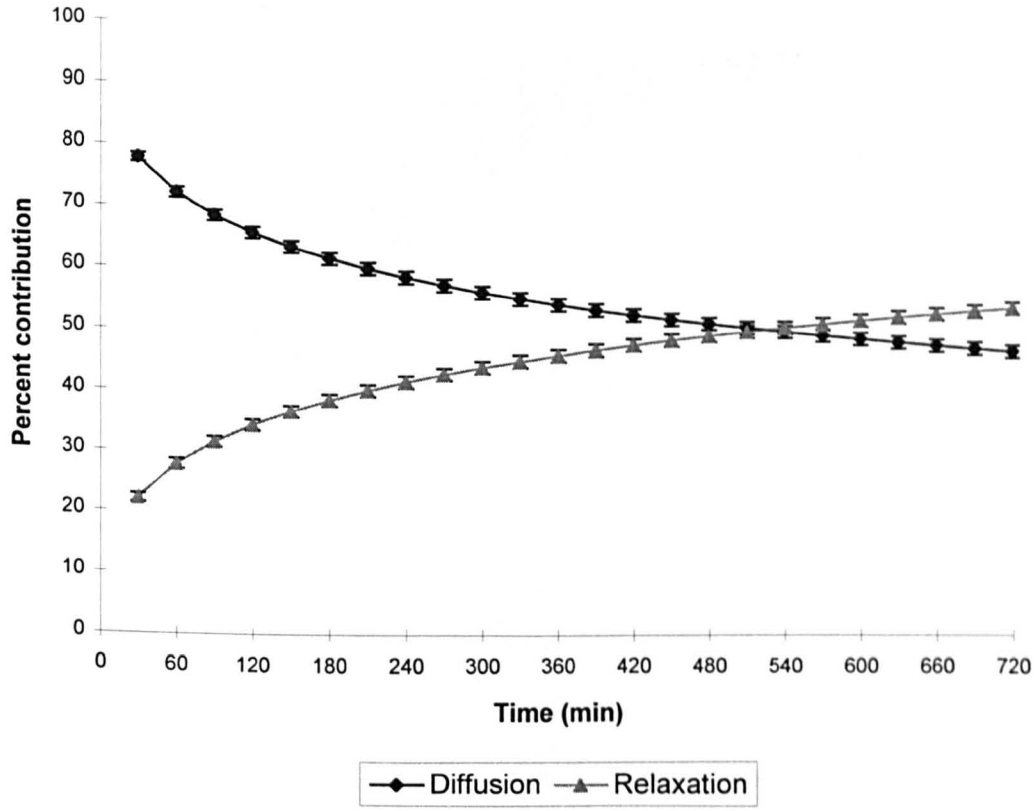


Figure 6.3b. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing S(+) ibuprofen, xanthan gum and Encompress® (mean values ± SD; n = 3).

The release profiles of S(+) ibuprofen mini-matrices containing karaya gum and lactose, Encompress® or Avicel® are shown in Figure 6.4. The rank order of release rate is Avicel® > Encompress® > lactose, the same order as mini-matrices containing xanthan gum. The maximum accumulated drug release were 99% for lactose and Encompress®, and 94% for Avicel®. The release mechanisms are Super Case II transport with n values of 1.143, 1.248 and 1.620 and release rates of 6.91, 7.79 and 10.18 % $min^{-1/2}$ for lactose, Encompress® and Avicel® respectively (Table 6.2).

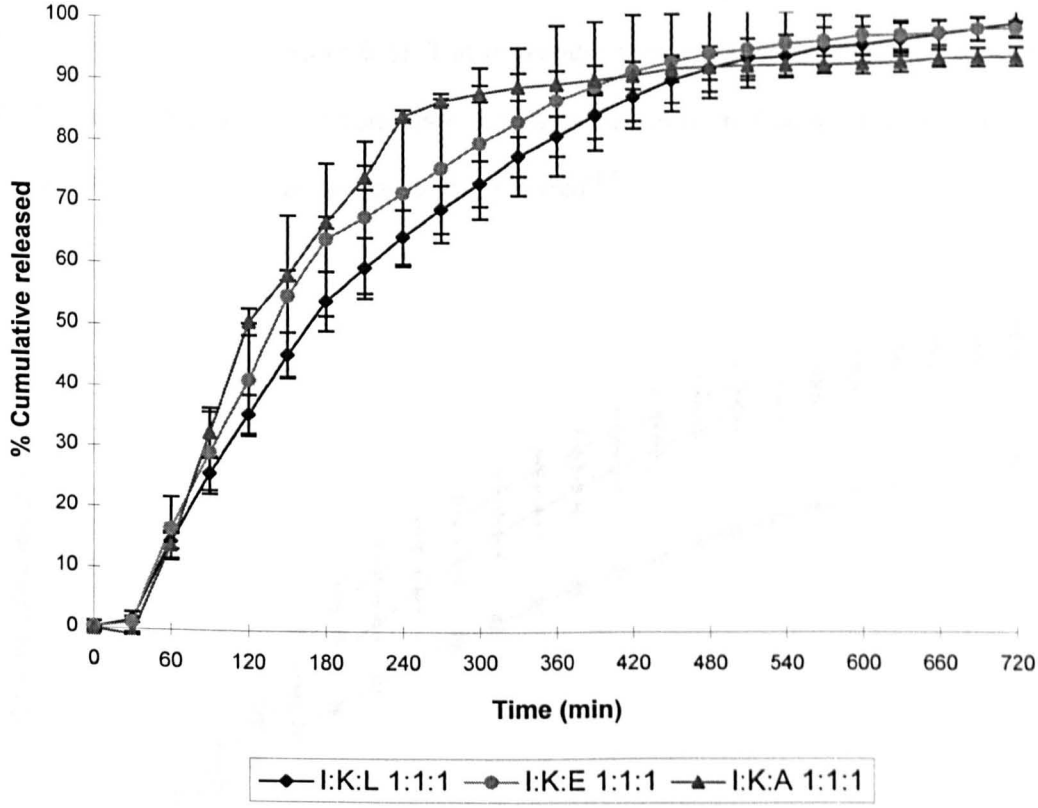


Figure 6.4. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen (I), karaya gum (K) and lactose (L), Encompress® (E) or Avicel® (A) enclosed in a hard gelatin capsule (mean values ± SD; n =3).

The percentage contributions of Fickian diffusion (F) and Relaxation (R) over the first 60% of drug release from mini-matrices containing karaya gum and lactose, Encompress® or Avicel® were calculated according to Equation 1.2. The contribution of polymer relaxation occurs almost exclusively throughout the entire dissolution time period for all three excipients, and therefore the graph for these are not shown. These results correlate with the high release exponents (super Case II transport).

The encapsulated S(+) ibuprofen mini-matrices containing HPMC and lactose in a ratio of 1:1:1 showed an intermediate release profile between S(+) ibuprofen:

xanthan gum: lactose 1:1:1; which is lower, and S(+) ibuprofen: karaya gum: lactose 1:1:1; which is higher (Figure 6.5). The maximum accumulated drug release was 100% at 12 hours. The release mechanism was anomalous (non-Fickian) transport with a n value of 0.763 and a release rate of 4.80 % $min^{-1/2}$.

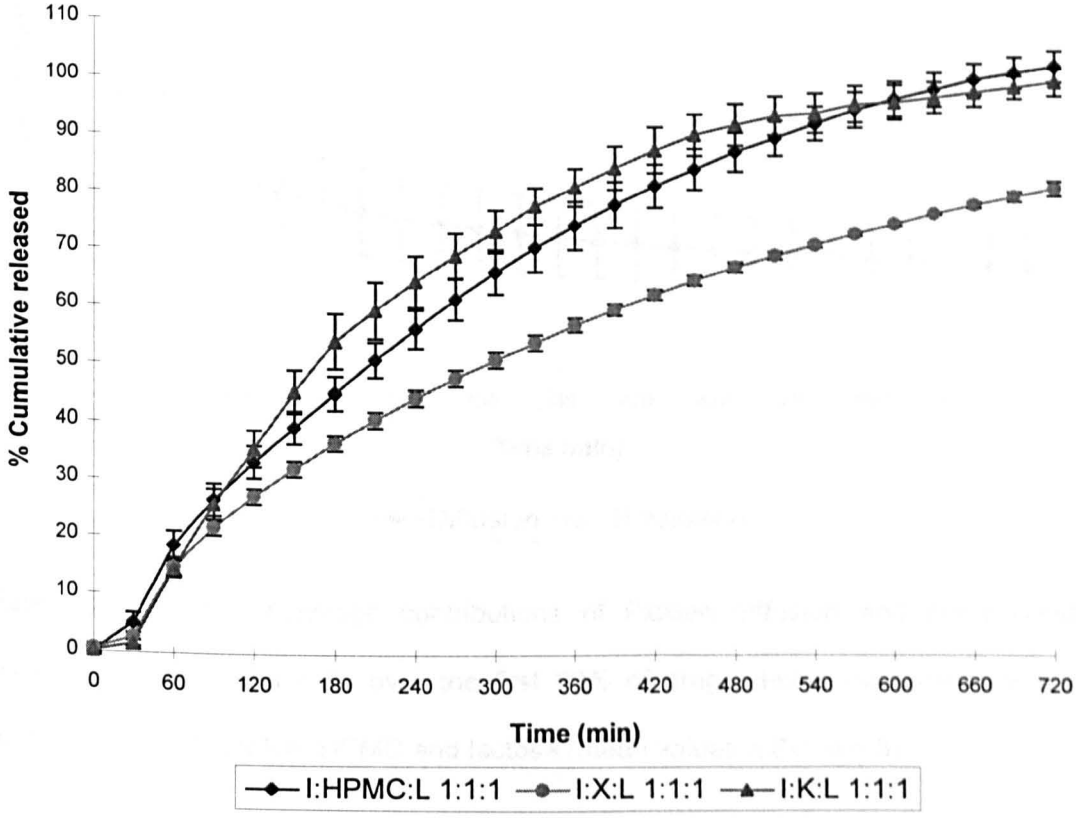


Figure 6.5. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen (I), various gums; xanthan gum (X), karaya gum (K) or HPMC, and lactose (L) enclosed in a hard gelatin capsule (mean values ± SD; n=3).

The percentage contributions of Fickian diffusion (F) and Relaxation (R) over the first 60% of drug release is shown graphically in Figure 6.6. The contribution of Fickian diffusion is relatively small whilst release due to Relaxation is dominant for the entire dissolution time period.

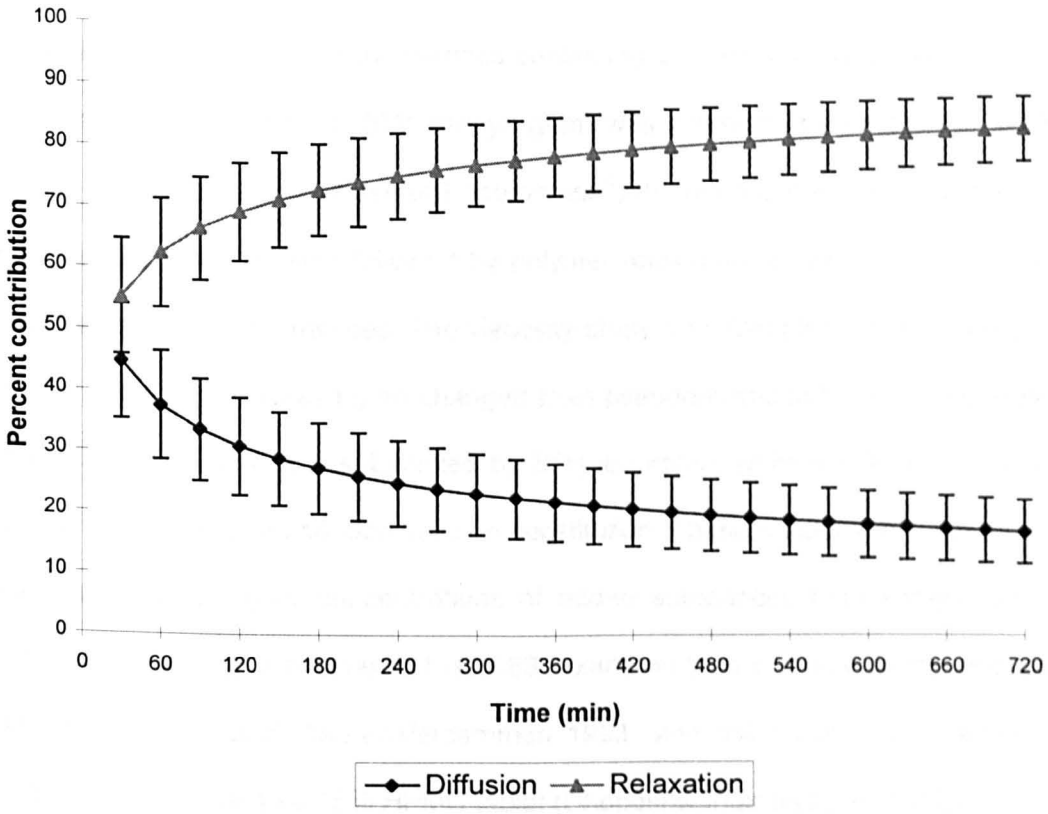


Figure 6.6. The percentage contributions of Fickian diffusion and the polymer relaxation mechanisms valid over the first 60% of drug release from mini-matrices containing S(+) ibuprofen, HPMC and lactose (mean values ± SD; n = 3).

It is noticeable that the release rates of S(+) ibuprofen mini-matrices containing xanthan gum and various excipients were lower than those containing karaya gum. These results are opposite to the results from previous studies (see Chapter 4) in which encapsulated mini-matrices containing diclofenac sodium: xanthan gum 1:1 release the active drug faster than those containing diclofenac sodium: karaya gum 1:1.

For diclofenac sodium: karaya gum 1:1 mini-matrices, the Fickian diffusion was dominant for the first 7 hours of the dissolution period (see Chapter 4), but with S(+) ibuprofen: karaya gum: excipients 1:1:1 mini-matrices, the polymer relaxation was

mostly dominant for the entire dissolution time period. This means that the release mechanism of karaya gum mini-matrices containing diclofenac sodium (49.5% karaya gum) and S(+) ibuprofen (32.67% karaya gum) was different. But for S(+) ibuprofen: xanthan gum: excipients (lactose or Encompress®) the release mechanism at the early period was Fickian diffusion followed by polymer relaxation, similar to the result from diclofenac sodium mini-matrices. The viscosity study from Chapter 3 also showed that the flow behaviour of karaya gum changed from pseudoplastic to the Herschel-Bulkley model when 50% of it was substituted by S(+) ibuprofen, while the flow behaviour of xanthan gum remained pseudoplastic on substitution. These results imply that xanthan gum can tolerate higher concentrations of added substances than karaya gum. In addition, previous reports showed that 5.83% xanthan gum can sustain the release of caffeine (Talukdar and Plaizier-Vercammen 1993) and 5% xanthan gum exhibits a release profile similar to a 15% HPMC tablet (Dhopeshwarkar and Zatz 1993).

6.4.3.2 Effect of dissolution medium on release characteristics

The release profiles of encapsulated mini-matrices comprised of S(+) ibuprofen, xanthan gum or HPMC, and lactose in a ratio of 1:1:1 using the pH change dissolution method are shown in Figure 6.7. The release rate of S(+) ibuprofen from these two formulations depends on the pH of the medium. For the first hour, in hydrochloric acid medium pH 1.5, the accumulated release was <1% which slightly increased in citrate phosphate buffer pH 5 (second hour) but was still negligible (<10%). The release was greatly increased in phosphate buffer pH 6.5 (the next 3 hours). The difference in release rate from these two formulations was clearly noticed in phosphate buffer pH 6.5 and 7.2. The release patterns were similar but the mini-matrices containing HPMC showed the higher degree of release. The pH solubility profile carried out with S(+) ibuprofen (see Chapter 3) showed that S(+) ibuprofen was

practically insoluble in acid medium pH 2 (0.1 mg/ml). The solubility increased slightly in the pH range 2 to 5.7 and rapidly increased at pH >5.7. The release profiles from the pH change dissolution method are consistent with the pH solubility profile. This implied that the release of S(+) ibuprofen from the mini-matrices depended on the solubility of S(+) ibuprofen in the dissolution medium, the pH of this medium being the main determining factor. Both polymers used achieved a sustaining effect on drug release.

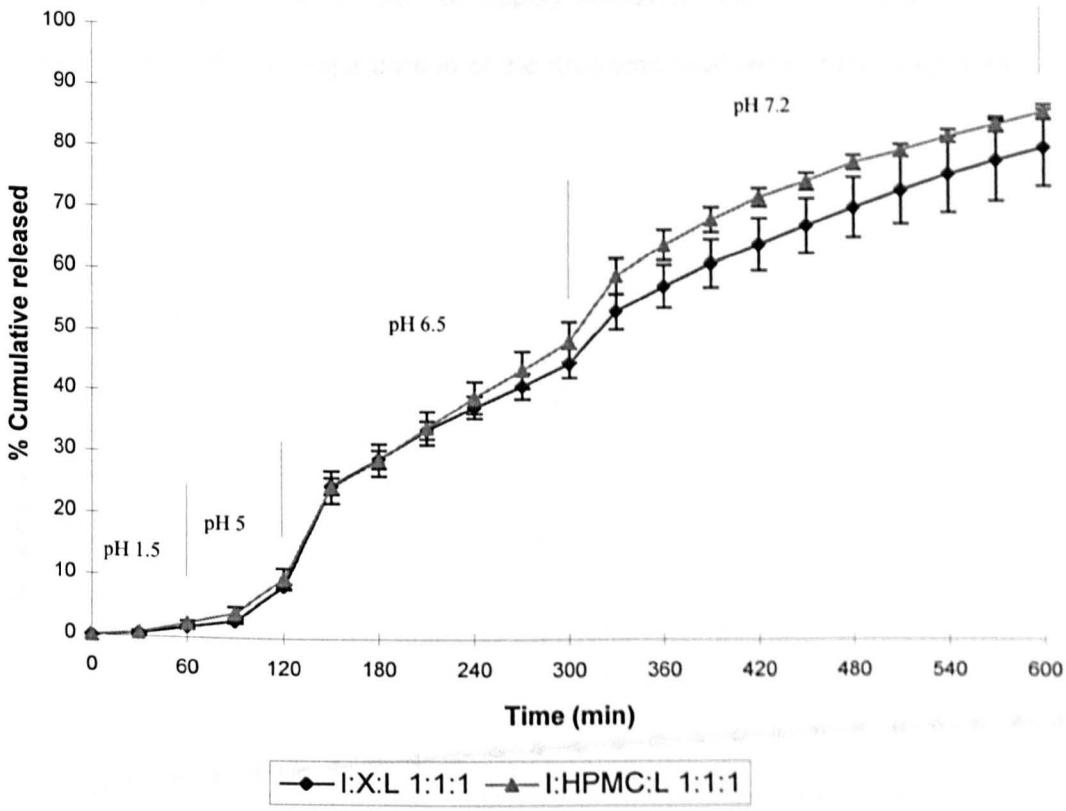


Figure 6.7. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen (I), xanthan gum (X) or HPMC, and lactose (L) enclosed in a hard gelatin capsule using pH change method (mean values ± SD; n =3).

6.4.3.3 Dissolution profile of commercially available ibuprofen sustained release products

The release profile of Brufen Retard® and Fenbid Spansule® in 0.05 M phosphate buffer pH 7.0 are shown in Figure 6.8. The maximum accumulated release of ibuprofen was 11.77% at 12 hours for Brufen Retard®. The release of ibuprofen from Fenbid Spansule® reached 100% within 90 minutes. Under these *in vitro* dissolution conditions, Fenbid Spansule® did not display sustained release of the drug, whereas with Brufen Retard® the major portion of the drug was retained in the dosage form.

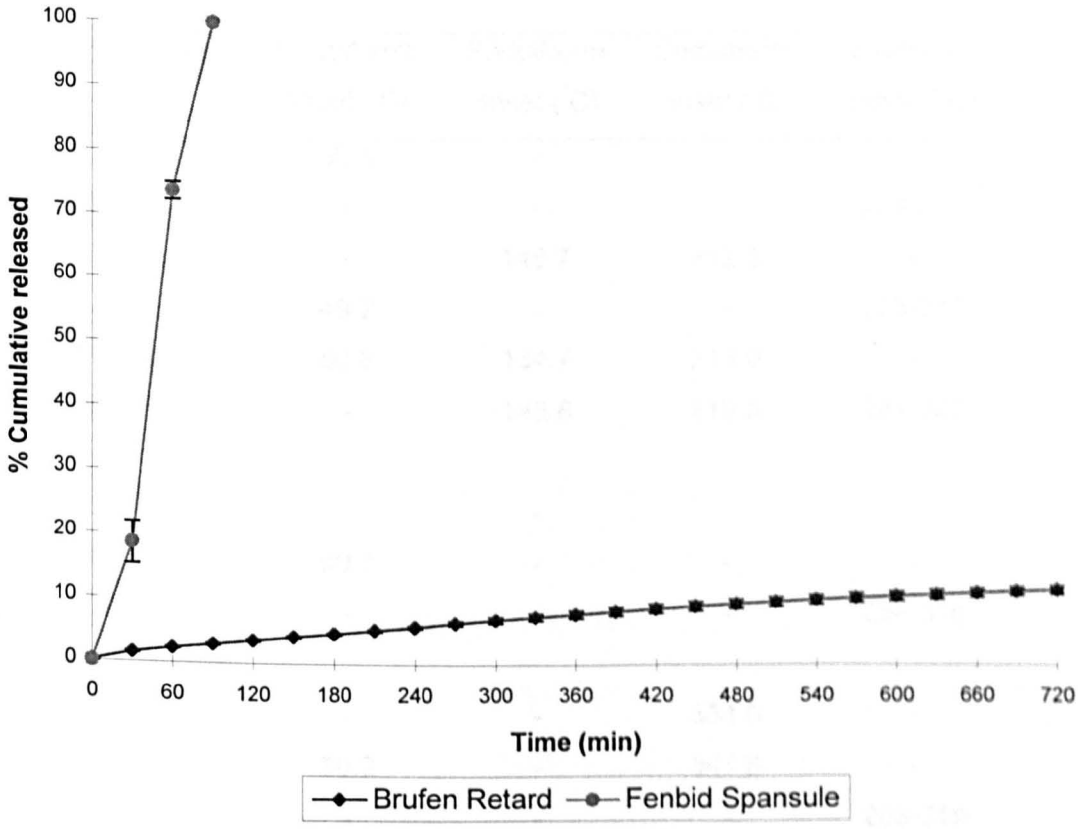


Figure 6.8. Percentage of ibuprofen release against time from Brufen Retard® and Fenbid Spansule® in 0.05 M phosphate buffer pH 7.0 (mean value±SD; n=3).

6.4.4 Compatibility of model drug and excipients

The components of formulations 15A-C and 18A (Table 6.1) were studied in this experiment. The thermal characteristics of each component and mixtures of them were tabulated in Table 6.3. The compatibility between S(+) ibuprofen and lubricants; talc and Lubritab®, were also studied.

Table 6.3. The onset temperature and range of transition (°C) of S(+) ibuprofen, xanthan gum, excipients and 1:1 physical mixtures of each of these substances from DSC thermograms.

Substance*	Endotherm onset (°C)	Endotherm onset (°C)	Endotherm onset (°C)	Exotherm range (°C)
I	50.4	-	-	-
X	-	-	-	254-316
L	-	146.7	212.3	-
I:X	49.2	-	-	253-311
I:L	50.8	134.7	213.0	-
X:L	-	145.8	210.5	281-303
E	-	-	-	-
I:E	50.7	-	-	-
X:E	-	-	-	254-316
A	-	-	331.0	-
I:A	50.3	-	341.6	-
X:A	-	-	-	263-319
I:Talc	50.6	-	-	-
I:Lubritab®	48.5	-	-	-

*I; S(+) ibuprofen, X; Xanthan gum, L; Lactose, E; Encompress®, A; Avicel®, and K; Karaya gum.

The thermogram of S(+) ibuprofen exhibited one endotherm at an onset temperature of 50.4°C. The physical mixture of S(+) ibuprofen and xanthan gum or lactose 1:1 combined the characteristics of the thermograms of each component with the onset temperatures and transition ranges as shown in Table 6.3.

The thermogram of Encompress® exhibited no transition over the temperature range of 30-400°C. The 1:1 physical mixture of S(+) ibuprofen and Encompress® exhibited the endotherm of S(+) ibuprofen at the onset temperature of 50.7°C. The physical mixture of xanthan gum and Encompress® 1:1 exhibited the exotherm of xanthan gum at the range of 254-316°C. Encompress® is reported to decompose below 100°C (Perikh 1994) but from this experiment there was no exotherm of decomposition of Encompress®. However, the thermal characteristics of S(+) ibuprofen and xanthan gum still remained in the mixture of these substances and Encompress®. These results indicated no interaction between S(+) ibuprofen, xanthan gum and Encompress®.

The thermogram of Avicel® exhibited one endotherm at the onset temperature of 331.0°C. The physical mixture of S(+) ibuprofen and Avicel® 1:1 combined the characteristics of the thermograms of each component with onset temperatures of 50.3 and 341.6°C respectively (Table 6.3). The physical mixture of xanthan gum and Avicel® 1:1 exhibited a broad exotherm of xanthan gum over the range of 263-319°C. The transition range of pure Avicel® was 320-361°C, very close to the transition range of xanthan gum. Therefore, it was possible that the transitions of xanthan gum and Avicel® overlapped resulting in only one exotherm.

The physical mixtures of S(+) ibuprofen and talc or Lubritab® 1:1 exhibited an endotherm of S(+) ibuprofen at the onset temperatures of 50.6 and 48.5°C, respectively.

The thermograms of these physical mixtures exhibited the combination of transitions for each component. Some transitions may have shifted slightly to lower or higher temperatures but there was no evidence of any new endotherms or exotherms. These results implied that all the substances studied in this experiment were unlikely to produce interactions in the final product in the solid state.

6.4.5 Stability study of S(+) ibuprofen mini-matrices

The force ratio (R), i.e., the ratio between lower punch maximum force and upper punch maximum force, is one of the indicators for efficiency of lubricant action. The maximum value of the force ratio is unity. In order to improve the lubricant action, by reducing the force loss at the die wall and interparticulate friction, Lubritab® 1% was used in this production run (Formulation 18A, Table 6.1) instead of 2% talc (Formulation 15A, Table 6.1). The force ratio increased from 0.686 when using 2% talc to 0.935 when using 1% Lubritab®; compared at 15 kN maximum upper force. The force ratio slightly decreased at higher compression forces.

It is noticeable that the release rate of S(+) ibuprofen slightly decreased when the lubricant was changed from 2% talc to 1% Lubritab® (3.74 and 2.96 $\%min^{-1/2}$, respectively). The release mechanism was still anomalous with n values of 0.732 for 2% talc and 0.588 for 1% Lubritab®. The lower release rate of mini-matrices containing Lubritab® might be due to higher hydrophobicity of Lubritab®. However, the difference in the two release rates was very little.

6.4.5.1 Uniformity of weight

The weights of 20 mini-matrices were individually measured. The average weight was 30.23±0.64 mg. None of the weights deviated from the average weight by

more than 10%; the maximum weight was 31.16 mg and the minimum weight was 29.20 mg. This batch of mini-matrices met the requirement for uniformity of weight (BP 1993).

6.4.5.2 Uniformity of content

The amount of S(+) ibuprofen in each of 10 mini-matrices was determined. The average percentage was 105.22±5.22. None of the amounts are outside the range of 85.0 to 115.0% of the stated amounts; the maximum percentage was 114.41 and the minimum percentage was 98.56. This batch of mini-matrices also met the requirement of content uniformity (BP 1993).

6.4.5.3 Friability

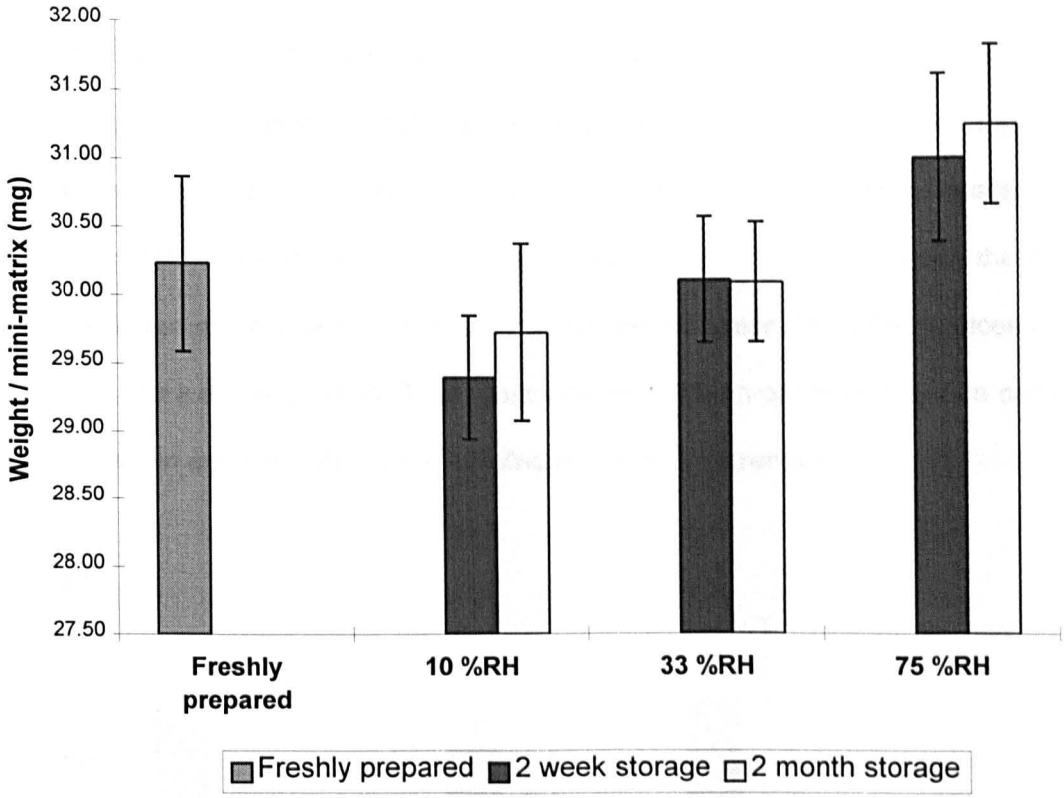
The friability (weight loss) of 20 mini-matrices was 1.22%. It is slightly higher than 1%, the acceptable value for most products (USP XXIII 1994). However, the tablets produced for this study were very small, 4.5 mm in diameter and 30 mg in weight, and none of them showed signs of capping after the friability test. This result is considered to be satisfactory.

6.4.5.4 Effect of moisture on physical properties of S(+) ibuprofen mini-matrices

The effect of moisture on the properties of the mini-matrices maintained isothermally at 22°C was examined. The weight of the mini-matrices were individually determined after being kept in 10, 33 and 75% relative humidity chambers, at 22°C, for 2 week and 2 month periods. The average weight and standard deviation were calculated and are shown in Figure 6.9.

The weight of the mini-matrices, after long storage (2 months), varied in accordance with the relative humidity conditions during the study. This indicates that there is an exchange of water between the atmosphere and the matrix depending on the relative humidity of the environment. The weight of the mini-matrices maintained at 10% and 33% relative humidity for 2 months (29.72±0.65 and 30.09±0.44 mg respectively) were lower than the weight of the freshly prepared mini-matrices (30.23±0.64 mg) indicating that drying had taken place. On the other hand, the weight of the mini-matrices maintained at 75% relative humidity for 2 months (31.24±0.58 mg) was higher than the freshly prepared mini-matrices indicating absorption of moisture.

The freshly prepared mini-matrices contained moisture and when they were maintained at low relative humidity (10% relative humidity), this moisture was lost to the atmosphere. At high relative humidity (75% relative humidity), the mini-matrices absorbed moisture from the atmosphere. This process was continued until equilibrium was reached, exhibited by constant weight. At 33% relative humidity, the weight of mini-matrices after either short or long storage periods was the same. This meant that the moisture in the atmosphere and in the mini-matrices reached equilibrium within 2 weeks. The moisture content in the mini-matrices and the atmospheric relative humidity should be similar, so as to prevent significant changes in tablet weight during the shelf life. At 10% and 75% relative humidity, the weights of the mini-matrices after short and long storage periods were different (Figure 6.9). This indicated that equilibrium between the moisture content in the mini-matrices and in the atmosphere was not reached within 2 weeks but the weight continued to increase up to 2 months. It appears that the movement of water molecules between the phases takes place gradually over extended periods until eventually equilibrium should be attained. However, most of this movement takes place during the initial 2 weeks.



F

igure 6.9. The weight of the mini-matrices containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 10, 33 and 75% relative humidity (RH) chambers, at 22°C, for 2 week and 2 month periods compared with the weight of the freshly prepared mini-matrices (mean values ±SD; n=20).

The crushing strengths of the S(+) ibuprofen mini-matrices stored at 10, 33 and 75% relative humidity, 22°C for 2 week and 2 month periods is shown in Figure 6.10. At high (75%) relative humidity, the crushing strengths of long storage mini-matrices (8.1±0.6 N) was higher than short storage mini-matrices (6.1±0.8 N). Whereas at medium (33%) and low (10%) relative humidity the crushing strengths of short and long storage mini-matrices (10.4±0.6 and 10.3±0.9 N for low relative humidity and 11.6±0.9 and 12.2±1.2 N for medium relative humidity) was similar. The rank order of the crushing strengths of mini-matrices stored at different relative humidity was 33%

>10% >75% relative humidity. This result indicated that moisture affected the crushing strengths of the mini-matrices. At low relative humidity, the mini-matrices lost their moisture content resulting in insufficient water to keep the ingredients bound together. The mini-matrices were brittle so the crushing strength was lower when compared with the mini-matrices stored at medium relative humidity. On the other hand, the mini-matrices stored at high relative humidity had excessive water. The mini-matrices were softer and more easily crushed. This result indicated that an optimum moisture content is necessary in order to achieve the satisfactory crushing strength.

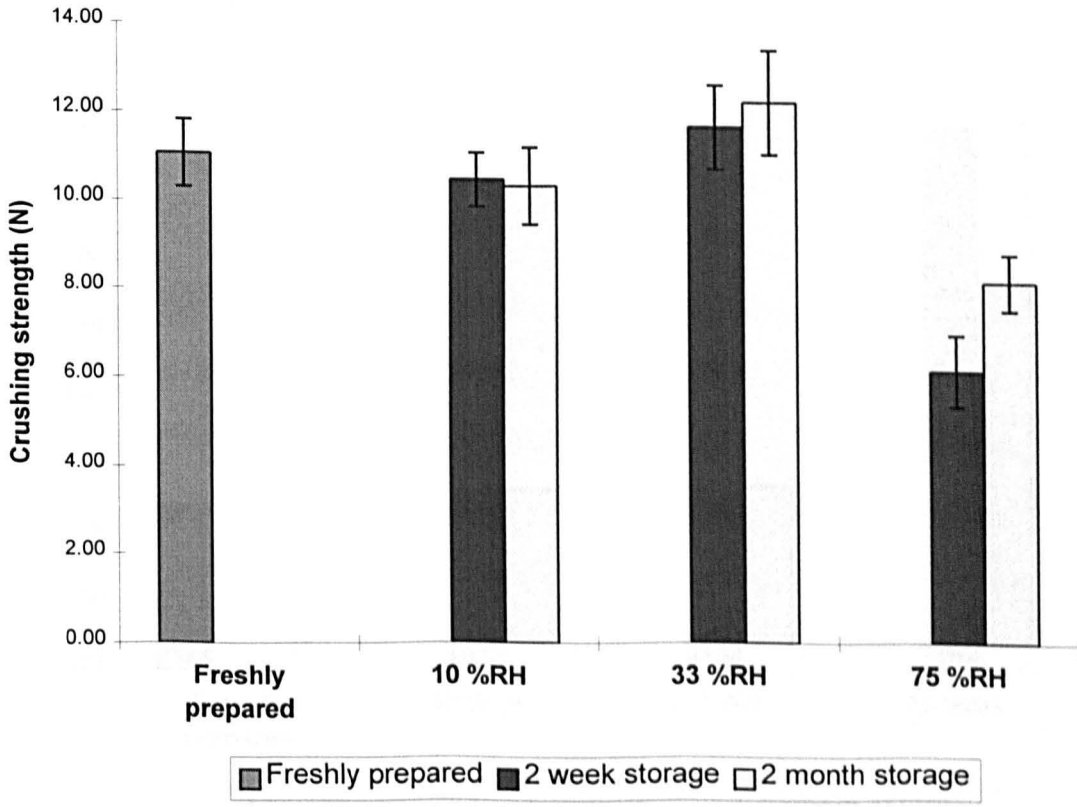


Figure 6.10. The crushing strengths of the mini-matrices comprised of S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 10, 33 and 75% relative humidity (RH) chambers, at 22°C, for 2 week and 2 month periods compared with the crushing strengths of the freshly prepared mini-matrices (mean values±SD; n = 20).

The percentage friabilities, the relative property of crushing strength, of these mini-matrices is shown in Figure 6.11. The obviously high percentage of friability and also the remarkably low crushing strength (Figure 6.10) were observed with the mini-matrices stored at high (75%) relative humidity. The friability of the mini-matrices stored at low (10%) and medium (33%) relative humidity was similar to the freshly prepared mini-matrices. This result was consistent with the crushing strength measurement (Figure 6.10) which showed only slightly different crushing strengths for mini-matrices maintained at 10% and 33% relative humidity and freshly prepared mini-matrices.

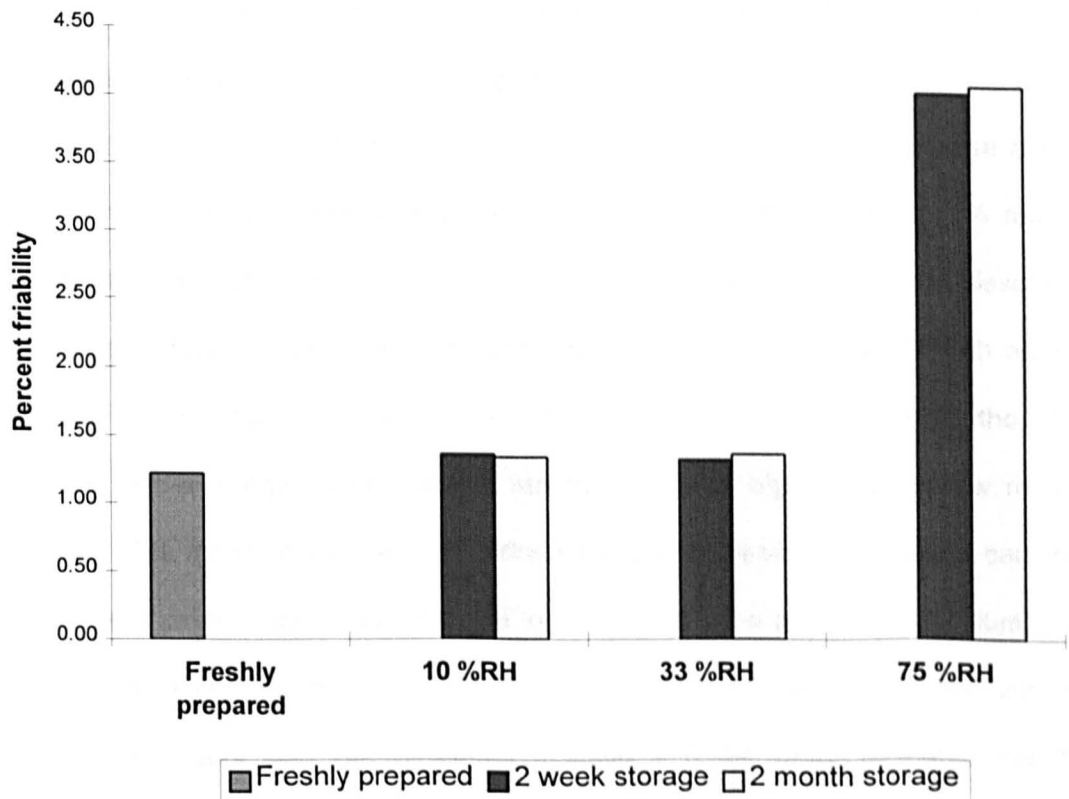


Figure 6.11. The percentage friabilities of mini-matrices containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 10, 33 and 75% relative humidity (RH) chambers, at 22°C, for 2 week and 2 month periods compared with the percentage friability of freshly prepared mini-matrices.

6.4.5.5 Effect of moisture on release characteristics

The release profiles of the mini-matrices stored at various relative humidities (10, 33 and 75% relative humidity), 22°C, for a 2 month period are shown in Figure 6.12. The values of release exponent (n), kinetic constant (k) and correlation coefficient (r) of these mini-matrices stored at various conditions and durations are shown in Table 6.4. The values of release rate with the correlation coefficient (r) are also shown in Table 6.5. The release mechanisms were still anomalous (non-Fickian) diffusion with n values of 0.640, 0.797 and 0.564 (Tables 6.4) and release rates of 3.92, 4.26 and 2.82 $\%min^{-1/2}$ (Table 6.5) for 10%, 33% and 75% relative humidities, respectively. The drug release from mini-matrices stored at 75% relative humidity was nearly the same as the freshly prepared mini-matrices, while the mini-matrices stored at 10 and 33% relative humidities had faster release rates. The drug release rate of mini-matrices stored at 33% relative humidity was slower than that at 10% relative humidity for the first 6 hours and became faster in the second half of the dissolution time period. However, the overall release rates of both were similar. At high relative humidity, the equilibrium moisture content, i.e., the moisture content of the mini-matrices that is in equilibrium with the atmosphere, was higher than at low relative humidity. This moisture will partially hydrate the gum. These mini-matrices can then hydrate and swell faster, when they are in contact with the dissolution medium, than matrices with low moisture content. This results in slow release rates. In addition, this result is consistent with the calculated n value = 0.564 which indicated that the dominant mechanism in drug release was diffusion. While for 10% and 33% relative humidities, the calculated n values = 0.640 and 0.797 respectively, indicated that both diffusion and polymer relaxation played a part in drug release. Although the moisture might slow the release rate of the mini-matrices, the risk of chemical instability and

also the physical properties of the final product at high relative humidity need to be considered.

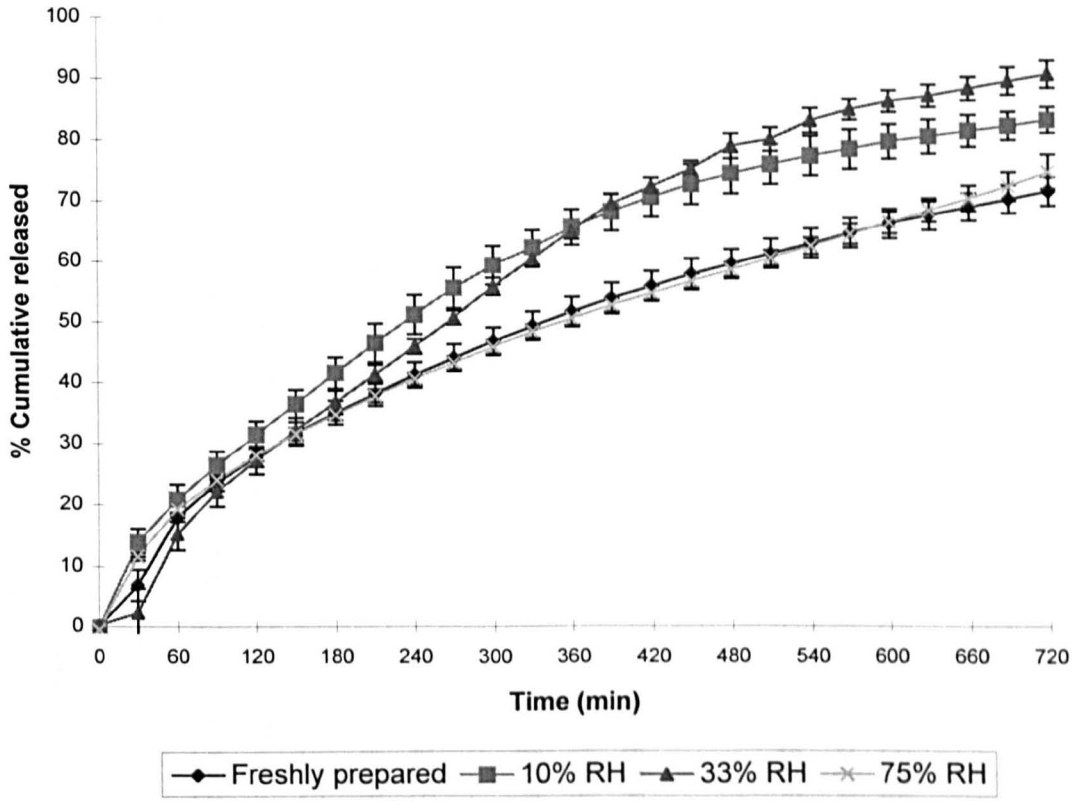


Figure 6.12. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1. The matrices were stored in the 10, 33 and 75% relative humidity (RH) chambers, at 22°C, for a 2 month period, and enclosed in a hard gelatin capsule. Results are compared with the release profile of freshly prepared mini-matrices (mean values ±SD; n=3).

Table 6.4. Release parameters from the encapsulated mini-matrices, containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1, after stored at various relative humidities and temperatures, using Equation 1.1 to derive the release exponent (n) and the kinetic constant (k) (mean values±SD; n=3).

% Relative humidity	Temperature (°C)	2 week storage			2 month storage		
		Release exponent (n)	Kinetic constant (k) (min^{-n})×10^{-3}	Correlation coefficient (r)	Release exponent (n)	Kinetic constant (k) (min^{-n})×10^{-3}	Correlation coefficient (r)
10	5	-	-	-	-	-	-
	22	0.867±0.092	5.17±2.07	0.999	0.640±0.055	15.68±4.91	0.999
	37	0.643±0.025	12.04±1.69	0.998	0.574±0.039	21.93±6.12	0.999
33	5	0.711±0.073	10.97±3.80	0.998	0.885±0.009	5.31±0.14	0.996
	22	0.653±0.100	15.52±8.60	0.997	0.797±0.111	6.82±3.90	0.998
	37	0.684±0.126	13.03±6.90	0.999	0.742±0.019	7.02±0.93	0.998
75	5	-	-	-	-	-	-
	22	0.611±0.059	18.16±7.07	0.994	0.564±0.023	18.53±2.10	0.998
	37	0.578±0.005	19.95±0.09	0.996	0.655±0.089	14.62±7.30	0.995

Release exponent of freshly prepared mini-matrices was 0.588±0.023.

Table 6.5. Release rates of encapsulated mini-matrices, containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1, after stored in various relative humidities and temperatures (mean values±SD; n=3).

% Relative humidity	Temperature (°C)	2 week storage		2 month storage	
		Release rate (%$min^{-1/2}$)	Correlation coefficient (r)	Release rate (%$min^{-1/2}$)	Correlation coefficient (r)
10	5	-	-	-	-
	22	5.13±0.52	0.992	3.92±0.16	0.996
	37	3.19±0.04	1.000	3.55±0.18	0.997
33	5	4.02±0.36	0.998	3.51±0.23	0.999
	22	3.70±0.30	0.998	4.26±0.35	0.996
	37	3.80±0.78	0.998	3.62±0.02	0.999
75	5	-	-	-	-
	22	3.46±0.02	0.998	2.82±0.10	1.000
	37	3.29±0.07	0.999	3.62±0.39	1.000

Release rate of freshly prepared mini-matrices was 2.96±0.13 % $min^{-1/2}$.

6.4.5.6 Effect of temperature on physical properties of S(+) ibuprofen mini-matrices

The effect of temperature (5, 22 and 37°C) on the properties of the mini-matrices maintained at constant relative humidity (33%) was examined. The weights of the mini-matrices stored in the 33% relative humidity chambers, at various temperatures (5, 22 and 37°C), for 2 week and 2 month periods are shown in Figure 6.13. The weights of the mini-matrices stored under various conditions were similar to each other and slightly lower than the weights of the freshly prepared mini-matrices. The weights were in the range of 29.80 to 30.11 mg. This implied that the moisture content in the freshly prepared mini-matrices was close to the moisture content at 33% relative humidity. This result is consistent with the result from the effect of moisture on the weights of the mini-matrices which showed little weight variation between freshly prepared mini-matrices and the mini-matrices stored at 33% relative humidity.

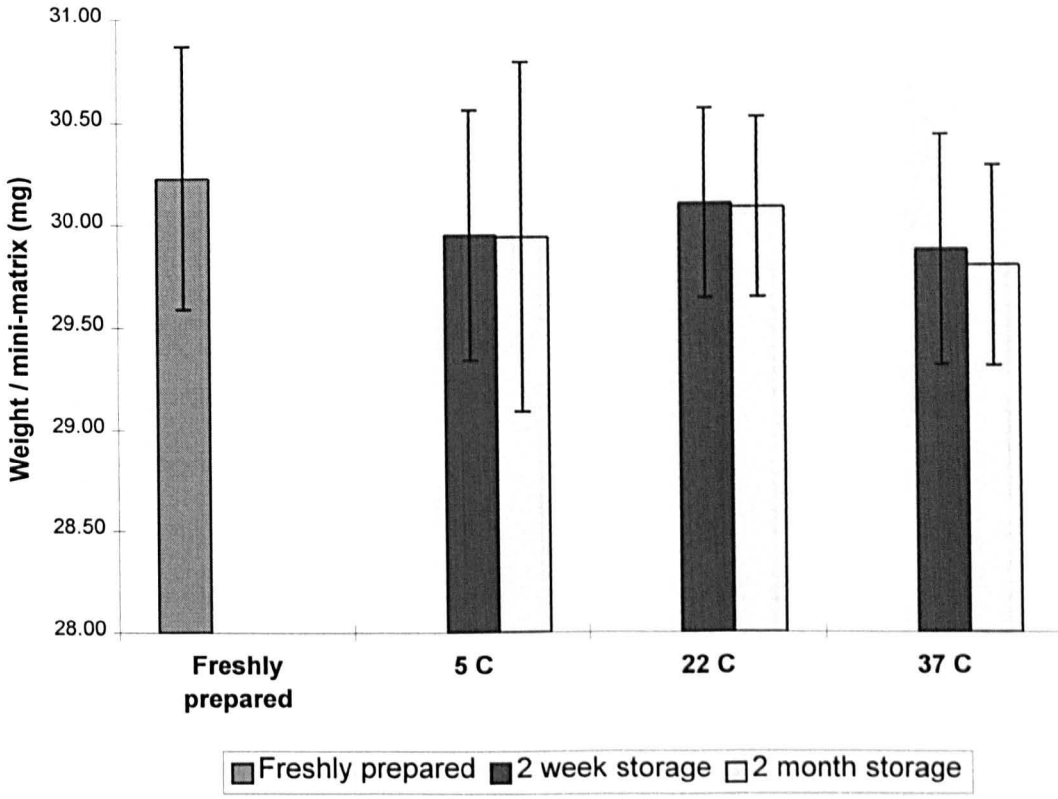


Figure 6.13. The weights of the mini-matrices containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 33% relative humidity chamber, at 5, 22 and 37°C, for 2 week and 2 month periods compared with the weights of freshly prepared mini-matrices (mean values±SD; n = 20).

The crushing strengths and the percentage friabilities of the mini-matrices stored in the 33% relative humidity chamber, at various temperatures (5, 22 and 37°C), for 2 week and 2 month periods are shown in Figures 6.14 and 6.15 respectively. The crushing strength increased with increasing temperature and vice versa for the percentage friability. At higher temperatures, the mini-matrices lost more moisture to the atmosphere, resulting in the higher crushing strength and lower friability.

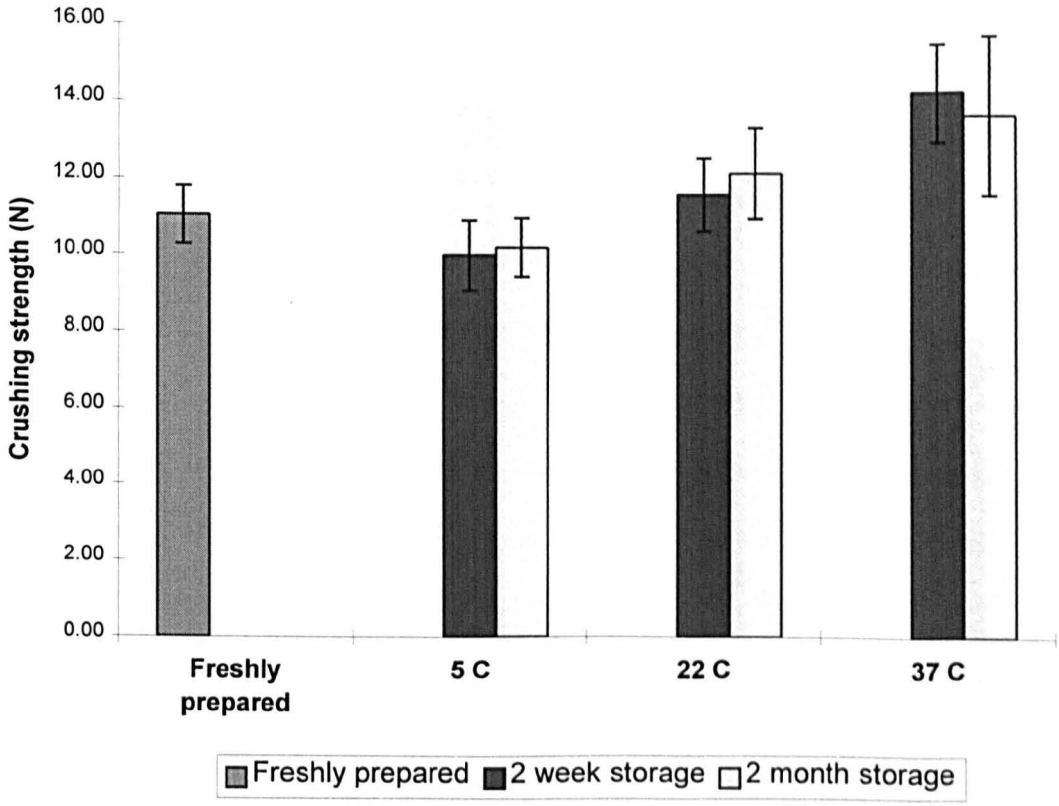


Figure 6.14. The crushing strengths of the mini-matrices containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 33% relative humidity chamber, at 5, 22 and 37°C, for 2 week and 2 month periods compared with the crushing strengths of freshly prepared mini-matrices (mean values±SD, n = 20).

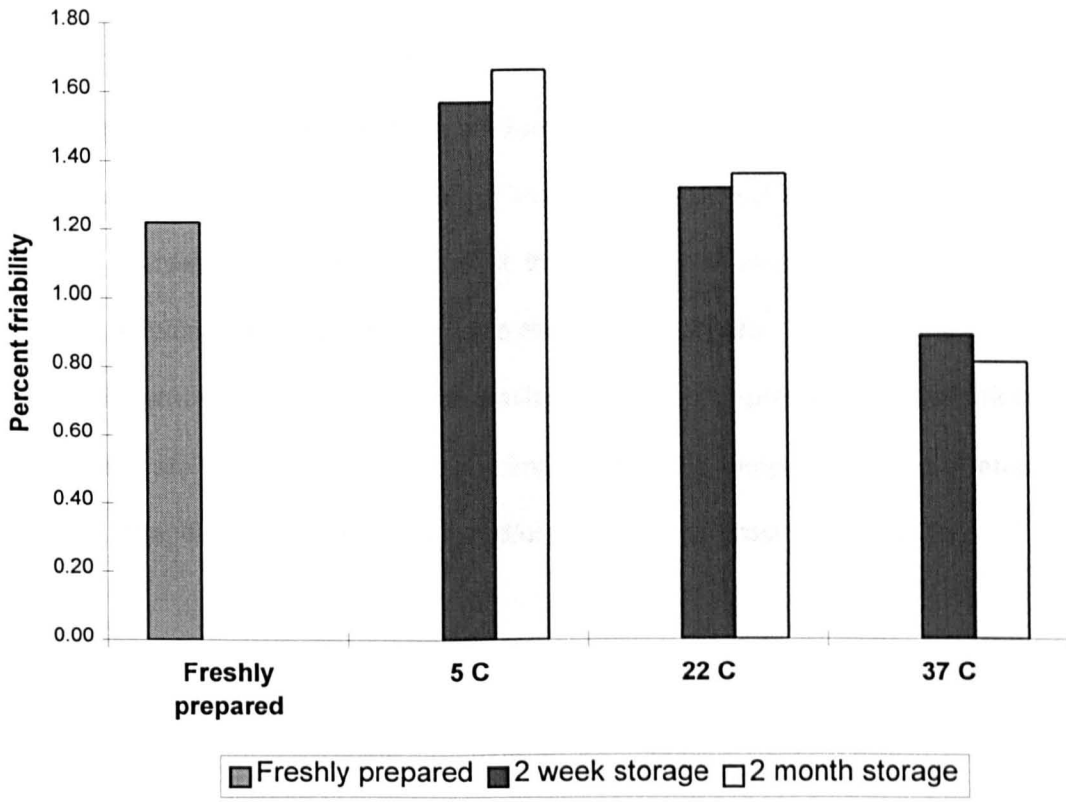


Figure 6.15. Percent friabilities of mini-matrices containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1 stored in the 33% relative humidity chamber, at 5, 22 and 37°C, for 2 week and 2 month periods compared with the percent friability of freshly prepared mini-matrices.

6.4.5.7 Effect of temperature on release characteristics

The release profiles of mini-matrices stored in the 33% relative humidity chamber, at various temperatures (5, 22 and 37°C), for a 2 month period are shown in Figure 6.16. The release mechanisms were still anomalous (non-Fickian) diffusion but approaching Case II transport with n values of 0.885, 0.797 and 0.742 (Table 6.4) and release rates of 3.51, 4.26 and 3.62 $\%min^{-1/2}$ at 5, 22 and 37°C respectively (Table 6.5). The release rates of these mini-matrices were higher than the release rate of freshly prepared mini-matrices, 2.96 % $min^{-1/2}$ (Table 6.5). The release profiles of the

mini-matrices stored at 22 and 37°C were close to the release profile of freshly prepared mini-matrices for the first 2.5 and 4.5 hours respectively, and became higher later. These profiles implied that the mini-matrices had hydration rates fast enough to retard the release of the drug during initial stages. However, the release profile markedly increased later indicating that the increase of storage temperature might lower the swelling extent or enhance the erosion of the gum. The drug release profile from mini-matrices stored at 5°C was similar to the freshly-prepared mini-matrices but the release rate was higher. This result implied that low temperature might retard the hydration rate, decrease the swelling and/or enhance the erosion of the gum.

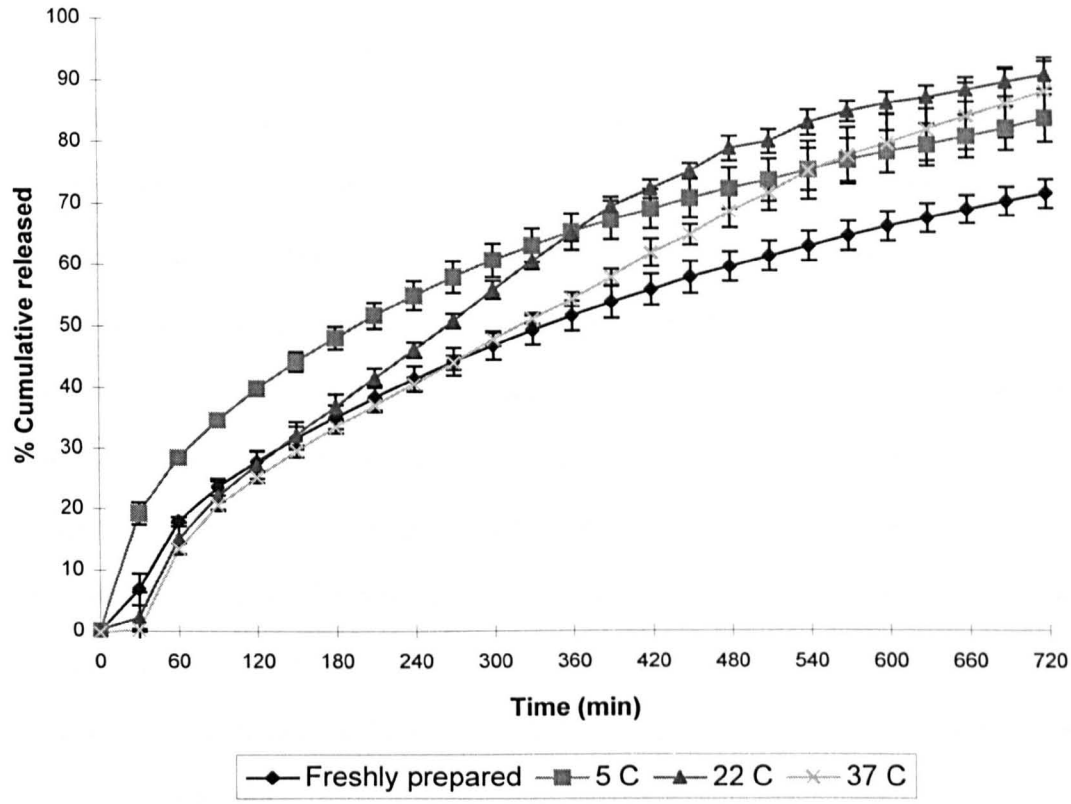


Figure 6.16. Percentage of S(+) ibuprofen released against time from 8 mini-matrices (4.5 mm diameter) containing S(+) ibuprofen, xanthan gum and lactose in a ratio of 1:1:1. The matrices were stored in the 33% relative humidity chamber, at 5, 22 and 37°C, for a 2 month period, and enclosed in a hard gelatin capsule. Results are compared with the release profile of freshly prepared mini-matrices (mean values ±SD; n=3).

6.5 CONCLUSION

S(+) ibuprofen mini-matrices can be produced by the wet granulation method using xanthan and karaya gums as the retarding agents. Excipients with good compressibility were needed in the formulation. Compression forces in the range of 11-26 kN had little effect on the crushing strengths of mini-matrices. The crushing

strengths were in the range of 23.3-28.0 N. Xanthan gum produced a greater sustaining effect on the release of S(+) ibuprofen compared with karaya gum. The excipients used; lactose, Encompress® and Avicel®, affected the release rate of S(+) ibuprofen from encapsulated mini-matrices. The release rate from xanthan gum mini-matrices containing lactose and Encompress® were very similar; 3.74 and 3.69 $\%min^{-1/2}$ respectively, and slower than those containing Avicel®; 5.56 $\%min^{-1/2}$. The release mechanisms were anomalous with n values of 0.732, 0.644 and 0.881 for lactose, Encompress® and Avicel® respectively. From the contribution of Fickian diffusion and Relaxation, the release of S(+) ibuprofen from mini-matrices containing lactose and Encompress® in the initial stages was Fickian diffusion, gradually declining and changing to polymer relaxation in the later stages of the dissolution time period. For mini-matrices containing Avicel®, polymer relaxation was dominant throughout the dissolution time period.

The release mechanism of S(+) ibuprofen from karaya gum mini-matrices containing lactose, Encompress® and Avicel® was Super-Case II with n values of 1.143, 1.248 and 1.620 and release rates of 6.91, 7.79 and 10.18 $\%min^{-1/2}$, respectively. Polymer relaxation was dominant throughout the dissolution time period.

The release of S(+) ibuprofen from S(+) ibuprofen: HPMC: lactose 1:1:1 was faster than xanthan gum mini-matrices but slower than karaya gum mini-matrices. The release mechanism was anomalous with a n value of 0.763 and a release rate of 4.80 $\%min^{-1/2}$. Polymer relaxation was dominant throughout the dissolution time period.

The release of S(+) ibuprofen from mini-matrices containing xanthan or HPMC and lactose depended greatly on the pH of the medium. This result was consistent with the pH solubility profile of S(+) ibuprofen (see Chapter 3).

The gums and excipients used in formulations 15A-C and 18A were unlikely to have any interaction with each other in the solid state, as shown by the DSC screening studies.

All three polymers used, xanthan gum, karaya gum and HPMC, had a sustaining effect on the release of S(+) ibuprofen from the mini-matrix formulations. Xanthan gum and HPMC were particularly suitable with release exponents approaching zero-order (constant) release over 12 hour time periods *in vitro*, especially when using the pH change method. However the commercially available products, Brufen Retard® and Fenbid Spansule®, did not demonstrate suitable sustained release profiles under these *in vitro* dissolution study conditions.

Isothermal storage of the mini-matrices at 22°C with different relative humidities, 10, 33 and 75%, for a 2 month period did not change the mechanism of the drug release from S(+) ibuprofen mini-matrices. At 10 and 33% relative humidities, there were small changes in the release rate, crushing strength, friability and weight of the mini-matrices. At 75% relative humidity, the crushing strength decreased whereas the friability and weight increased significantly. The release rate was close to the release rate of freshly prepared mini-matrices.

After storage of the mini-matrices, at 33% relative humidity and various temperatures (5, 22 and 37°C), for 2 months, there was no change in the mechanisms of drug release. But there were small changes in release rate, crushing strength, friability and weight of the mini-matrices.

CHAPTER 7

OVERALL CONCLUSION

7.1 CONCLUSION

Sustained-release drug delivery systems are developed in order to overcome the fluctuation in drug serum concentration, which may lead to low efficiency of treatment. Many methods are used to prepare sustained-release drug delivery systems. Each method has its own advantages and disadvantages that suit certain situations. This study attempted to prepare sustained-release diclofenac sodium and S(+) ibuprofen in the form of mini-matrices using the tabletting technique. A precise number of mini-matrices were enclosed in hard gelatin capsules to produce multiple unit dosage forms (MUDFs).

Diclofenac sodium and S(+) ibuprofen sustained-release mini-matrices were prepared by the wet granulation method. Due to the low melting point of S(+) ibuprofen (53-55°C), a serious capping problem occurred during the compaction of mini-matrices. A suitable excipient was needed in the preparation of S(+) ibuprofen mini-matrices to improve the compression characteristics. From four natural hydrophilic gums studied (xanthan, karaya, locust bean and carrageenan gums), at 50% gum concentration, xanthan and karaya gums exhibited good retarding characteristics. These two gums delayed the release of the drug for up to ≥ 12 hours. At low gum concentration (about 33% w/w), karaya gum cannot retain its sustaining property.

The release of the drug from the mini-matrices was regulated by drug diffusion and polymer relaxation which were both occurring simultaneously. The release rate of the drug increased with decreasing gum concentration and/or increasing the excipient concentration with the release mechanism changing from anomalous to Case II and

then to Super Case II transport. Solubility differences between the excipients did not affect the release rate. The stirring speed and the tablet volume had a relatively small effect on drug release. Xanthan gum mini-matrices produced a lower release rate than HPMC mini-matrices at both 33 and 50% w/w gum concentration. While karaya gum mini-matrices produced a lower release rate than HPMC mini-matrices only at 50% w/w gum concentration.

Compression forces (11-26 kN) slightly affected the crushing strength of S(+) ibuprofen mini-matrices. S(+) ibuprofen mini-matrices were relatively stable to variation in temperature (5-37°C) and relative humidity (10-75%) over a 2 month time period.

These results have shown that near zero-order release of diclofenac sodium and S(+) ibuprofen can be achieved using encapsulated mini-matrices. At low gum concentration, xanthan gum could sustain the release of the drug better than karaya gum. The release rate of the drugs is influenced by the gum concentration.

The method of preparation can be applied to the other model drugs to produce sustained-release mini-matrices MUDFs. It is a simple and practical method for all who have tabletting facilities. The amount of gums and excipients used can be varied to obtain the optimum release profile for each model drug.

7.2 SUGGESTION FOR FURTHER WORK

In order to develop the formulation, further studies that should be considered are:

- investigation of the optimum concentration of the gums that can retain their sustaining properties
- microcrystalline cellulose loses its compaction property during the wet granulation method (Staniforth 1997), so for S(+) ibuprofen, using better compressibility excipients, e.g. silicified microcrystalline cellulose, or varying the method of

production, e.g. dry mixing excipient with the drug and gum granules, should be attempted in order to reduce the amount of excipient in the formulation

- xanthan gum mini-matrices containing water soluble model drug should be studied in order to investigate the retarding property of xanthan gum
- *In vivo* bioavailability should be investigated before launching these products.

REFERENCES

ADAMS, S.S., BRESLOFF, P. and MASON, C.G., 1976. Pharmacological differences between the optical isomers of ibuprofen evidence for metabolic inversion of the (-) isomer. *J. Pharm. Pharmacol.*, 28, 256-257.

ALDERMAN, D.A., 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. *Int J Pharm Technol Prod Manuf*, 5 (3), 1-9.

ALDERMAN, D.A. and SCHULZ, G.J., 1989. Method of making a granular, cold water dispersible coating composition for tablets. US Patent 4816298.

ALFREY, T.Jr., GURNEE, E.F. and LLOYD, W.G., 1966. Diffusion in glassy polymers. *J. Polym. Sci.*, C12, 249-261.

ALIGHIERE, T., BERLINI, S., AVANESSIAN, S. and DELUIGI, P., 1994. Multiparticulate forms from non-pareil coating. In: C.D. MELIA, N. WASHINGTON and C.G. WILSON, eds. *Multiparticulate oral dosage forms: technology and biopharmaceutics.* Edinburgh: Scottish Academic Press.

ANSEL, H.C., POPOVICH, N.G. and ALLEN, L.V. Jr, 1995. Peroral solids, capsules, tablets and controlled-release dosage forms. *Pharmaceutical dosage forms and drug delivery systems.* 6th ed. Philadelphia: William&Wilkins.

BACKENSFELD, T., MULLER, B.W. and KOLTER, K., 1991. Interaction of NSA with cyclodextrins and hydroxypropyl-cyclodextrin derivatives. *Int. J. Pharm.*, 74, 85-93.

BAIN, J.C., TAN, S.B., GANDERTON, D. and SOLOMON, M.C., 1991. Comparison of the *in vitro* release characteristics of a wax matrix and a hydrogel sustained release diclofenac sodium tablet. *Drug. Dev. Ind. Pharm.*, 17 (2), 215-232.

BANKER, G., PECK, G., JAN, S. and PIRAKITIKULR, P., 1981. Evaluation of hydroxypropyl cellulose and hydroxypropyl methyl cellulose as aqueous bases film coations. *Drug. Dev. Ind. Pharm.*, 7, 693-716.

British Pharmacopoeia, 1993. London: HM Stationery Office.

BRYANT, E.F., 1941. Use of thorium nitrate to distinguish between pectin and certain gums. *Ind. Eng. Chem. Anal. Ed.*, 13, 103.

BUDAVARI, S., 1996. *The Merck Index: an encyclopedia of chemicals, drugs, and biologicals.* 11th ed. Whitehouse Station, NJ: Merck & Co.

BUDUKOVA, L.A., KONDRATYEVA, T.S., URIBE-ECHEVARRIA, V.D., ARZAMASTSEV, A.P. and VOLCHENOK, V.I., 1989. *Farmatsiya Moscow*, 38 (3),16-20.

BUMPHREY, G., 1986. Extremely useful new suspending agent. *Pharm. J.*, 237, 665,

BURGER, A., KOLLER, K.T. and SCHIERMEIER, W.M., 1996. RS-ibuprofen and S-ibuprofen (dexibuprofen)-binary system and unusual solubility behavior. *Eur. J. Pharm. Biopharm.*, 42 (2), 142-147.

CALANCHI, M., GENTILINI, L., MAPELLI, L., and MARCONI, M., 1987. Formulation for preparing sustained release drug for oral administration. Patent international publication number WO 87/05212. 1987-09-11.

CHANG, S.H. and PARROTT, E.L., 1991. Relationship of dissolution rate in anoionic polymeric solutions to viscosity. *Drug. Dev. Ind. Pharm.*, 17 (2), 201-213.

CHATTARAJ, S.C. and DAS, S.K., 1996. Effect of formulation variables on dissolution profile of diclofenac sodium from ethyl- and hydroxypropylmethyl cellulose tablets. *Drug. Dev. Ind. Pharm.*, 22 (7), 555-559.

CHENG, H., ROGERS, J.D., DEMETRIADES, J.L., HOLLAND, S.D., DEPUY, E., et al., 1994. Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans. *Pharm. Res.*, 11 (Jun), 824-830.

CHETTY, D.J., OGUNDEJI, M.O., DAMANI, L.A., DAWES, V.H. and SOLOMON, M.C., 1994. Susceptibility of diclofenac sodium tablet matrix formulation to dissolution test variables. *Pharm. Technol. Eur.*, Nov, 28, 32, 34-36, 38.

CHIEN. Y.W., 1992. Concepts and system design for rate-controlled drug delivery. *Novel drug delivery systems.* New York: Marcel Dekker.

CHOWHAN, Z.T., 1980. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on *in vitro* disintegration and dissolution. *J. Pharm. Sci.*, 69, 1-4.

COLOMBO, P., CONTE, U., CARAMELLA, C., GAZZANIGA, A. and La MANNA, A., 1985. Compressed polymeric mini-matrices for drug release control. *J. Controlled Release*, 1, 283-289.

CONTE, U., MAGGI, L. and MANNA, A.La., 1994. Compression barrier layers for constant drug release from swellable matrix tablets. *S.T.P. Pharma Sci.*, 4 (2), 107-113.

COOK, W.H., ROSE, R.C. and COLVIN, J.R., 1951. Macromolecular properties of carrageenin. *Biochem. Biophys. Acta.*, 7, 601.

COTTRELL, I.W., KANG, K.S. and KOVACS, P., 1980. Xanthan gum. In: R.L. DAVIDSON, ed. *Handbook of water-soluble gums and resins.* New York: McGraw-Hill.

DAHL, T.C., CALDERWOOD, T., BORMETH, A., TRIMBLE, K. and PIEPMEIER, E., 1990, Influence of physicochemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets. *J. Controlled Release*, 14, 1-10.

DASH, B.H., BLANK, R.G., SCHACHTEL, B.P. and SMITH, A.J., 1988. Ibuprofen tablets. Dissolution versus bioavailability. *Drug. Dev. Ind. Pharm.*, 14 (11), 1629-1645.

DASKALAKIS, S.A., 1994. Xanthan gum. In: A. WADE and P.J. WELLER, eds. *Handbook of pharmaceutical excipients*. 2nd ed. London: Pharmaceutical Press.

DESHPANDE, A.A., RHODES, C.T., SHAH, N.H. and MALICK, A.W., 1996. Controlled release drug delivery system for prolonged gastric residence: An overview. *Drug. Dev. Ind. Pharm.*, 22 (6), 531-539.

DHOPESHWARKAR, V. and ZATZ, J.L., 1993. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. *Drug. Dev. Ind. Pharm.*, 19 (9), 999-1017.

DIGRANES, A., JOSEFSSON, K. and SCHREINER, A., 1984. Influence of food on the absorption of erythromycin from enteric coated pellets and stearate tablets. *Curr. Ther. Res.*, 35 (Mar), 313-320.

DONDONI, A., DALL-OCCO, T., FANTIN, G., MEDICI, A. and ROSSETTI, V., 1986. Studies on the actual and potential impurities in ibuprofen. *Farmaco. Ed. Prat.*, 41 (Jul), 237-244.

EDGAR, B., BOGENTOFT, C., and LAGERSTROM, P.O., 1984. Comparison of two enteric-coated acetylsalicylic acid preparations by monitoring steady-state levels of salicylic acid and its metabolites in plasma and urine. *Biopharm. Drug Dispos.*, 5, 251-260.

EL-SAYED, Y.M., ABDEL-HAMEED, M.E., SULEIMAN, M.S. and NAJIB, N.M., 1988. A rapid and sensitive high-performance liquid chromatographic method for the determination of diclofenac sodium in serum and its use in pharmacokinetic studies. *J. Pharm. Pharmacol.*, 40, 727-729.

EVANS, A.M., NATION, R.L., SANSOM, L.N., BOCHNER, F. and SOMOGYI, A.A., 1990. The relationship between the pharmacokinetics of ibuprofen enantiomers and the dose of racemic ibuprofen in humans. *Biopharm. Drug Dispos.*, 11, 507-518.

EVANS, B.K. and FENTON-MAY, V., 1986. Keltron (letter). *Pharm. J.*, 237, 736-737.

FEELY, L.C. and DAVIS, S.S., 1988A. Influence of surfactant on drug release from hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 41, 83-90.

FEELY, L.C. and DAVIS, S.S., 1988b. The influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices. *Int. J. Phram.*, 44, 131-139.

FEELY, L.C. and SIMS, E.E., 1994. Other types of oral multiparticulate dosage forms: Minitablets. In: C.D. MELIA, N. WASHINGTON and C.G. WILSON, eds. *Multiparticulate oral dosage forms: technology and biopharmaceutics.* Edinburgh: Scottish Academic Press.

FEELY, L.C., DAVIS, S.S. and PARR G.D., 1985. Investigating the gastrointestinal transit of controlled release mini-matrices using gamma scintigraphy. *Proceed. Int. Symp. Contr. Rel. Bioac. Mater.*, 12, 94-95.

FINI, A., LAUS, M., ORIENTI, I. and ZECCHI, V., 1986. Dissolution and partition thermodynamic functions of some nonsteroidal anti-inflammatory drugs. *J. Pharm. Sci.*, 75 (1), 23-25.

FISCHER, E., 1992. Calcium phosphate as a pharmaceutical excipient. *Mfg. Chem.*, 64 (6), 25-27.

FISCHER, J.H., DOROCIAK, J.V., BARR, A., PALONCEK, F.P. and SPUNT, A., 1985. Effect of meals on the absorption of enteric-coated valproic acid. *Drug. Intell. Clin. Pharm.*, 19, 460.

FITZPATRICK, J.P., 1995. Xanthan gum in hydrophilic matrix drug delivery systems. In: D.R. KARSA and R.A. STEPHENSON, eds. *Excipients and delivery systems for pharmaceutical formulations.* Cambridge: The Royal Society of Chemistry.

FORD, J.L., RUBINSTEIN, M.H. and HOGAN, J.E., 1985a. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulose matrices. *Int. J. Pharm.*, 24, 327-338.

FORD, J.L., RUBINSTEIN, M.H. and HOGAN, J.E., 1985b. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.*, 24, 339-350.

FORD, J.L., RUBINSTEIN, M.H., McCAUL, F., HOGAN, J.E. and EDGAR, P.J., 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J. Pharm.*, 40, 223-234.

FOWLER, P.D., SHADFORTH, M.F., CROOK, P.R. and JOHN, V.A., 1983. Plasma and synovial fluid concentration of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur. J. Clin. Pharmacol.*, 25 (3), 389-394.

FREER, A.A., BUNYAN, J.M., SHANKLAND, N. and SHEEN, D.B., 1993. Structure of (S)-(+)-ibuprofen. *Acta. Cryst.*, c49, 1378-1380.

GEISSLINGER, G., STOCK, K.P., LOEW, D., BACH, G.L. and BRUNE, K., 1993. Variability in the stereoselective disposition of ibuprofen in patients with rheumatoid arthritis. *Br. J. Clin. Pharmacol.*, 35, 603-607.

GOLDSTEIN, A.M. and ALTER, E.N., 1973. Gum karaya. In R.L. WHISTLER, ed. *Industrial gums: polysaccharides and their derivatives.* 2nd ed. New York: Academic Press.

GORDON, R.E., VAN KOEVERING, C.L. and REITS, D.J., 1984. Utilization of differential scanning calorimetry in the compatibility screening of ibuprofen with the stearate lubricants and construction of phase diagrams. *Int. J. Pharm.*, 21, 99-105.

GORING, D.A.I. and YOUNG, E.G., 1955. Carrageenin: comparison of fractions obtained with potassium chloride and by successive extraction at elevated temperatures. *Can. J. Chem.*, 33, 480-495.

GRAFFNER, C., JOSEFSSON, K. and STOCKMAN, O., 1986. Intra- and intersubject variation of erythromycin absorption from single unit and multiple unit enteric coated products. *Biopharm. Drug Dispos.*, 7 (Mar-Apr), 163-171.

GREMINGER Jr, G.K. and KRUMEL, K.L.,1980. Alkyl and hydroxyalkylcellulose. In: R.L. DAVIDSON, ed. *Handbook of water-soluble gums and resins.* New York: McGraw-Hill.

GUISELEY, K.B., STANLEY, N.F. and WHITEHOUSE, P.A., 1980. Carrageenan. In: R.L. DAVIDSON, ed. *Handbook of water soluble gums and resins.* New York: McGraw-Hill.

HALL, S.D., RUDY, A.C., KNIGHT, P.M. and BRATER, D.C., 1993. Lack of presystemic inversion of (R)- to (S)- ibuprofen in humans. *Clin. Pharmacol. Ther.*, 53 (Apr), 393-400.

HARDY, J.G., KENNERLEY, J.W., TAYLOR, M.J., WILSON, C.G. and DAVIS, S.S., 1982. Release rates from sustained-release buccal tablets in man. *J. Pharm. Pharmacol.*, 34 (Suppl), 91p.

HARWOOD, R.J. and JOHNSON, J.L., 1994. In: A. WADE and P.J. WELLER, eds. *Handbook of pharmaceutical excipients.* 2nd ed. London: Pharmaceutical Press.

HERZFELDT, C.D. and KUMMEL, R., 1983. Dissociation constants, solubilities and dissolution rate of some selected non-steroidal anti-inflammatories. *Drug. Dev. Ind. Pharm.*, 9 (5), 767-793.

HIGUCHI, T.,1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.*, 50, 874-875.

HODSDON, A.C. and MELIA, C.D., 1994. Multiparticulate dosage forms from extrusion/spheronisation. In: C.D. MELIA, N. WASHINGTON and C.G. WILSON, eds. *Multiparticulate oral dosage forms: technology and biopharmaceutics.* Edinburgh: Scottish Academic Press.

HOGAN, J.E., 1989. Hydroxypropylmethylcellulose sustained release technology. *Drug. Dev. Ind. Pharm.*, 15 (6&7), 975-999.

HUBER, H.E. and CHRISTENSON, G.L., 1968. Utilization of hydrophilic gums for the control of drug substance release from tablet formulations. II Influence of tablet hardness and density on dissolution behavior. *J. Pharm. Sci.*, 57 (1), 164-166.

HUTT, A.J. and CALDWELL, J., 1983. The metabolic chiral inversion of 2-acrylpropionic acids- a novel route with pharmacological consequences. *J. Pharm. Pharmacol.*, 35, 693-704.

JANSSON, P.E., KENNE, L. and LINDBERG, B., 1975. Structure of extracellular polysaccharide from *Xanthomonas compestris*. *Carbohydrate Res.*, 45, 275-282.

JEFFREY, P., TUCKER, G.T., BYE, A., CREWE, H.K. and WRIGHT, P.A., 1991. The site of inversion of R(-) ibuprofen: studies using rat in-situ isolated perfused intestine/liver preparations. *J. Pharm. Pharmacol.*, 43 (10), 715-720.

JOSEFFSON, K., BERGAN, T. and MAGNI, L., 1982. Dose related pharmacokinetics after oral administration of a new formulation of erythromycin base. *Br. J. Clin. Pharmacol.*, 13 (May), 685-691.

JOSEFSSON, K., LEVITT, M.J., KANN, J. and BON, C., 1986. Erythromycin absorption from enteric-coated pellets given in multiple doses to volunteers, in comparison with enteric-coated tablets and film-coated stearate tablets. *Curr. Ther. Res.*, 39 (Jan), 131-142.

JOVANOVIC, M., JOVICIC, G., DURIC, Z., AGBABA, D., KARLJIKOVIC-RAJIC, K., RADOVANOVIC, J. and NIKOLIC, L., 1997. Effect of fillers and lubricants on acetylsalicylic acid release kinetics from Eudragit matrix tablets. *Drug. Dev. Ind. Pharm.*, 23 (6), 595-602.

KABANDA, L., LEFEBVRE, R.A., VAN BREE, H.J. and REMON, J.P., 1994. *In vitro* and *in vivo* evaluation in dogs and pigs of a hydrophilic matrix containing propylthiouracil. *Pharm Res*, 11 (11), 1663-1668.

KAPLAN, S.K., 1972. Biopharmaceutical considerations in drug formulation design and evaluation. *Drug. Metab. Rev.*, 1, 15-34.

KARARLI, T.T., NEEDHAM, T.E., SEUL, C.J. and FINNEGAN, P.M., 1989. Solid state interaction of magnesium oxide and ibuprofen to form a salt. *Pharm. Res.*, 6 (Sept), 804-808.

KLEIN, G., NEFF, H., KULLICH, W., PHLEPS, W. and KOLLENZ, C.J., 1992. S(+) versus racemic ibuprofen. *Lancet*, 339 (Mar 14), 681.

KNIHINICKI, R.D., DAY, R.O. and WILLIAMS, K.M.,1991. Chiral inversion of 2-arylpropionic acid non-steroidal anti-inflammatory drug. II Racemization and hydrolysis of (R)- and (S)- ibuprofen-CoA thioesters. *Biochem. Pharmacol.*, 42 (10), 1905-1911.

KOPARKAR, A.D., AUGSBURGER, L.L. and SHANGRAW, R.F., 1990. Intrinsic dissolution rates of tablet filler-binders and their influence on the dissolution of drugs from tablet formulations. *Pharm. Res.*, 7, 80-86.

KORSMEYER, R.W., GURNY, R., DOELKER,E., BURI, P. and PEPPAS, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15, 25-35.

KOVAC, P., 1973. Useful incompatibility of xanthan gum with galactomannans. *Food Technol.*, 3, 26-30.

KUBULA, T., GAMBHIR, B. and BORST, S.I., 1993. A specific stability indicating HPLC method to determine diclofenac sodium in raw materials and pharmaceutical solid dosage forms. *Drug. Dev. Ind. Pharm.*, 19 (7), 749-757.

LAPIDUS, H. and LORDI, N.G., 1968. Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.*, 57 (8), 1292-1301.

LEE, E.J.D., WILLIAMS, K., DAY, R., GRAHAM, G. and CHAMPION, D., 1985. Stereoselective disposition of ibuprofen enantiomers in man. *Br. J. Clin. Pharmacol.*, 19, 669-674.

LEE, V.H. and ROBINSON, J.R., 1979. Method to achieve sustained drug delivery. The physical approach: oral and parenteral dosage forms. In: J.R. ROBINSON, ed. *Sustained and controlled release drug delivery systems.* New York: Marcel Dekker.

LEONARD, J.R. and LEVY, G., 1965. Absorption and metabolism of aspirin administered in enteric-coated tablets. *J. Am. Med. Assoc.*, 193, 93-98.

LEVY, G. and JUSKO, W.J., 1967. Case history of a pharmaceutical formulation failure. *Clin. Pharmacol. Ther.*, 8, 887-889.

LI, G., TREIBER, G., MAIER, K., WALKER, S. and KLOTZ, U., 1993. Disposition of ibuprofen in patients with liver cirrhosis. Stereochemical consideration. *Clin. Pharmacokinet.*, 25 (2), 154-163.

LIEBERMAN, H.A., LACHMAN, L. and SCHWARTZ, J.B., 1990. Preface. *Pharmaceutical dosage forms: Tablets* Volume 3. 2nd ed. New York: Marcel Dekker.

LIN, S.Y., CHENG, C.L. and LIN, P.C., 1995. Preparation and evaluation of sodium diclofenac controlled-release tablets. II Dibasic calcium phosphate as a retardant in mixtures for direct compression. *Pharm. World Sci.*, 17 (2), 42-47.

LORDI, N.G., 1986. Sustained release dosage forms. In: L. LACHMAN, H.A. LIEBERMAN and J.L. KANIG, eds. *The theory and practice of industrial pharmacy.* 3rd ed. Philadelphia: Lea&Febiger.

LU, M.F., WOODWORD, L. and BORODKIN, S., 1991. Xanthan gum and alginate based controlled release theophylline formulations. *Drug. Dev. Ind. Pharm.*, 17 (14), 1987-2004.

LUND, W., 1994. *The Pharmaceutical Codex: Principles and Practice of Pharmaceutics.* 12th ed. London: Pharmaceutical Press.

MAGGI, C.A., LUALDI, P. and MAUTONE, G., 1990. Comparative bioavailability of diclofenac hydroxy-ethylpyrrolidone vs diclofenac sodium in man. *Eur. J. Clin. Pharmacol.*, 38 (2), 207-208.

MALAMATARIS, S. and GANDERTON, D., 1991. Sustained release from a matrix system comprising hydrophobic and hydrophilic (gel-forming) parts. *Int. J. Pharm.*, 70, 69-75.

MARIN BOSCA, M.T., ISMAIL SALEM, I., SANCHEZ MORCILLO, J. and CEREZO GALAN, A., 1995. Dissolution study of prolonged release morphine tablets using hydrophilic matrices. *Drug. Dev. Ind. Pharm.,* 21 (13), 1557-1562.

MARTIN, A., 1993. Drug product design. *Physical pharmacy: physical chemical principles in the pharmaceutical sciences.* 4th ed. Philadelphia: Lea&Febiger.

MASSON, C.R. and CAINES, G.W., 1954. Viscosity and molecular weight of degraded carrageenin. *Can. J. Chem.*, 32, 51-58.

MASSON, C.R. and GORING, D.A.I., 1955. Studies on carrageenin. The effect of shear rate on viscosity. *Can. J. Chem.*, 33, 895-903

McCONNELL, J.F., 1974. Structure of ibuprofen. *Cryst. Struct. Commun.*, 3, 73-75.

McNEELY, W.H. and KANG, K.S., 1973. Xanthan and some other biosynthetic gums. In: R.L. WHISTLER, ed. *Industrial gums: polysaccharides and their derivatives.* 2nd ed. New York: Academic Press.

McNEELY, W.H. and O'CONNELL, J.J., 1966. *Xanthomonas hydrophilic colloid.* U.S. patent 3,232,929.

MEER, W., 1980. Gum karaya. In: R.L. DAVIDSON, ed. *Handbook of water-soluble gums and resins.* New York: McGraw-Hill.

MELIA, C.D., 1994. An introduction to oral multiparticulate dosage forms. In: C.D. MELIA, N. WASHINGTON and C.G. WILSON, eds. *Multiparticulate oral dosage forms: technology and biopharmaceutics.* Edinburgh: Scottish Academic Press.

MELIA, C.D., WASHINGTON, N. and WILSON, C.G., 1994. Advantages and disadvantages of multiparticulate dosage systems. In: C.D. MELIA, N. WASHINGTON and C.G. WILSON, eds. *Multiparticulate oral dosage forms: technology and biopharmaceutics.* Edinburgh: Scottish Academic Press.

MEYER, J.H., DRESSMAN, J., FINK, A., and AMIDON, G., 1985. Effect of size and density on canine gastric emptying of nondigestible solids, *Gastroenterology*, 89, 805-813.

MITCHELL, K., FORD, J.L., ARMSTRONG, D.J., ELLIOTT, P.N.C., ROSTRON, C. and HOGAN, J.E., 1993. The influence of concentration on the release of drug from gels and matrices containing Methocel®. *Int. J. Pharm.*, 100, 155-163.

MITCHELL, K., FORD, J.L., ROSTRON, C., ARMSTRONG, D.J. ELLIOTT, P.N.C. and HOGAN, J.E., 1991. Swelling behaviour of cellulose ether matrix tablets. *J. Pharm. Pharmacol.*, 43, 76p.

MOCKEL, J.E. and LIPPOLD, B.C., 1993. Zero-order release from hydrocolloid matrices. *Pharm. Res.*, 10 (7), 1066-1070.

MONEY, R.W., 1951. Karaya gum: Physico-chemical properties with particular reference to the effect of dry grinding. *J. Sci. Food. Agric.*, 2, 385.

MULYE, N.V. and TURCO, S.J., 1994. Use of dicalcium phosphate dihydrate for sustained release of highly water soluble drugs. *Drug. Dev. Ind. Pharm.*, 20 (17), 2621-2632.

MUNDAY, D.L., FASSIHI, A.R. and De VILLIERS, C., 1991. Bioavailability study of a theophylline oral controlled release capsule containing film coated mini-tablets in beagle dogs. *Int. J. Pharm.*, 69, 123-127.

NAGGAR, V.F., EL-KHAWAS, M., ISMAIL, F.A. and BORAIE, N.A., 1992. Pectin, a possible matrix for oral sustained-release preparation of water-soluble drugs. *S.T.P. Pharma Sci.*, 2 (3), 227-234.

NAVARRO, A. and BALLESTEROS, M.P., 1994. Dissolution efficiency and release kinetics of three diclofenac sodium controlled-release formulations. *S.T.P. Pharma Pratiques*, 4 (2), 108-115.

NISHIHATA, T., KAMADA, A., SAKAI, K., TAKAHASHI, K., MATSUMOTO, K., SHIMOZAKI, K., TABATA, Y., KEIGAMI, M., MIYAGI, T. and TATSUMI, N., 1988. Percutaneous absorption of diclofenac in rats and humans: aqueous gel formulation. *Int. J. Pharm.*, 46, 1-7.

OKHAMAFE, A.O. and YORK, P., 1982. Moisture permeation mechanism of some aqueous-bases film coats. *J. Pharm. Pharmacol.*, 34 (Suppl), 53p.

OLIARY, J., TOD, M., NICOLAS, P., PETITJEAN, O. and CAILLE, G., 1992. Pharmacokinetics of ibuprofen enantiomers after single and repeated doses in man. *Biopharm. Drug Dispos.*, 13 (5), 337-344.

PALIWAL, J.K., SMITH, D.E., COX, S.R., BERARDI, R.R., ELTA, G.H., et al., 1993. Stereoselective, competitive, and nonlinear plasma protein binding of ibuprofen enantiomers as determined in vivo in healthy subjects. *J. pharmacokinet. Biopharm.*, 21 (Apr), 145-161.

PANOMSUK, S.P., HATANAKA, T., AIBA, T., KATAYAMA, K. and KOIZUMI, T., 1995a. A study of the hydrophilic cellulose matrix: effect of indomethacin and a water-soluble additive on swelling properties. *Int. J. Pharm.*, 126, 147-153.

PANOMSUK, S.P., HATANAKA, T., AIBA, T., KATAYAMA, K. and KOIZUMI, T., 1995b. A study of the hydrophilic cellulose matrix: Effect of indomethacin and a water-soluble additive on release mechanisms. *Chem. Pharm. Bull.*, 43 (6), 994-999.

PARIKH, N.H., 1994. Dibasic calcium phosphate dihydrate. In: A. WADE and P.J. WELLER, eds. *Handbook of pharmaceutical excipients*. 2nd ed. London: Pharmaceutical Press.

PATELL, M.K., 1990. *Hydroxypropyl methyl cellulose phthalate as a taste masking agent.* US Patent 4,916,161.

PEPPAS, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta. Helv.*, 60 (4), 110-111.

PEPPAS, N.A. and SAHLIN, J.J., 1989. A simple equation for the description of solute release. III Coupling of diffusion and relaxation. *Int J Pharm*, 57, 169-172.

PHAM, A.T., and LEE, P.I., 1994. Probing the mechanisms of drug release from hydroxypropyl methylcellulose matrices. *Pharm Res*, 11 (10), 1379-1384.

RAJABI-SIAHBOOMI, A.R., HENDERSON, A., DAVIES, M.C. and MELIA, C.D.,1993. HPMC hydrophilic systems: structure-activity relationships and release behaviour of diclofenac sodium. *J. Pharm. Pharmacol.*, 45, 1109.

REYNOLD, J.E.F., 1996. *Martindale: The extra pharmacopoeia.* 31st ed. London: Royal Pharmaceutical Society of Great Britain.

RITGER, P.L. and PEPPAS, N.A., 1987. A simple equation for description of solute release. II Fickian and anomalous from swellable devices. *J. Controlled Release*, 5, 37-42.

ROGOVIN, S.P. and ALBRECHT, W.J., 1964. *Recovering microbial polysaccharides from their fermentation broths.* U.S. patent 3,119,812.

ROL, F., 1973. Locust bean gum. In: R.L. WHISTLER, ed. *Industrial gums: polysaccharides and their derivatives.* 2nd ed. New York: Academic Press.

ROMERO, A.J. and RHODES, C.T., 1991. Approaches to stereospecific preformulation of ibuprofen. *Drug. Dev. Ind. Pharm.*, 17 (5), 777-792.

ROMERO, A.J., RACKLEY, R.J. AND RHODES, C.T., 1991. An evaluation of ibuprofen bioinversion by simulation. *Chirality,* 3 (5), 418-421.

ROWE, R.C., 1977. The adhesion of film coatings to tablet surfaces -the effect of some direct compression excipients and lubricants. *J. Pharm. Pharmacol.*, 29, 723-726.

ROWE, R.C., 1980. The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in the film coating of tablets. *J. Pharm. Pharmacol.*, 32, 116-119.

ROWE, R.C., 1983. Spheronisation, a novel pill making process. *Pharm. Ind.*, 5, 119-123.

RUBINSTEIN, M.H. and BODEY D.M., 1976. Disaggregation of compressed tablets. *J. Pharm. Sci.*, 65, 1749-1753.

SAKELLARIOU, P., ROWE, R.C. and WHITE, E.F.T., 1985. The thermomechanical properties and glass transition temperatures of some cellulose derivatives used in film coating. *Int. J. Pharm.*, 27, 267-277

SARISUTA, N. and MAHAHPUNT, P., 1994. Effect of compression force and type of fillers on release of diclofenac sodium from matrix tablets. *Drug. Dev. Ind. Pharm.*, 20 (6), 1049-1061.

SEAMAN, J.K., 1980. Locust bean gum. In: R.L. DAVIDSON, ed. *Handbook of water-soluble gums and resins*. New York: McGraw-Hill.

SHAH, A.C., BRITTEN, N.J., OLANOFF, L.S. and BADALAMENTI, J.N., 1989. Gel-matrix systems exhibiting bimodal controlled release for oral drug delivery. *J. Controlled Release*, 9, 169-175.

SHESKEY, P.J., ROBB, R.T., MOORE, R.D. and BOYCE, B.M.,1995. Effect of lubricant level, method of mixing and duration of mixing on a controlled-release matrix tablet containing hydroxypropyl methylcellulose. *Drug. Dev. Ind. Pharm.*, 21 (19), 2151-2165.

SHEU, M.T., CHOU, H., KAO, C., LIU, C. and SOKOLOSKI, T.D., 1992. Dissolution of diclofenac sodium from matrix tablets. *Int. J. Pharm.*, 85, 57-63.

SINCLAIR, G.W. and PEPPAS, N.A., 1984. Analysis of non-Fickian transport in polymers using simplified exponential expressions. *J. Memb. Sci.*, 17, 329-331.

SMALL, R.E., 1989. Diclofenac sodium. *Clin. Pharm.*, 8 (8), 545-558.

SMITH, D.B., O'NEILL, A.N. and PERLIN, A.S., 1955. The heterogeneity of carrageenin. *Can. J. Chem.*, 33, 1352-1360.

STANIFORTH, J.N., 1997. Turning drugs into efficient medicines: the need for high functionality excipients and the rate of physicochemical research in providing them, *J. Pharm. Pharmacol.*, 49, Suppl 4, 21.

STOCK, K.P., GEISSLINGER, G., LOEW, D., BECK, W.S., BACH, G.L. and BRUNE, K., 1991. S-ibuprofen versus ibuprofen-racemate. A randomized double-blind study in patients with rheumatoid arthritis. *Rheumatol. Int.*, 11 (4-5), 199-202.

STOLOFF, L., 1950. Solution of Irish moss extractives by acidulation. *Food Technol.*, 4, 138-141.

SUNG, K.C., NIXON, P.R., SKONG, J.W., JU, T.R., GAO, P., TOPP, E.M. and PATEL, M.V., 1996. Effect of formulation variables on drug and polymer release from HPMC-based matrix tablets. *Int. J. Pharm.*, 142, 53-60.

TALUKDAR, M.M. and KINGET, R., 1995. Swelling and drug release behaviour of xanthan gum matrix tablets. *Int. J. Pharm.*, 120, 63-72.

TALUKDAR, M.M. and PLAIZIER-VERCAMMEN, J., 1993. Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparations. *Drug. Dev. Ind. Pharm.*, 19 (9), 1037-1046.

TALUKDAR, M.M., MICHOEL, A., ROMBAUT, P. and KINGET, R., 1996. Comparative study on xanthan gum and HPMC as matrices for controlled-release drug delivery. I Compaction and *in vitro* drug release behaviour. *Int J Pharm*, 129, 233-241.

TAPIA, C., BUCKTON, G. and NEWTON, J.M.,1993, Factors influencing the mechanism of release from sustained release matrix pellets, produced by extrusion/spheronisation. *Int. J. Pharm.*, 92, 211-218.

TODD, P.A. and SORKIN, E.M., 1988. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs*, 35 (3), 244-285.

TOWLE, G.A., 1973. Carrageenan. In: R.L. WHISTLER, ed. *Industrial gums: polysaccharides and their derivatives*. 2nd ed. New York: Academic Press.

United States Pharmacopeia XXIII and *National Formulary XVIII*, 1994. Rockville, MD: United States Pharmacopeial Convention.

VANDELLI, M.A. and CAMERONI, R., 1993. Selective coating of cylindrical matrices with a central hole I. An interpretation of the swelling process. *Int. J. Pharm.*, 100, 107-114.

VAZQUEZ, M.J., PEREZ-MARCOS, B., GOMEZ-AMOZA, J.L., MARTINEZ-PACHECO, R., SOUTO, C. and CONCHEIRO, A., 1992. Influence of technological variables on release of drugs from hydrophilic matrices. *Drug. Dev. Ind. Pharm.*, 18 (11&12), 1355-1375.

WADE, A., 1980. Pharmaceutical handbook. 19th ed. London: The Pharmaceutical Press.

WAGNER, J.G., WILKINSON, P.K., SEDMAN, A.J. and STOLL, R.G., 1973. Failure of USP tablet disintegration test to predict performance in man, *J. Pharm. Sci.*, 62 (5), 859-860.

WALKER, C.V. and WELLS, J.I., 1982. Rheological synergism between ionic and non-ionic cellulose gums. *Int. J. Pharm.*, 11, 309-322.

WAN, L.S.C., HENG, P.W.S. and WONG, L.F., 1993. Relationship between swelling and drug release in a hydrophilic matrix. *Drug. Dev. Ind. Pharm.*, 19 (10), 1201-1210.
WHORLOW, R.W., 1992. Deformation and stress. *Rheological techniques.* 2nd ed. West Sussex: Ellis Horwood.

WILDING, I.R., HARDY, J.G., SPARROW, R.A., DAVIS, S.S., ENGLISH, J.R., et al., 1992. In vivo evaluation of enteric-coated naproxen tablets using gamma scintigraphy. *Pharm. Res.*, 9 (Nov.), 1436-1441.

WILLIAMS, A.L., 1928. Locust-kernel gum and oil. *Analyst*, 53, 411-445.

WILLIAMS, K., DAY, R., KNIHINICKI, R. and DUFFIELD, A., 1986. The stereoselective uptake of ibuprofen enantiomers into adipose tissue. *Biochem. Pharmacol.*, 35, 3403-3405.

WILSON, H.C. and CUFF, G.W., 1989. Sustained release of isomazole from matrix tablets administered to dogs. *J. Pharm. Sci.*, 78, 582-584.

XU, G. and SUNADA, H., 1995. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Chem. Pharm. Bull.*, 43 (3), 483-487.

ZATZ, J.L., FIGLER, D. and LIVERO, K., 1986. Fluidization of aluminium hydroxide gels containing xanthan gum. *Drug. Dev. Ind. Pharm.*, 12, 561-568.

RELATED ACTIVITIES

The following training courses at The Robert Gordon University were attended:

1. Research methodologies.
2. Literature reviews.
3. Writing a thesis.
4. Preparing for thesis presentation and viva.
5. Introduction to Windows
6. Microsoft WORD
7. Microsoft EXCEL
8. Microsoft Power Point
9. Various English courses.

Visits to Knoll (formerly Boots) Pharmaceuticals, Nottingham:

1. February 1996
2. November 1996

Prof. Khan and Dr. Smith from Knoll Pharmaceuticals also visited RGU to discuss the research in this thesis, June 1997.

Posters presented:

1. "Dissolution of diclofenac sodium encapsulated natural gum mini-matrices"

The RGU Faculty Research Day, November 1995.

2. "Swelling and drug release kinetics from gum mini-matrices"

The Third European Congress of Pharmaceutical Sciences, Edinburgh, September, 1996.

3. "Mechanisms of controlled S(+) ibuprofen release from multiple-unit oral capsule formulations"

The 134th British Pharmaceutical Conference, Scarborough, September, 1997.

Oral presentation:

1. "Preparation of Novel Modified-Release Dosage Forms of Diclofenac Sodium and Ibuprofen"

Pharmacy Postgraduate Presentations, RGU, March, 1997.

Papers:

1. "Swelling and drug release kinetics from gum mini-matrices"

Eur. J. Pharm. Sci. 1996, 4, S158.

2. "Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations"

Int. J. Pharm., 1996, 139, 53-62.

3. "Relationship between swelling, erosion, and drug release in hydrophilic natural gum mini-matrices formulations"

Eur. J. Pharm. Sci., 1997, in the press.

4. "Mechanisms of controlled S(+) ibuprofen release from multiple-unit oral capsule formulations"

J. Pharm. Pharmacol., 1997, 49, Suppl 4, 75.