THE EFFECTS OF FORMULATION VARIABLES ON APPARENT SOLUBILITY AND RELEASE CHARACTERISTICS OF IBUPROFEN

by

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(Under the Direction of H. Won Jun & James Price)

ABSTRACT

Aqueous solubility is an important parameter in formulation development studies of oral dosage forms as it is a determinant of oral bioavailability. Ibuprofen (IB), which is a chiral non-steroidal anti-inflammatory drug (NSAID), exists in two enantiomeric forms. The racemic form (racIB) is widely used clinically, although S (+)-ibuprofen (SIB) is the potent isomer primarily responsible for the anti-inflammatory activity. Preformulation studies were carried out to identify the effect of solid and liquid additives on the solubility behavior of the racemate and the isomer. The study also investigated the effect of formulation variables such as release controlling polymers on racemic ibuprofen tablet matrices. Equilibrium phase solubility studies that were carried out on racIB and SIB in the presence of common pharmaceutical solvents indicated that nonpolar solvents like PEG 300 and propylene glycol exponentially increased the aqueous solubility of both the compounds. Derivatized cyclodextrins also increased their solubility by molecular inclusion complexation. Comparison of equilibrium solubilities showed that the S-form was solubilized to a greater extent than the racemic form.

Further, binary solid dispersion systems that were formulated to study the effect of PEG 8000 on the dissolution rate of SIB showed positive changes in solubility. The addition of nonionic

surfactant (Pluronic ® (PL-F68)) to the dispersion system increased the release of SIB by about 70% at the end of 2 hrs, while the addition of anionic surfactant ((sodium lauryl sulfate (SLS)) resulted in more than 50% of the drug being released within 10 min, especially at low drug loadings. In general, the ternary systems fared much better than the binary systems for solubility enhancement. Physicochemical characterization by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) indicated interstitial solid formation at low drug loadings. Finally, the effect of polymer blends on the dissolution rate and release kinetics of racemic ibuprofen from tablet matrices was studied. Carrageenans and cellulose ethers in combination prolonged ibuprofen release for up to 12-16 hrs and released the drug by non-Fickian (anomalous) mechanisms.

INDEX WORDS: Ibuprofen; S(+)-ibuprofen; Solubility; Cosolvency; Cyclodextrins; Inclusion complexation; Solid dispersions; Ternary solid dispersions; Interstitial solids; DSC; XRD; Direct compression; Oral hydrophilic matrices; Carrageenans; Cellulose ethers; Swellable tablets; Hydroxypropyl methylcellulose

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DEDICATION

To my dear husband, Utkarsh for his love, encouragement and patience....

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CHAPTER 1

INTRODUCTION

Poorly water-soluble drugs administered by the oral route often encounter problems of low bioavailability as a result of their limited dissolution rates. Improving the dissolution profiles of such water insoluble drugs has gained much attention in recent times due to the vast number of hydrophobic moieties entering the market as potential drug candidates. Numerous approaches have been sought to improve the dissolution characteristics of such water insoluble drugs. Briefly these approaches include: [1]

1. Particle size reduction
2. Crystal habit modification
3. Polymorphism
4. Complexation using cyclodextrins
5. Micellar solubilization using surfactants
6. Drug dispersion systems
7. Prodrug approach
8. Salt formation

The most effective technique used for increasing the aqueous solubility is often dependent on the final dosage form (solid or liquid) to be formulated. Aqueous solubility of poorly water soluble drugs that are formulated as liquid dosage forms (parenteral or oral liquids) is vastly improved by techniques such as changing pH, temperature and using cosolvents, surfactants or complexing agents.[2] From all the above mentioned techniques, cosolvency is the

oldest and the most powerful means of altering the solubility of drugs. [3] Cosolvents are highly water miscible organic compounds which are generally liquids but could also include solids such as sugars and high molecular weight hydrophilic polymers like polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). [4] An increase in drug solubility in an aqueous cosolvent system is primarily due to an alteration in the polarity of the system by the addition of the cosolvent. [5]

Novel approaches, such as inclusion complexation with cyclodextrins (CD), are also gaining popularity due to the favorable effect these compounds have on solubility as well as stability. [6] Chemically, cyclodextrins are cyclic oligosaccharides containing either six (α-CD), seven (β-CD) or eight (γ-CD) α-1, 4-linked glucopyranose units and are characterized by an outer polar part consisting of hydrophilic hydroxyl groups and a hydrophobic core. They are known to form inclusion complexes with many nonpolar drugs; these complexes are a result of the accommodation of the lipophilic parts of the drug molecule into the hydrophobic cavity. [7] Many derivatives of β-cyclodextrin such as the partially alkylated (dimethyl and trimethyl β-CD) and partially hydroxyl-alkylated (hydropropyl β-CD) are popularly used for solubilization of water insoluble drugs. Drugs which have been solubilized by complexation using CDs include nonsteroidal anti-inflammatory drugs (NSAID) (tenoxicam, ketoprofen) and the antimalarial drug artemisinin, to name a few. [8-10]

A popular approach for enhancing the rate of dissolution of sparingly soluble drugs is the formulation of solid dispersion systems. [1] The use of solid dispersions for improving drug dissolution rates was first reported in the 1960s. Chiou and Riegelman defined the dispersion systems as “the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method”. [11] Commonly, hydrosoluble polymers such as PEG and PVP are used as the dispersion carriers. Other carriers

that have been studied are sugars, urea, cellulose derivatives, polyacrylates and polymethacrylates. [1] The advantage of solid dispersions is that they allow for increased wetting while maximizing the surface area of the drug particles. The dispersion systems can be classified as either eutectic systems, solid solutions (molecular dispersion of drug in the carrier) or solid dispersions of the drug in a glassy or semi-crystalline matrix. [12] Physicochemical characterization of solid dispersions using differential scanning calorimetry (DSC), infrared spectroscopy (IR), X-ray diffraction (XRD) is often done to observe any solid state interactions which may have led to increased solubility .[13]

In addition to the challenges encountered during the preformulation stages of drug development, the development of the final dosage form is dictated by numerous parameters such as biological half-life, safety and efficacy of the active molecule. Patient compliance also plays a dominant role in drug development plans with once-a-day regimens being preferred over frequent dosing schedules. Controlled drug delivery systems primarily aim at sustaining the therapeutic action of the drug by maintaining relatively constant therapeutic drug levels in the body. [14] The prime advantages of controlled-release products include: [15]

1. Reduced local and systemic toxicity due to decreased variations in blood concentration
2. Potential clinical benefits of sustained c/t profiles
3. Reduced frequency of dosing resulting in increased patient compliance
4. Reduction in patient care time

Although controlled-release products seem very attractive in being able to sustain therapeutic effects and reduce toxicity, they are also associated with disadvantages that include dose dumping phenomena and are generally expensive to manufacture. Since the oral route is the preferred route of drug administration, controlled-release formulations given by the oral route are

highly favored. Design of oral controlled-release products depends on the delivery system. Many polymers can be used to control the release of the drug from the delivery system. Hydrophilic swellable polymers such as cellulose ethers, xanthan gum, guar gum and carrageenans are very popular and have been used to prepare matrix tablets that can sustain the release of drugs for extended time periods. [16] These polymers have very good compression properties thus allowing for the use of direct compression technology to form sustained release swellable matrices. The preparation of matrix tablets for controlled release by direct compression technology eliminates numerous granulation steps in the process of tablet manufacturing resulting in a highly cost-effective method. [17]

The study investigated the preformulation and formulation aspects of the ibuprofen isomers. The effect of molecular structure on physicochemical properties of drugs is well known. Drugs that exhibit isomerism differ in their physicochemical properties such as melting point, solubility, crystallinity and efficacy. [18] Ibuprofen ((α-methyl-4- (2-methylpropyl) benzene acetic acid)), a popular NSAID is widely used for the treatment of pain and inflammation and is practically insoluble in water.[19] As with most NSAIDs, it exhibits chirality and is available in two enantiomeric forms, the R and S form. Preformulation and formulation development studies were done on the ibuprofen molecule to determine its behavior under different solvent conditions and with different excipients.

The objectives of the study were:

1. To improve the aqueous solubility of racemic and S(+)- ibuprofen using common pharmaceutical cosolvents such as propylene glycol, polyethylene glycol, glycerol and sorbitol solution and complexing agents such as cyclodextrins.
2. To observe for differences in the solubility behavior of racemic and S-form of ibuprofen under similar solvent environments.
3. To increase the solubility of S (+)-ibuprofen via the formation of solid dispersions using polyethylene glycol 8000 as the primary dispersion carrier (binary systems).
4. To observe the effect of surfactants such as sodium lauryl sulfate (anionic) and Pluronic® F68 (nonionic) on the dissolution rate of S (+)-ibuprofen via the formation of ternary dispersion systems.
5. To characterize the binary and ternary solid dispersion systems using Differential Scanning Calorimetry and X-ray Diffraction to observe for any solid state interactions.
6. To investigate the effect of carrageenans and cellulose ethers on the release rates of ibuprofen from directly compressible tablet matrices.
7. To study formulation optimization and analyze the release kinetics of ibuprofen from oral controlled-release tablet matrices.
8. To characterize the tablet matrices using cryogenic Scanning Electron Microscopy (SEM) for topographical changes on hydration.

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CHAPTER 2

LITERATURE REVIEW

2.1. Solubility and Solubilization

Solubility is defined as the concentration of a solute in a saturated solution at a certain temperature. Thermodynamically, it is the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. [1] Of the various states of matter that exist and the corresponding solutions that they can possibly form, the solutions of solids in liquids are the most frequently encountered type in pharmaceutical formulations. The solubility of a solid in an ideal solution depends upon a number of factors such as the temperature of the system, the melting point of the solid and the molar heat of fusion. Molar heat of fusion is the heat absorbed when the solid melts. For ideal solutions, the heat of fusion is equal to the heat of solution. Ideal solubility is expressed by the following equation:

$$-\log X^{i}_{2} = (\Delta H_f / 2.303\ R).\ \{(T_0 - T)/ (TT_0)\} \qquad \text{Eqn. (1)}$$

where X^{i}_{2} is the ideal solubility of the solute expressed in mole fraction, ΔH_f is the molar heat of fusion, R is the ideal gas constant and T_0 and T are the melting point of the solute and the absolute temperature of the solution respectively. Ideal solutions are a rare occurrence and are generally used as a reference to describe real solutions. The majority of pharmaceutical solutions are regular solutions of nonpolar or moderately polar character. The solubility of a solute is dependent on its activity coefficient which, in turn, is dependent on the nature of both the solute and the solvent as well as the temperature of the solution. Solubility can be thought of as the

equilibrium of a solute that exists between its dissolved and undissolved states. Solubilization of any solute requires work to be done in transferring a solute molecule by removing it from the undissolved solute and depositing it in the solution phase. [2] Thus the thermodynamic parameters that are associated with the solubilization process can be calculated using the third law of thermodynamics as described by the following equation. [3]

$$\Delta G^0 = \Delta H^0 - T\,\Delta S^0 \qquad \text{Eqn. (2)}$$

where ΔG^0 is the free energy change, ΔH^0 is the change in enthalpy and ΔS^0 is the change in entropy associated with the process. Real solutions are conveniently described in terms of their deviations from ideality, which could be non-ideal enthalpy of mixing or nonideal entropy of mixing or both.

The screening of potential drug candidates via advanced techniques such as high throughput screening has sharply increased the number of water insoluble drugs entering the market. Since a high number of molecules that are potential drug candidates are nonpolar in nature with low aqueous solubility, the solubilization of these molecules for delivering them to the appropriate site of action via a feasible delivery system remains a major challenge. Newer approaches in formulation development of such candidates have primarily focused on improving their solubility. In addition to the previously mentioned energy changes that occur during solubilization, the solubility of any given solute in a solvent system is dependent on numerous factors such as the dielectric constant or the polarity of the solvent, the pH of the solution, the octanol/water partition coefficient of the solute and the temperature of the system to name a few.

2.2. Solubilization by pH

A majority of drugs that have a therapeutic effect are either weak acids or weak bases. Changing the pH of the solution so that the drug molecules undergo ionization, can solubilize these compounds. The solubility of a weak acid at any pH is described by its pK_a and its intrinsic solubility (which is the solubility of the unionized species). Thus the total concentration of a weakly acidic solute (C_{tot}) is given by the following equation:

$$C_{tot} = C_{HA} + C_A^- \quad \text{Eqn. (3)}$$

where C_{HA} and C_A^- are the concentration of the unionized and ionized forms respectively. A similar relationship holds for weak bases. The Henderson-Hasselbalch equation which gives the relationship between the concentration of the ionized and the unionized forms of a drug (weak acid) and the pH is as follows: [1, 4]

$$pH = pK_a + \log [C_A^- / C_{HA}] \quad \text{Eqn. (4)}$$

And for a weak base the equation is:

$$pH = pK_a + \log [C_B^- / C_{HB}^+] \quad \text{Eqn. (5)}$$

where pH and pK_a are the negative logarithms of the hydrogen ion concentration and equilibrium constant for the weak acid/base, respectively. These equations are only applicable to infinitely dilute solutions. Hence when the pH of the solution equals the pK_a of the drug, 50% of the drug is ionized and 50% is in the un-ionized form. In other words, the total solubility is twice the intrinsic solubility. Alteration of pH is frequently used to solubilize weak electrolytes in aqueous media. Although, this method is very straightforward, it does have some limitations. The solubility product or the apparent solubility is dependent on the concentration as well as the chemical nature of the counterion. Monovalent counterions produce salts that are more soluble as compared to divalent counterions, which in turn, fare better than trivalent counterions. This is

evident from the fact that hydrochloride salts make up almost 43% of the FDA-approved salt forms of anionic drugs. [5]

The counter-ion effect is a severe limitation to the solubilization by pH control. Addition of excessive counterions could lead to a reduction in solubility and consequently cause precipitation of the drug. Salting-out can also occur due to the presence of electrolytes or additives that may have a higher affinity for water molecules. The aqueous solubilities of diclofenac sodium and diclofenac diethylamine were compared in the presence of electrolytes and other pharmaceutical additives. At low concentrations the electrolytes caused salting-in while a reverse effect was observed at high electrolyte concentration for the diethylamine salt. Diclofenac sodium was precipitated out of the solution due to common ion effect. [6] Additives like sugars can also significantly decrease the solubility as observed from the effect of glucose, sucrose and sorbitol solutions on paracetamol solubility. [7] Salting out due to addition of salts was also reported for a highly water soluble drug guaifenesin. [8]

Another reason for experimental deviations in solubility, from those predicted by the Henderson-Hasselbalch equation, is self-association of solutes where the self-associated entity has a different solubility than the parent compound. [9] Many classes of drugs such as antihistamines, anticholinergics, antidepressants, tranquilizers, phenothiazines and non-steroidal anti-inflammatory drugs (NSAID) such as diclofenac exhibit surface activity. [10] Dexverapamil showed dimeric self-association with the dimmers having a lower pK_a compared to the monomeric species which resulted in higher solubility than expected from the intrinsic solubility and pK_a of the monomer. [11]

2.3. Solubilization by Cosolvents

The most common and the oldest approach for increasing drug solubility is the cosolvency approach. Cosolvents are defined as organic compounds which are substantially miscible in water. These are primarily liquids, but can also include solids such as sugars and high molecular weight hydrophilic polymers such as polyethylene glycol (PEG), and polyvinylpyrrolidone (PVP). [12] Pharmaceutical solvents are classified on the basis of their polarity. Properties used to characterize polarity include dielectric constant, surface tension, solubility parameter, and logarithm of octanol/water partition coefficient. The low water solubility of nonpolar solutes like ibuprofen is predominantly due to the strongly self-associating nature of water which tends to "squeeze out" the aromatic bulky group from the water structure thus restricting the amount of ibuprofen that can go into solution. [3] Cosolvents are known to reduce the cohesive interactions of water so that solubilization can occur. Further cosolvents such as PEG, propylene glycol also act by decreasing the polarity of the aqueous system. Reduction in the dielectric constant of the system is an important mechanism by which cosolvency works. [13] The mathematical approximation of the solubilizing power of a cosolvent in a water-based system is popularly described by the log-linear model and given by the following equation: [12]

$$\log S_m = f(\log S_c) + (1-f) \log Sw \qquad \text{Eqn. (6)}$$

where S_m is the solubility of the drug in the water-cosolvent mixture, f is the cosolvent volume fraction, and S_w and S_c are the solubility of the drug in pure water and cosolvent, respectively. Equation 6 predicts an exponential increase in the solubility of the drug with increasing cosolvent fractions. The solubilizing power of the cosolvent can then be determined from:

$$\log S_m = \log S_w + a_1 f \qquad \text{Eqn. (7)}$$

where a_1 is the solubilizing power of the cosolvent. Other models that have been used to predict the solubility of nonpolar solutes include the excess free energy model, phenomenological model and the UNIFAC model. Experimental deviations from the log-linear model may occur in real practice due to several reasons. These include non-ideal water-cosolvent behavior, change in the crystal structure of the solute, change in the solvation of the solute and conformational changes.

Solubilization can also be achieved by using multiple techniques such as cosolvency and pH control, cosolvency and inclusion complexation, especially for drugs that cannot be optimally solubilized using one technique. Some researchers have reported that cosolvents increase drug solubility in the cyclodextrin complex. [14] A reverse phenomenon was reported for a poorly water soluble drug NSC-639829, which resulted in decreased solubility due to the combination of cosolvency and inclusion complexation. [15] The decrease in solubility was probably due to competitive displacement of the drug from its complex by cosolvents while the increase in solubility can be explained by the formation of a ternary drug-ligand-cosolvent complex. [16]

2.4. Solubilization by micellar and inclusion complexation

Use of surfactants and complexation aids is another method for improving the solubility of drugs. Surfactants are amphiphilic molecules having a polar head and nonpolar tail. They are categorized as anionic, cationic, zwitterionic or nonionic. Anionic surfactants, which include sodium lauryl sulfate, sodium laurate, and potassium myristate, have a sulfate, sulfonate or carboxyl group in the polar regions. Cationic surfactants such as cetyl trimethylammonium bromide and cetyl pyridinium chloride have a positively charged polar head, while zwitterionic surfactants such as amino acids, betaines and phosphatidyl cholines have both cationic and anionic groups in their polar regions. Nonionic surfactants are characterized by hydroxyl, ether

or a combination of hydroxyl and ether groups in their polar regions. Examples of some commonly used nonionic surfactants include brij, myrj, poloxamer, tweens and spans. As discussed previously, some drugs may also exhibit surface activity. The aggregations of these amphiphiles are called micelles and the concentration at which there is no further decrease in the surface tension is characterized by the critical micelle concentration. Inclusion complexation is very similar to micellar solubilization, in that the total nonpolar–water interfacial area is reduced by insertion of the guest, either wholly or partially, into the complexing agent. This association is predominantly non-covalent in nature and known to increase the drug's aqueous solubility and rate of dissolution. [17]

2.5. Solid dispersion technology

The feasibility of using solid dispersion systems of water insoluble drugs to improve their solubility behavior has been extensively reviewed in recent times. This technology dates back to the 1960's. Chiou and Riegelman defined these systems as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method" while Corrigan defined the same systems as being a "product formed by converting a fluid drug-carrier combination to the solid state". [18, 19] Traditionally, water soluble carriers such as polyethylene glycol (PVP) or polyvinylpyrrolidone (PVP) were used to increase the dissolution rates. [20] However, recently the carriers used for preparation of solid dispersions are not just limited to water soluble polymers. The feasibility of using dispersion carriers such as gelucire, Eudragits ® and cellulose ethers are also being investigated. Eudragits® were used to formulate solid dispersions of drugs to either increase or decrease the solubility and in some cases to impart some protection to the drug (example diflunisal

coevaporated with Eudragit ® RS100 and RL100 decreased its photosensitivity) [21, 22] Similarly, gelucire was also successfully used to improve the solubility and bioavailability of drugs such as piroxicam, nifedipine and halofantrine, all of which are very poorly soluble in water. [23-25] The suitability of such techniques for the preparation of orally administered drugs is obvious through the increasing number of published articles that are currently available. Dissolution rates of drugs can be altered by increasing surface area or decreasing the particle size as described by the Noyes-Whitney equation: [26]

$$dC/dt = DS (C_s - C) /Vh \qquad \text{Eqn. (8)}$$

where dC/dt is the rate of dissolution, S is the surface area, D is the diffusion coefficient of the drug, V is the volume of the solution, C_s is the solubility of the drug in the dissolution medium, C is the concentration of the drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving drug. Solid dispersions of drugs often present drugs in the finest sub-divided state, sometimes at a molecular level, thus combining the benefits of increasing the apparent solubility of the drug and maximizing the surface area of the compound. The dispersion systems can be classified as either eutectic systems, solid solutions (molecular dispersion of the drug in the carrier) or solid dispersions of the drug in a glassy or semi-crystalline matrix. [20]

2.5.1. Methods of preparation

Traditionally, solid dispersions have been formed by the following methods:

1. Hot melt method: In this method the dispersion is formed by heating a mixture of the drug and the carrier in the molten state followed by resolidification via cooling. [27] For the dispersion to be formulated, miscibility of the components in the molten state is

essential. This is because any miscibility gaps in the phase diagram will lead to a product that is not dispersed at a molecular level. Thermostability of the drug and the carrier need to be considered during the formulation. Simple eutectic mixtures of sulphathiazole with urea were prepared by this method in the early 1960s. [28]

2. Solvent method: The solvent method was developed as an alternative for the preparation of solid dispersions whereby the drug and the carrier were dissolved in a common volatile solvent followed by evaporation under vacuum. This method was introduced by Mayersohn and Gibaldi. [29] They successfully increased the release rate of griseofulvin (from the dispersion containing PVP) about 5 to 11 times higher than that of the micronized drug. Solid dispersions prepared by this method are commonly referred to as co-precipitates or co-evaporates.
3. Hot melt extrusion: This method is currently the method of choice for preparing solid dispersions. Its origins lie in the plastic industry where polymers are often processed by extrusion. [30] In this method, the drug and the carrier are simultaneously melted and homogenized for uniform distribution and finally extruded into the shape that is desired. These extrudates can be further processed into tablets.

2.5.2. Characterization of solid dispersion systems

Solid dispersion systems are frequently characterized to observe for any solid state interactions which may have led to their increased solubility. The methods most commonly used for characterization of solid dispersions are dissolution testing, differential scanning calorimetry (DSC), infrared spectroscopy (IR), X-ray diffraction (XRD). [27, 31] These techniques can differentiate between true solid solutions (molecular dispersions) and solid dispersions (non

molecular dispersions). Loss of crystallinity is often used as a differentiating factor between solid solutions and dispersions.

2.6. Oral Controlled-Release Drug Delivery Systems

Controlled-release drug delivery systems have received a great deal of attention in recent years due to a variety of reasons. Various new technologies have evolved that can predict and thus control the release rate of the drug from its delivery system. Ideally any drug delivery system should be able to deliver the drug at a rate that is dictated by the needs of the body over the period of treatment and should be able to target the active entity solely to the site of action. [32] Such ideality although desirable is a lofty goal to achieve. Controlled drug delivery systems primarily aim at sustaining the therapeutic action of the drug by maintaining relatively constant effective drug levels in the body consequently leading to a reduction in the dosing frequency and minimizing potential side effects. These systems predominantly control the drug release rate from the delivery system by manipulating the dosage form or delivery system. They do not alter the drug's inherent kinetic properties. Of all the various routes that are available for the administration of drugs, the oral route is by far the most preferred route. About 90% of all drugs with systemic effects are given by the oral route. [33] The prime reasons are the ease and convenience associated with self-administration of oral dosage forms. Further, these systems enjoy flexibility in terms of dosage design since barriers such as sterility and potential damage at the site of administration are drastically minimized. Market trends indicate that about two-thirds of the US drug market consists of drugs taken orally and more than 85% of these are oral solids. [34] The commercial success of oral controlled-release drug delivery systems is evident from the fact that their market revenue in the US is about $13 billion. [35]

The terms “sustained-release”, “controlled-release”, “prolonged-release” are often used interchangeably and in a confusing manner. In reality, sustained-release refers to any drug delivery mechanism that provides medication over an extended time. Controlled-release, however, denotes that the system is able to provide some actual therapeutic control, either of a temporal or a spatial nature, or both. [36] Generally, such delivery systems can maintain constant blood or tissue levels in the therapeutic range by attempting to attain “zero-order” release. Zero-order release constitutes drug release from the delivery system which is independent of the amount of drug loaded in the device. In addition to delivering drugs at a zero-order rate some systems are also able to target the active molecules at their site of action. Figure 2.1 shows idealized comparative profiles of the blood levels that are obtained after the administration of conventional, sustained- and controlled-release dosage forms. From the figure it can be seen that conventional dosage forms such as a tablets or capsules give a one time rapid release of drug. As long as the drug concentration lies within the therapeutic window a pharmacological action is elicited. Oral controlled-release dosages by contrast are characterized zero-order release mechanisms. [32, 36-39]

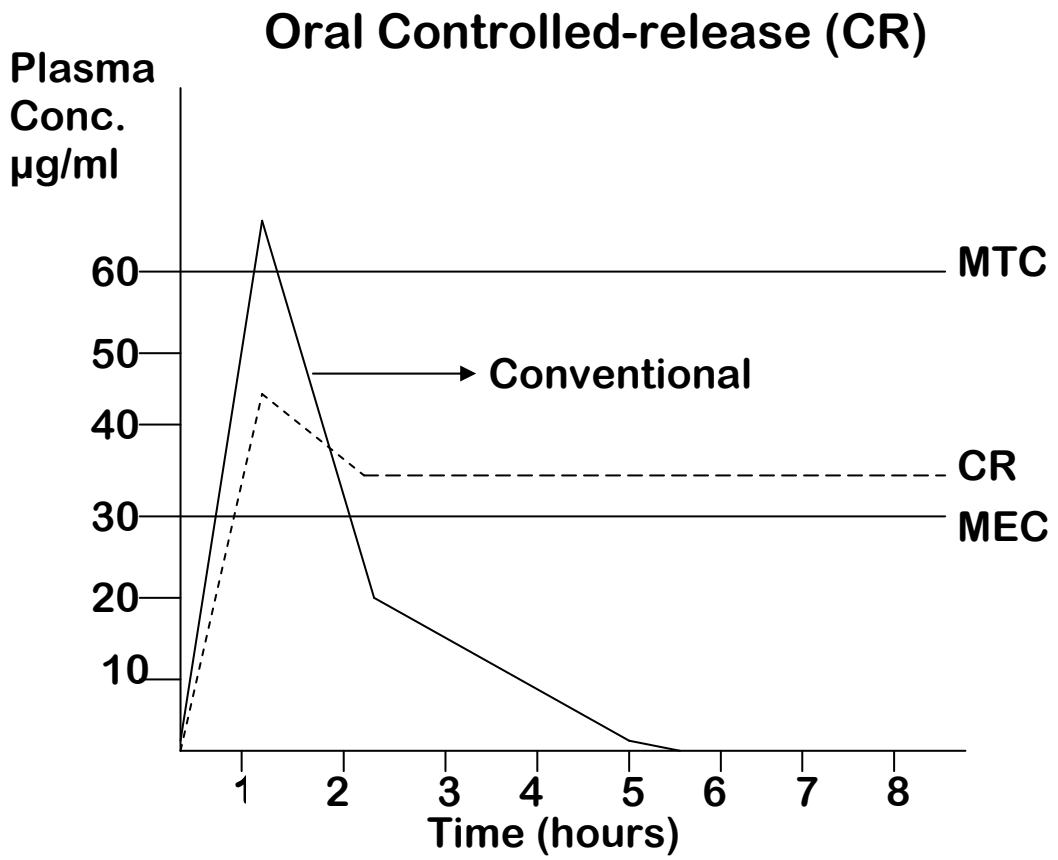

Figure 2.1. Comparison of oral controlled-release and conventional release systems

2.7. Hydrophilic matrices

For conventional dosage forms given orally, the drug is generally mixed or dispersed with soluble or insoluble excipients which rapidly liberate the drug. The oral controlled-release system, in contrast, is extensively made of polymers that retard the release of the drug. A variety of polymers are used to achieve an extension or control on the release of drug molecules. Based on the mechanism of drug release from the devices, delivery systems are broadly classified into four major categories: [36]

1. Diffusion controlled
2. Dissolution controlled
3. Osmotically controlled
4. Chemically controlled systems

Diffusion controlled systems are classified as either reservoir or matrix systems. The reservoir system, as the name suggests, contains the drug in the core surrounded by a membrane through which the drug diffuses. The monolithic devices/matrix systems consists of a uniform distribution of the drug through a polymer matrix, wherein the drug molecules dislodge themselves from the polymer network and diffuse out of the system at a uniform rate. Of late, matrix systems have gained significant importance and are used to control the release of both water soluble and water insoluble drugs. The polymers that are frequently used in the monolithic tablet systems are swellable in aqueous fluids in the gut. They can be divided into two categories: water-insoluble polymers referred to as hydrogels and water soluble hydrophilic polymers. [40] Hydrophilic matrices are generally prepared by mixing the drug with hydrophilic, swellable gums followed by compressing the mixture into tablets. The key element to drug release from such matrices is the use of polymers that will undergo transition from the glassy to

the rubbery state which is characterized by a gel-like layer, on hydration by water. This transition should occur fairly rapidly so that the drug has to pass through the viscous gel layer to be released. [41] The rate at which the drug is released from the swellable hydrophilic matrices is determined by numerous processes such as hydration of the polymer that leads to swelling, diffusion of the drug through the hydrated polymer, drug dissolution and polymer erosion. Many of these processes occur simultaneously to release the drug. [42] To simplify gel layer dynamics during drug release, the boundaries of the layer are defined. Three fronts are known to exist in a swellable matrix tablet. They are: [43, 44]

1. The swelling front: The boundary between the glassy polymer and the rubbery state.
2. The diffusion front: The boundary between the solid (undissolved) drug and the dissolved drug.
3. The erosion front: The outermost boundary between the matrix and the dissolution medium.

Various mathematical models have been used to describe the drug release mechanisms from such swellable matrices. Fick's law of diffusion, which is generally used to describe diffusion of solid drugs from homogenous matrices, cannot be applied to the swellable systems. Fick's law, which is essentially used to describe one dimensional transport from thin films, is rendered inadequate in explaining drug release due to complications in the geometry of the matrix after water penetration. The release of drugs from hydrophilic matrices involves the following phenomena:

1. Imbibition of water in the matrix. Water acts as a plasticizer and decreases the glass transition (T_g) of the system. The T_g of the polymer is an important parameter especially in controlling the release of the drug. Below the T_g the mobility of macromolecules is low

and the material is in a glassy state. Above the T_g the material is in a rubbery state and the mobility of the polymer chains is markedly increased. This leads to higher rates of mass transfer of the drug and water. [45]

2. Swelling of the matrix. Due to water imbibition, the matrix swells and the dimensions of the system increase.
3. Development of a concentration gradient. This is due to dissolution of the drug in contact with water and its subsequent diffusion from the swollen matrix.
4. For poorly water soluble drugs, the dissolved and undissolved drug coexists in the matrix.
5. Polymer erosion. This occurs due to the dissolution of the polymer itself. Polymer erosion is especially important for water insoluble drugs that may be released due to erosion of the swollen matrix. [41]

These phenomena have to be adequately incorporated in equations that are used to describe the release kinetics of the drug from such systems.

2.8. Release kinetics

The Higuchi equation is the most popular equation to describe the release of drugs from planar matrix systems.

$$M_t / M_\infty = K\sqrt{t} \qquad \text{Eqn. (9)}$$

where M_t is the amount of drug released at time t, M_∞ is the initial amount of drug incorporated in the system and K is a constant reflecting the design variables of the system. However, this equation does not adequately describe the aforementioned processes. This is because it is based on one-dimensional diffusion from planar systems where the swelling of the polymer is negligible. Further, the Higuchi equation is based on the assumption that the diffusivity of the

drug is constant and perfect sink conditions are maintained. Hence a more comprehensive equation was derived by Peppas which is called the Power Law Equation. [46, 47]

$M_t / M_\infty = kt^n$ Eqn. (10)

where M_t / M_∞ is the fraction of drug released at time t, k is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and n is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms are classified based on the values that n assumes. For cylindrical devices such as tablets, the drug transport mechanism is by Fickian diffusion when n=0.45, Anomalous (non-Fickian) for values of $0.45 < n < 0.89$, and for values of n = 0.89, Case II or zero-order release kinetics is indicated. Case II relates to processes which occur when polymer relaxation becomes the rate controlling step. Non-Fickian release is described by two mechanisms, the coupling of drug diffusion and polymer relaxation. [46, 47]

2.9. Polymers in oral controlled-release drug delivery

As stated previously, hydrophilic matrices are generally formulated using swellable polymers. Cellulose ethers such as hydroxypropyl methylcellulose (HPMC) have gained popularity in the formulation of such swellable matrices due to their swelling properties. Further, cellulose ethers have good compression characteristics so that they can be directly compressed to form sustained release devices. [48, 49] In addition to synthetic cellulose ethers, naturally occurring polymers such as carrageenans, xanthan and guar gums have also been utilized to effectively control the release of drugs from swellable matrix systems. [50-52] Carrageenans are naturally occurring high molecular weight sulfated polysaccharides extracted from marine plants belonging to class *Rhodophyceae*. They are widely used in the food industry as viscosity

enhancing, gelling and stabilizing agents. There are three main types of carrageenans, the first is lambda (λ-carrageenan), which gives viscous solutions but does not gel the second is iota (ι-carrageenan) and the third is kappa (κ-carrageenan). Kappa and iota carrageenans do not dissolve in water, but form gels. [53]

The success of controlling the release of drugs by formulating them as hydrophilic matrices is evident from the enormous number of papers that are published and the commercial success of such systems. Recently, a combination of gelling polymers is used in the matrix to achieve the desired effects on drug release. [54]

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CHAPTER 3

TRENDS IN PROTEIN DRUG DELIVERY [1]

[1] Jayanti Nerurkar and H. W. Jun. To be submitted to *Pharmaceutical Technology*.

Abstract

The advent of proteins and peptide drug therapy has opened a new window of possibility for treating diseases. However, these molecules are fraught with a variety of problems such as short circulation times, rapid degradation, and poor diffusivities to name a few. The article gives a broad overview of the various innovative technologies that are being developed to deliver such sensitive molecules to the human body.

Keywords: Gene delivery; Protein delivery; PEGylation; Nanoparticles; Non-viral vectors; Liposomes; Iontophoresis; Microneedles

Introduction

Drug delivery technology today is in the midst of a renaissance. A review of the recent papers published in this area indicates that drug delivery is becoming a multidisciplinary science due to great advances in the area of biotechnology and molecular biology. Until recently this technology primarily relied on traditional formulation approaches and was restricted to the oral route due to the ease of administration and manufacturing. [1] However, with the recent decoding of the human genome, there is now a better understanding of diseases that affect the human body. Proteins and peptides, which are the building blocks of the human body, are now being evaluated as viable prophylactic and therapeutic options to prevent and treat diseases. Further innovative genetic engineering and recombinant DNA techniques have made it possible to obtain large quantities of pure proteins. These molecular entities are currently being used for a variety of ailments such as the treatment of cancer, in hormone therapy, as growth factors, and thrombolytics. [2] Their popularity lies in their ability to mimic endogenous compounds, while eliminating the administration of exogenous chemicals. Technologies such as gene therapy and DNA are hailed as the medical treatments of the future. The discovery of small RNAs (short stretches of RNA that range in length between 21 and 28 nucleotides) were selected as the scientific breakthrough of 2002. [3] These newer treatment modalities for existing conditions have demanded a more efficient delivery system and started focusing on macromolecular and protein drug delivery. To meet the challenges of delivering these molecules, novel and innovative drug delivery technologies such as transdermal patches, nanodevices, bioadhesive systems, nasal delivery, monoclonal antibodies, liposomes and cell encapsulation, to name a few, are being devised.[4] The ever expanding role of drug delivery systems is reflected in its vast economic growth in recent years. The US market for drug delivery systems was estimated at

approximately $44 billion in 2003 and is predicted to reach approximately $75 billion by 2008, growing at a rate of 11.3%. [5] Further, research initiatives taken by countries such as the United States, Japan and European Union in the field of nanotechnology have also propelled the expansion of drug delivery systems. Non-traditional routes of delivering drugs such as the nasal and the transdermal routes are being explored to view the possibility of administering macromolecules which would otherwise have limited absorption through the gastro-intestinal tract. Examples include intranasal vaccination against influenza using a live attenuated virus (FluMist™, MedImmune Vaccines, Inc.), which has met with much commercial success due to its noninvasive technique. Sustained transdermal delivery of steroids such as estradiol has also being successfully achieved (Alora® estradiol transdermal system, Watson Pharma, Inc.).

Although bioactive molecules seem as promising therapeutic candidates, their delivery to the target site is stunted by their molecular weight and their inherent labile nature. A large majority of these molecules are extremely sensitive to proteolysis and gastric degradation, which makes them nearly impossible to be given by the oral route. Additionally, due to their hydrophilic nature, proteins and peptides are characterized with low partition coefficients and poor diffusivity through biological barriers. [6] The gastro-intestinal tract (GIT) is impermeable to large molecules and hence protein delivery via the oral route has not yet achieved great success, with less than one percent of the dose being absorbed after oral administration. [7] Other barriers to their formulation include short circulating half-lives and poor pharmacokinetic profiles due to rapid renal excretion, even when administered by parenteral routes.[8] Concerns of toxicity and elicitation of immunological reactions augment existent obstacles. Examples include the damage to normal cells by cytostatic drugs in cancer chemotherapy. [9] Targeting these molecules to the appropriate site reproducibly is often the primary challenge for the pharmaceutical scientists. The

various considerations that are required for formulating peptide drugs have led to the development of novel strategies that enhance the delivery of these agents to the human body while protecting the active molecule. Some of these include the formulation of biodegradable nanoparticles, liposomes and covalent conjugation with natural or synthetic polymers like poly (ethylene glycol) (PEG). [10] These strategies allow for controlled and prolonged duration of pharmacological action along with significant reduction in the adverse effects, especially in the case of nanoparticles which can be administered by a single injection.

Nanoparticles

Nanoparticles (NP) are colloidal polymeric systems ranging in size from 10 nm to 1000 nm. [11] Based on the method of preparation, they are termed as nanoparticles, nanospheres or nanocapsules. Matrix systems in which the drug is uniformly dispersed are referred to as nanospheres, while nanocapsules are “reservoir” vesicular systems in which the drug is confined to a cavity surrounded by a polymer membrane. From studies done on the uptake of nanoparticles, it is seen that the submicronic size facilitates efficient drug targeting due to a higher cellular uptake.[12-14] NPs are prepared using a variety of polyesters such as poly (D,L-lactide) (PLA), poly (D,L-glycolide) (PLG), poly (D,L-lactide-co-glycolide) (PLGA), poly (Є-caprolactone), poly (orthoesters) and poly (cyanoacrylate) . [15] In the majority of cases, the peptides were encapsulated in PLGA. [16] Biodegradable polymers such as PLGA offer an advantage in being tissue compatible, while being able to sustain the release of the drug. Proteins and peptides are in general, characterized by very poor diffusivities; hence the dominant mechanism of release of the drug from the NPs is by polymer erosion or degradation. [6] Nanoparticles are commonly prepared by the dispersion of preformed polymers by using the

double emulsion solvent evaporation technique. [6] A variety of proteins and peptides have been successfully formulated as NPs. Modification of the emulsification method includes the solvent diffusion technique which was used to encapsulate thyrotropin releasing hormone (TRH) and luteinizing hormone-releasing hormone (LH-RH) analog, nafarelin acetate. [17, 18]

Novel modifications of formulating NPs include the use of divalent cations and inorganic materials instead of the polymers. These cations (Ca^{2+}, Mg^{2+}, Mn^{2+}) and inorganic materials like calcium phosphate, silica, magnesium phosphate have the ability to form ionic complexes with macromolecules (negatively charged proteins and peptides) and hence they are frequently used as nonviral vectors in gene delivery. [19, 20] Such non-viral vectors can effectively condense the negatively charged plasmid DNA into nanoparticulate structures.[21] Ceramic nanoparticles, which are primarily formed by electrostatic attraction between a nonviral vector and the DNA often have a greater stabilizing effect on the genetic material as compared to viral vectors. Further, they are also characterized by a higher uptake by the target cells. [22] Cationic polymers such as chitosan, gelatin and polyethyleneimine are also being investigated as potential nonviral vectors for use in gene delivery. [22, 23]

Polymer Conjugated Proteins

Another strategy for delivering biomolecules to the target sites is by protein modification such as conjugation with polymers. A prerequisite of the protein conjugation technique is that the activity of the protein or peptide should be retained. Often such conjugation results in the modification of the molecular identity. The polymers used for this purpose could be either natural or synthetic in nature. A vastly popular method called PEGylation, which is the conjugation with poly (ethylene glycol) (PEG), has been very successful. [24] This technique has

received much attention in recent years due to the numerous advantages associated with it. PEGylation causes an increase in apparent size of the biomolecule (thus reducing renal filtration), changes the hydrodynamic volume and results in surface masking of the protein. Further, PEGylation reduces clearance by reticulo-endothelial system (RES) and thus exhibits a protective effect on the protein by decreasing its proteolytic degradation. Protein modification is also known to reduce the antigenicity and immunogenicity of the molecule with which it is conjugated. Increasing circulation half-life while sustaining clinical response and minimizing the dosing are additional advantages. PEG- conjugates also show better tolerance, altered biodistribution and enhanced membrane penetration. [25-27] Improved clinical properties are in addition to enhanced physicochemical properties of the protein such as higher stability and biocompatibility, that PEG imparts to the peptide molecules on conjugation.[28] These alterations due to PEGylation are largely explained by changes in the conformational structure, steric interferences and hydrophobicity of the conjugate. [29] The clinical advantages of PEGylation are evident by the commercial success achieved by PEG-alpha-interferon 2a and PEG-alpha-interferon 2b, which are clinically approved for the treatment of Hepatitis C. Another example is the recent approval of PEG-filgrastim, PEG-conjugated granulocyte-colony stimulating factor, which is indicated to accelerate recovery from neutropenia. [30]

In addition to the highly popular PEGylation technique, other polymers are also being investigated for protein delivery via conjugation. Some of them include gelatin which has been conjugated with human tumor necrosis factor alpha (TNF) for enhanced stability of TNF and poly (styrene-co-maleic acid anhydride) (SMA), which is conjugated with anti cancer proteins and peptides. [31, 32] The conjugation of SMA with antimetastatic proteins has been shown to increase their plasma half-lives due to the tendency of SMA to bind to plasma albumin. [32]

Further, the SMA-antitumor protein neocarzinostatin (SMANCS) conjugate has shown promising results in preclinical studies and clinical trials due to effective targeting to the tumor tissue (enhanced permeability and retention effect), increased plasma half-life and reduced immunogenicity. [33]

Liposomes

Liposomes are microparticulate spherical vesicles consisting of phospholipid bilayers encapsulating an aqueous space. [34, 35] Hydrophilic drugs such as proteins and peptides are encapsulated in the aqueous compartments while lipophilic drugs are associated with the lipid bilayers. [36] Commonly, phospholipids such as phosphatidylcholine are used either alone or in combination with cholesterol to prepare liposomes. Cholesterol is used, as it is known to reduce the permeability of the bilayers and can prevent leakage of the entrapped drug. [34] Factors such as size, structure of the liposomes, composition of the bilayer and surface charge often affect the encapsulation efficiency as well as the release characteristics of the drug from the liposomes. [37] When liposomes are administered to the body via the widely used intravenous route, they are rapidly conditioned/coated by plasma proteins. This process is termed as surface opsonization. [21] Surface opsonization is followed by uptake by the reticulo-endothelial system cells (predominantly located in the liver and spleen). [38] Liposomes can also be destabilized by activating the complement system, or by interactions with circulating lipoproteins. [36, 39] Other potential problems include leakage of the active drug out of the liposomal vesicles while in circulation, thus causing difficulty in achieving their physicochemical stability. [40]

Since liposomes are preferentially taken up by the RES, they can be actively targeted to the macrophages in the liver. Examples include muramyldipeptides (MDP) which are known to

induce tumoricidal, antiviral and antimicrobial activities and are targeted to the liver. Liposomal preparations of MDP showed enhanced cellular immunity in mice. [41] Additionally, surface modification of the liposomes by PEG grafting has also helped in the attainment of long-circulating liposomes which are referred to as stealth liposomes. [42] The prolonged circulation of stealth liposomes is due to hindered or delayed protein opsonization. [43] Liposomes can also be used in gene delivery by conjugation with antibodies or ligands. [44]

Transdermal Protein Delivery

The delivery of macromolecules via the skin (transdermal drug delivery) has also gained momentum in recent times due to the noninvasive and patient-friendly nature of the therapy. Until recently, transdermal drug delivery was only limited to small molecules (<500 Da) which had good water and lipid solubility. Primarily the outer layer of the skin or the stratum corneum, which is approximately 20 μm in thickness, is generally impermeable to the passage of a majority of drugs. However, emerging technologies have focused on increasing the permeability of the stratum corneum to high molecular weight hydrophilic compounds, thus allowing for macromolecular transdermal delivery. Permeation enhancers used in the transdermal delivery systems may be either chemical or physical in nature. Chemical permeation enhancers generally work by altering the partitioning of the drug into the stratum corneum thus increasing its diffusion through the skin layers or by disrupting the skin lipids. [45]

Physical techniques such as iontophoresis, low-frequency sonophoresis (using ultrasound), electroporation and microstructured arrays (microneedles) have been heavily researched in the past few years due to their potential in allowing the passage of large molecules such as peptides and proteins through the skin. Further, such technologies can also be used for

diagnostic purposes such as in diabetes care. Electroporation, which was initially developed to introduce DNA into a cell, has now expanded its application in the area of transdermal drug delivery. [46] Although, both electroporation and iontophoresis utilize electrical stimuli to increase skin permeability, both of them differ in their mechanisms of transdermal delivery and the method of application of electricity. Electroporation causes a change in the skin permeability and consists of the application of a high voltage for a very short period of time. [47-49] In the case of iontophoresis, a low voltage current is applied via an electrode (which is of the same charge as the drug) that forces the drug through the skin due to repulsion. This technique is highly favorable for the delivery of peptides and oligonucleotides which are ionic in nature and can thus be potentially delivered through the skin. Iontophoresis has seen an enormous progress from the laboratory setting to the clinic with many companies applying for government approvals to market their products and many more in clinical trials. Another technique which is gaining rapid attention is the use of low-frequency ultrasound to deliver drugs transdermally. Sustained anticoagulant effect was observed when low-molecular weight heparin was administered transdermally using low-frequency ultrasound in the presence of a chemical permeant (sodium lauryl sulfate). [50] Recently, the use of laser technology is also being used to increase the permeation of macromolecular and hydrophilic drugs such as peptides through the skin. [51]

Microstructured arrays called as microneedles are also used to deliver drugs by creating micropores in the skin without causing pain. [52] Although, microneedles have been used to deliver local anesthetics such as lidocaine, their potential for delivery of peptides has shown some success in the laboratory. Insulin delivered transdermally using microneedles significantly lowered the blood glucose levels when tested on diabetic rats. [53] Most of the novel technologies mentioned above can be used in combination for a synergistic effect. For example when the

microneedle technology was combined with iontophoresis for oligonucleotide delivery there was approximately 100-fold increase in transdermal flux compared to using iontophoresis alone. [54, 55]

Conclusions

The field of protein and peptide drug delivery is at an exciting stage with the advent of newer technologies and delivery systems that can overcome the inherent challenges associated with delivering such sensitive molecules to the body. Further, successful targeting of these molecules has demonstrated the active role played by the delivery systems in achieving favorable aspects such as longer circulation half lives and absence of proteolytic degradation as seen by stealth liposomes and NPs respectively. The success of these therapies is evident from the various clinically approved formulations that are now available in the market. Protein and peptide delivery in the future can be expected to become more and more dominant with advances in the field of biotechnology and pharmacogenomics, where delivery systems can be tailored to meet individual needs.

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CHAPTER 4

SOLUBILITY OF (±)-IBUPROFEN AND S (+)-IBUPROFEN IN THE PRESENCE OF COSOLVENTS AND CYCLODEXTRINS[1]

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[1] Jayanti Nerurkar, J.W. Beach, M.O. Park and H. W. Jun. Submitted to *Pharmaceutical Technology and Development*, 06/10/2004.

Abstract

Aqueous solubility is an important parameter for the development of liquid formulations and in the determination of bioavailability of oral dosage forms. Ibuprofen (IB), a non-steroidal anti-inflammatory drug (NSAID), is a chiral molecule and is currently used clinically as a racemate (racIB). However, the S-form of ibuprofen (SIB) is the biologically active isomer and is primarily responsible for the anti-inflammatory activity. Phase solubility studies were carried out to compare the saturation solubilities of racIB and SIB in the presence of common pharmaceutical solvents such as glycerol, sorbitol solution, propylene glycol (PG) and PEG 300 over the range of 20 to 80% v/v in aqueous based systems. The solubilities of the two compounds were also compared in the presence of cyclodextrins such as beta cyclodextrin (CD), hydroxypropyl beta cyclodextrin (HPCD) and beta cyclodextrin sulfobutyl ether sodium salt (CDSB) over the range of 5 to 25% w/v. Solubility determinations were carried at 25 ^{0}C and 37^0 C. Cosolvents exponentially increased the solubility of both SIB and racIB, especially in the presence of PG and PEG 300. Glycerol was not very effective in increasing the aqueous solubilities of either compound, while sorbitol solution had a minimal effect on their solubility. PG and PEG 300 increased the solubility of SIB by 400-fold and 1500-fold, respectively, while the rise in solubility for racIB was 193-fold and 700-fold, respectively at 25 ^{0}C for the highest concentration of the cosolvents used (80%v/v). Of the two compounds studied, higher equilibrium solubilities were observed for SIB as compared to racIB. The derivatized cyclodextrins increased the aqueous solubility of racIB and SIB in a concentration dependent manner giving A_L type of phase diagrams. The phase solubility diagrams indicated the formation of soluble inclusion complexes between the drugs and HPCD and CDSB, which was of 1:1 stoichiometry. The addition of underivatized beta cyclodextrin reduced the solubility of racIB

and SIB via the formation of an insoluble complex. The S-form formed more stable complexes with HPCD and CDSB as compared to racIB. The solubilization process is discussed in terms of solvent polarity and differential solid-state structure of racIB and SIB. The thermodynamic parameters for the solubilization process are presented.

Keywords: Ibuprofen; S (+)-ibuprofen; Solubility; Cosolvents; Cyclodextrins; Inclusion complexation; Thermodynamic parameters

Introduction

The formulation of poorly water soluble drugs into liquid dosage forms remains a challenge for pharmaceutical scientists. Numerous techniques are now available that can enhance the aqueous solubility of such compounds. These include changing physicochemical parameters such as pH and temperature, use of cosolvents, complexing agents and other additives. The use of cosolvents to improve the solubility characteristics of poorly water soluble drugs is by far the most common and effective method. [1] Recently the use of complexing agents, such as cyclodextrins, for improving the solubility of drugs has risen rapidly due to their favorable effects on drug stability as well as bioavailability. [2] Cyclodextrins (CD) are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1, 4-linked glucopyranose units and are characterized by an outer polar part consisting of hydrophilic hydroxyl groups and a hydrophobic core. They are known to form inclusion complexes with many nonpolar drugs by the accommodation of the lipophilic parts of the drug molecules into the hydrophobic cavity. The inclusion complexation is very similar to micellar solubilization, in that the total nonpolar–water interfacial area is reduced by insertion of the guest, either wholly or partially, into the complexing agent. This association is predominantly non-covalent in nature and known to increase the drug's aqueous solubility and rate of dissolution. [3-4]

Ibuprofen ((α-methyl-4- (2-methylpropyl) benzene acetic acid)), a popular non-steroidal anti-inflammatory drug, is widely used for the treatment of pain and inflammation. [5] It is practically insoluble in water and has a pKa value of 4.41. [6] Due to its low aqueous solubility, ibuprofen is commonly formulated as suspensions for pediatric use. However, as is the case with most NSAIDs, patients can experience severe gastrointestinal irritation and in some cases bleeding. Techniques that could improve the solubility of ibuprofen would result in its faster

absorption after oral administration, while reducing its gastric side effects as a result of shorter dwell time in the stomach. [3] Ibuprofen exhibits chirality however only the racemic mixture is currently available for use. [7] Clinical studies have shown that S (+)-ibuprofen is the potent isomer and that a unidirectional metabolic inversion from the R-form to the S-form takes place within the body. [8-10] The S-form is reported to be about 160 times more potent than the R-form in the inhibition of prostaglandin synthesis. Improving the dissolution rate of S (+)-ibuprofen could give dual benefits of enhancing its effectiveness due to higher oral bioavailability, while reducing the gastric irritation.

It is well known that chiral isomers may differ in their physicochemical properties such as melting point, solubility, crystallinity as well as their efficacy. This study investigated the differences in the saturation solubilities of racemic ibuprofen and the pure enantiomer S (+)-ibuprofen in the presence of commonly used co-solvents and several cyclodextrin derivatives. The data obtained could be beneficial for the development of liquid dosage forms of ibuprofen isomers.

Materials and Methods

Materials

(±)-Ibuprofen (racIB) and S (+)-ibuprofen (SIB) were gifts from Albemarle Co. (Baton Rouge, LA). Propylene glycol and glycerol were obtained from JT Baker Co. (Phillipsburg, NJ). Polyethylene glycol 300 was obtained from Van Waters and Rogers, Inc. (Charleston, SC). Sorbitol solution was obtained from SPI Polyols, Inc. (Wilmington, DE). Beta cyclodextrin (CD) and hydroxypropyl beta cyclodextrin (HPCD) were gifts from Cerestar USA, Inc. (Hammond,

IN). Beta cyclodextrin sulfobutyl ether sodium salt (CDSB) was a gift from Cydex, Inc. (Overland Park, KS). These compounds were used as received.

Methods

The saturation solubilities of (±)-ibuprofen (racIB) and S (+)-ibuprofen (SIB) in the presence of cosolvents and cyclodextrins were determined at 25^0 C and 37^0 C as described below.

Phase solubility studies in cosolvents and cyclodextrins

Stock solutions of the appropriate cosolvent/water mixtures equivalent to 20-80% v/v were made and sonicated for about 10 min to ensure complete mixing. Of these stock solutions, 25ml each was placed in a 50ml capped conical flask. The solubility of racIB and SIB was measured by adding excess drug to each of the 25ml cosolvent/water mixtures. Similarly solubility determinations in the presence of cyclodextrins were carried out by preparing stock solutions of 5-25% w/v of HPCD and CDSB and sonicating them for about 10 min to ensure complete mixing. 25ml of the solution was placed in a 50ml capped conical flask. The solubility of the drugs was measured by adding excess drug to each of the 25ml cyclodextrin solutions. In the case of CD, stock solutions were not prepared, rather the amount of CD required to make the desired concentration was added directly to the flask, the water added and then the drug was added to the mixture. These solutions were then equilibrated in a constant temperature shaking water bath (Precision® Reciprocal Shaking Water Bath, Model # 50, Precision Scientific, Winchester, VA) at 75rpm for 24hrs at 25 and 37^0 C. The water bath was maintained at a uniform temperature within $\pm 0.1^0$ C of the experimental temperature. All the readings were obtained in duplicate.

Thermal Analysis

The melting points of racIB and SIB were determined on a Perkin-Elmer differential scanning calorimeter DSC-7 (Perkin-Elmer, Norwalk, CT). Approximately 1-3 mg of the samples was weighed in aluminum pans, which were hermetically sealed, and the samples scanned from 25 to 150 ^{0}C at a scan rate of 2 ^{0}C per min. The thermograms were used to determine the melting points of both the compounds using the DSC-7 program.

Assay

A standard calibration curve was plotted for racIB and SIB and the absorption measured with a UV spectrophotometer (Spectronic 2000, Bausch and Lomb, Rochester, NY) at λ=263 and 221nm, respectively. Preliminary experiments indicated that 24 hrs were sufficient to attain saturation solubility of both the compounds under the test conditions. At the end of equilibration, the samples were filtered through a Whatman filter paper into glassware that was equilibrated at the experimental temperature to prevent any potential temperature effects on the drug solubility. The samples were filtered immediately and subsequently diluted with HPLC grade methanol. The cosolvents and cyclodextrins used did not interfere with the UV analysis and in cases where minimal interference was found, the appropriate blank was used.

Statistical analysis

The experimental values obtained were analyzed for their statistical significance using Statistical Analysis Software (SAS®), (SAS Institute Inc., Cary, NC, USA) version 8.0. The significance level was set at 0.05.

Results and Discussion

Phase Solubility Studies of (±)-Ibuprofen and S (+)-Ibuprofen in Cosolvents

The solubilities of racIB and SIB in the presence of glycerol, sorbitol, PG and PEG 300 based aqueous systems at 25 and 37 ^{0}C are shown in Figure 4.1. As the concentration of PEG 300 and PG in the system increased from 20 to 80% v/v, the solubilities of racIB and SIB increased exponentially. Marginal increases in the solubilities of these compounds were observed in the presence of glycerol, while the opposite effect was observed in the case of a highly self-associating solvent such as sorbitol solution. Increase in the solubility of the drugs at elevated temperatures was observed due to increased activity of water. [11]. This was in accordance to the Le Chatelier principle, which states that the system tends to adjust itself so as to counteract the stress due to increase in temperature. [12] Further, the breakdown of the crystal lattice also led to the improved solubilities at higher temperatures. [11] Solubilization of the compounds was also dependent on the polarity of the solvent system. The potential mechanisms of the solubilization of ibuprofen in the cosolvent systems are now described.

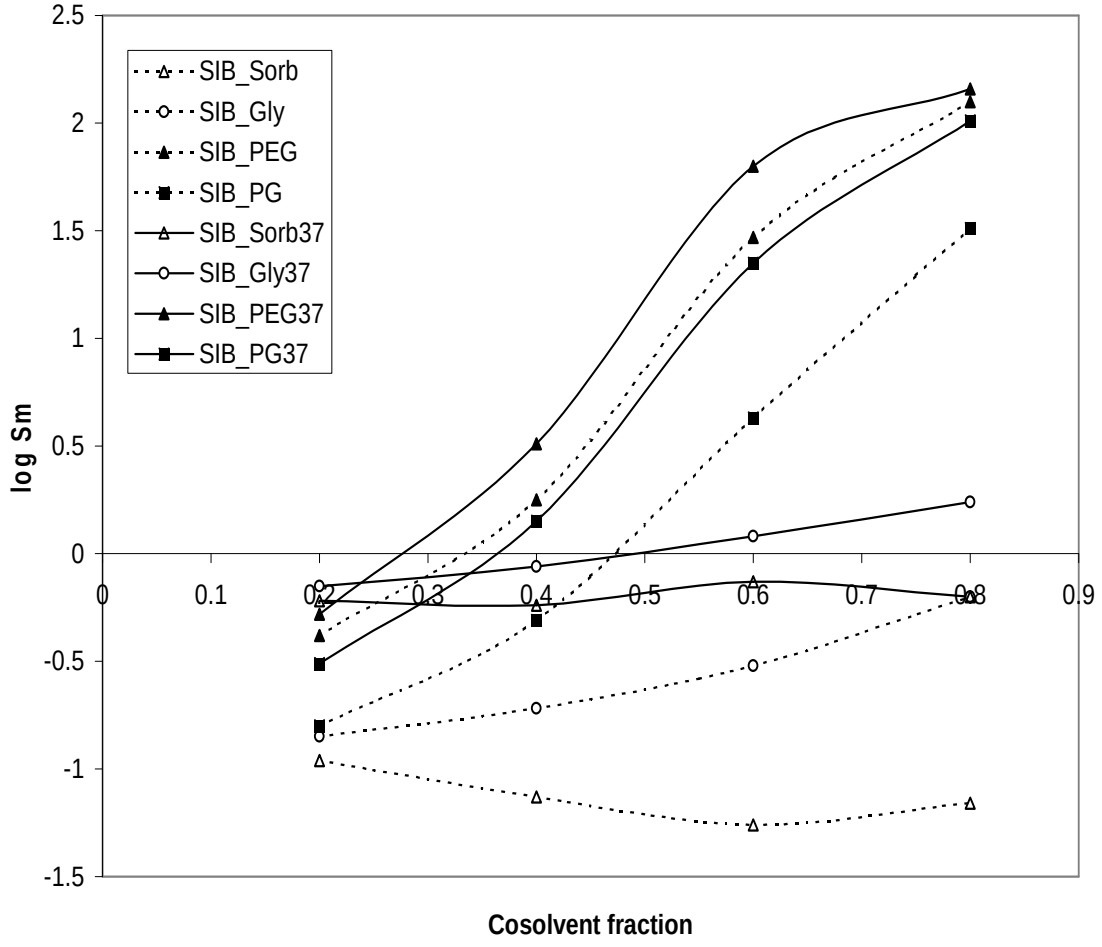


Figure 4.1.A. Log solubility of S (+)-ibuprofen in the presence of cosolvents at 25 and 37 deg. C

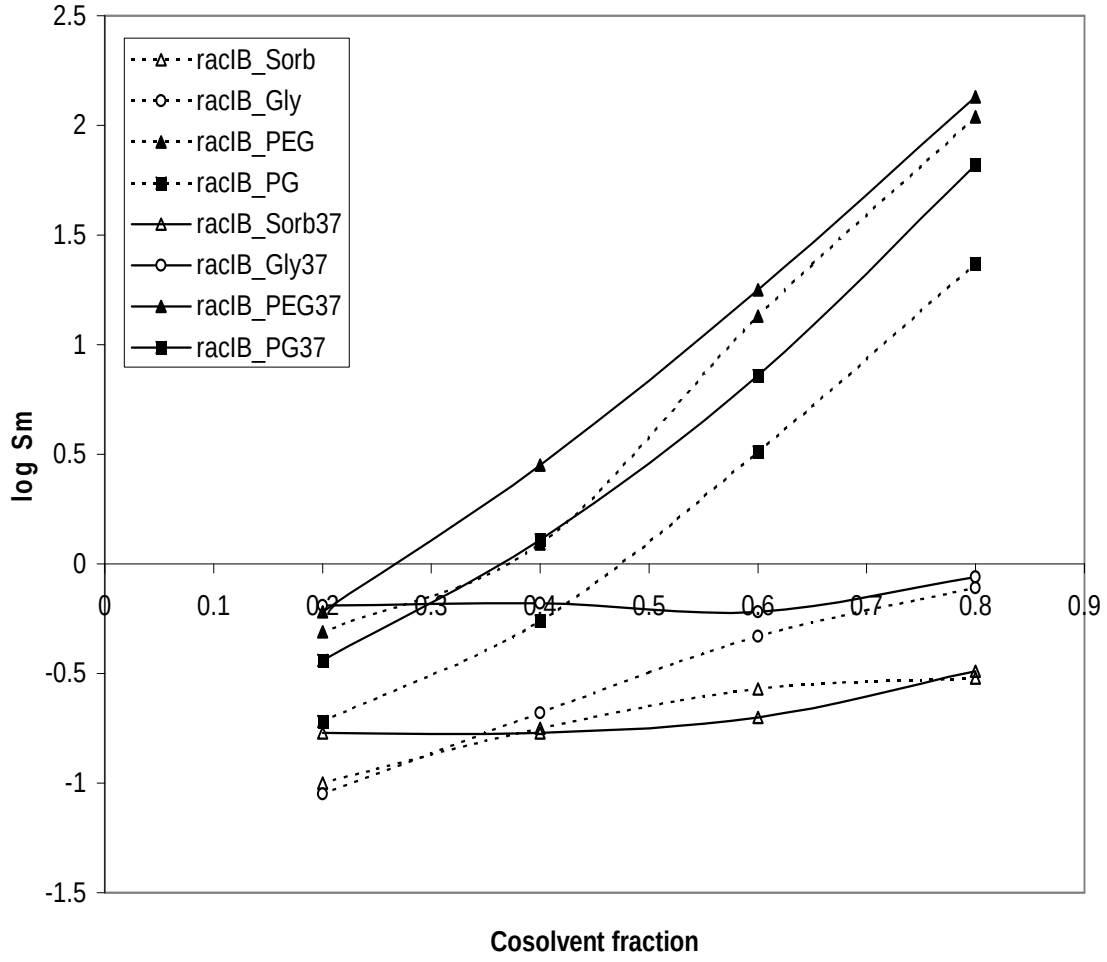


Figure 4.1.B. Log solubility of racemic ibuprofen in the presence of cosolvents at 25 and 37 deg. C

Note: Legends used in Figures 4.1.A and 4.1.B are as follows

Sorb: Sorbitol at 25 ^{0} C

Gly: Glycerol at 25 ^{0} C

PEG: Polyethylene glycol 300 at 25 ^{0} C

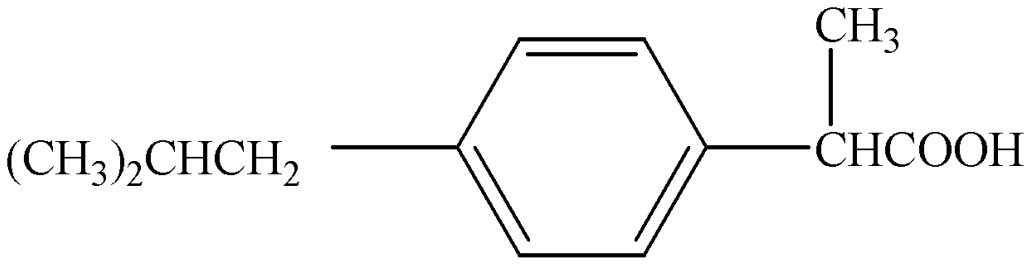
PG: propylene glycol at 25 ^{0} C

Sorb37: Sorbitol at 37 ^{0} C

Gly37: Glycerol at 37 ^{0} C

PEG37: Polyethylene glycol 300 at 37 ^{0} C

PG37: Propylene glycol at 37 ^{0} C



(α-methyl-4- (2-methylpropyl) benzene acetic acid)

Figure 4.2. Chemical structure of ibuprofen

Effect of solute structure on aqueous solubility

Ibuprofen (Figure 4.2) is a weak acid, which is characterized by a bulky aromatic ring with a methylpropyl side chain and one ionizable carboxyl group, making it highly nonpolar in nature and thus poorly water soluble especially below its pKa. [4, 12] At and above pH 4.41, ibuprofen undergoes ionization and the carboxyl group is available to form hydrogen bonds with water molecules. The dissolution of poorly water soluble drugs such as ibuprofen occurs primarily by hydrophobic interactions, such as hydrophobic hydration. Additionally, the dipole-dipole interactions between the ionized carboxyl group of ibuprofen and hydrogen bonding sites on the water molecules also aid in its solubilization. The low water solubility of ibuprofen is predominantly due to the self-associating nature of water molecules which tend to "squeeze out" the aromatic bulky group from the water structure thus restricting the amount of ibuprofen that can go into solution. [13] Hence, weakly self-interacting solvents , i.e., PEG and PG which are significantly less polar than water prove to be better solubilizers for both racemic and S(+)-ibuprofen as seen in Figure 4.1. Further, it has been previously documented that solvents which reduced the dielectric constant of water favored the solubilization of nonpolar solutes. [14-15] All the cosolvents used in the study except sorbitol solution were responsible for increasing the solubility of the drugs by decreasing the polarity of the cosolvent-water system. The solvents used in the study can be rank-ordered by their decreasing polarity as: water > sorbitol solution > glycerol > PG > PEG 300. [16]

Chemically, all the cosolvents used in the study i.e. sorbitol solution, glycerol, PG and PEG 300 are alcohols containing terminal hydroxyl groups. These groups can act as either hydrogen donors or acceptors based on the solvent environment. However, in the presence of water they primarily act as hydrogen acceptors. In the abundance of water molecules in the

system (20% cosolvent concentration), these solvents interact to a lesser degree with the drug and mainly hydrogen bond with water, However, as the number of water molecules in the system decreases, less hydrogen bonding sites are available for the solvent to interact with and thus they associate via aliphatic-aromatic type of interactions with the drug resulting in its solubilization at higher concentrations of PEG and PG. Interestingly, glycerol and sorbitol exhibited minimal effects on the solubility of both racIB and SIB. The presence of higher concentrations of sorbitol decreased the solubility of SIB, while the solubility of racemic ibuprofen was stabilized beyond 60%v/v of sorbitol. As the water content in the system dropped from 80 to 20%, there were fewer hydrogen binding sites available for both the drug and sorbitol to associate with. Sorbitol possesses many hydrogen bonding sites which by interacting with water may affect its structuring and compete with the drug. This could have led to the saturable solubility of racIB, while SIB was precipitated because of competition between the drug and sorbitol molecules for the available binding sites on water. A similar phenomenon was observed when salts were added to aqueous solution of a highly water soluble drug guaifenesin, resulting in its reduction of aqueous solubility. [17]

Both the racemic and the enantiomeric form of ibuprofen showed a differential solubilization behavior under similar solvent conditions which can be explained on the basis of their melting point. As an example, at 80% v/v of PEG 300, the solubility of SIB increased approximately 1,500-fold while that of racIB increased only about 900-fold at 25 ^{0} C. Observation of the DSC endotherms showed sharp endothermic peaks corresponding to the melting point of the isomers. Racemic ibuprofen and S (+)-ibuprofen are both crystalline in nature and melt at different temperatures with the pure enantiomer melting at approximately 20 ^{0} C lower than the racemic form (Table 4.1). Even though the melting points were different, the

aqueous solubilities of SIB and racIB in water at both 25 ^{0} C and 37 ^{0} C were not significantly different. [18] Previous studies have also shown that the aqueous solubility of SIB was not significantly different from the racemic form especially at pH lower than its pKa. [19] However, as previously stated, in the presence of a solubilizer such as PEG 300, SIB was solubilized to a much greater extent than the racemate since it required lesser energy (as seen from a lower melting point) to break the intermolecular bonds among the SIB crystals so that it could go into solution. Additionally, although the racemate and the S-form have the same number of molecules in a crystal unit, the way the molecules are arranged in the crystal lattice could be different, resulting in a different intermolecular network of interactions. The array of molecules arranged in the racemate may have led to a greater number of hydrogen bond type of interactions between the carboxyl groups. The SIB molecular network probably showed higher number of "exposed" carboxyl groups that were not hydrogen bonded in the network, thus resulting in less hydrophobic layers and consequently increasing the number of moles of SIB solubilized compared to the racemic form. [18] A statistical difference was observed between the aqueous solubility of SIB and racIB in the presence of increasing levels of cosolvent, except sorbitol solutions at 25 ^{0} C as seen in Table 4.2.

The mathematical approximation of the solubilizing power of a cosolvent in a water-based system is described by the following equation: [15]

$$\log S_m = f(\log S_c) + (1-f) \log Sw \qquad \text{Eqn. (1)}$$

where S_m is the solubility of the drug in the water-cosolvent mixture, f is the cosolvent volume fraction and S_w is the solubility of the drug in pure water. Equation 1 predicts an exponential increase in the solubility of the drug with increasing cosolvent fractions. The solubilizing power of the cosolvent can then be determined from:

$$\log S_m = \log S_w + a_1 f \qquad \text{Eqn.(2)}$$

where a_1 is the solubilizing power of the cosolvent. From equations 1 and 2, the solubilizing powers of the cosolvents were obtained (Table 4.3).

Table 4.1. Melting point and aqueous solubility of racemic and S (+)-ibuprofen

	racIB	SIB
Melting point ^{0}C	75-77	55
Solubility at 25^{0}C	0.12 mg/ml	0.08 mg/ml
Solubility at 37^{0}C	0.14 mg/ml	0.11mg/ml

Note: racIB is (±)-Ibuprofen

SIB is S (+)-Ibuprofen

Table 4.2. ANOVA of the solubility data for SIB and racIB in cosolvent systems at 25 deg C

Source	DF	Sum of squares	Mean squares	F value	Pr > F
SIB-PG	1	1010.6	1010.6	14.11	0.0094
Error	6	429.68	71.614		
Total	7	1440.3			
SIB-PEG	1	16016	16016	20.94	0.0038
Error	6	4589.6	764.94		
Total	7	20606			
SIB-Gly	1	0.2465	0.2465	35.5	0.001
Error	6	0.0417	0.0069		
Total	7	0.2882			
racIB-PG	1	511.87	511.87	14.3	0.0092
Error	6	214.77	35.795		
Total	7	726.64			
racIB-PEG	1	11740	11740	13.46	0.0105
Error	6	5231.6	871.93		
Total	7	16971			
racIB-Gly	1	0.5406	0.5406	89.53	<.0001
Error	6	0.0362	0.006		
Total	7	0.5768			

Note: DF is degrees of freedom

SIB-PG is SIB in propylene glycol at 25 ^{0} C

SIB-PEG is SIB in polyethylene glycol at 25 ^{0} C

SIB-Gly is SIB in glycerol at 25 ^{0} C

racIB-PG is racIB in propylene glycol at 25 ^{0} C

racIB-PEG is racIB in polyethylene glycol at 25 ^{0} C

racIB-Gly is racIB in glycerol at 25 ^{0} C.

Table 4.3. Solubilizing power of cosolvents

Cosolvent	S-ibuprofen		Ibuprofen	
	25 ^{0}C	37 ^{0}C	25 ^{0}C	37 ^{0}C
Sorbitol	-0.36	NA	0.81	NA
Glycerol	1.08	0.655	1.59	0.18
Propylene glycol	3.94	4.38	3.52	3.77
PEG 300	4.33	4.31	4.05	3.93

Cyclodextrin Complexation

The effects of beta cyclodextrin and its derivatives on the solubility of racIB and SIB at 25 ^{0}C and 37 ^{0}C are shown in Figure 4.3. The solubility of both the compounds increased linearly with increasing concentrations of HPCD and CDSB showing the A_L type of equilibrium phase-solubility diagram. [20] Both racIB and SIB formed inclusion complexes in 1:1 molar ratios, evident of a first order type of complexation. The statistical regression model which was used to analyze the effect of increasing concentration of HPCD and CDSB, on the equilibrium solubility of racIB and SIB, indicated that the solubilities of the drugs were significantly different and increased linearly as the concentration of HPCD and CDSB increased (Table 4.4). The slopes of the regression lines were used to calculate the stability constants (K mM^{-1}) of the substrate-ligand complexes. The values of the stability constants from Table 4.5 indicated that SIB formed more stable complexes with both HPCD and CDSB compared to the racemate, particularly at 25 ^{0}C. This may seem counter-intuitive as racIB showed the highest solubility at 25%w/v (173.97 mM) HPCD. Although quantitatively this seems true, the number of moles of SIB that were solubilized by HPCD were higher since the aqueous solubility of SIB was lower than racIB in pure water at 25 ^{0}C. Further, quantification of the rise in solubility for SIB in the presence of 25%w/v HPCD and CDSB was 242 and 176-fold respectively, while that for racIB under similar conditions was 175 and 113-fold respectively. Thus, the rank ordering of the soluble complexes were SIB-HPCD > racIB-HPCD > SIB-CDSB > racIB-CDSB at 25^{0} C. Amongst the derivatized cyclodextrins, the hydroxypropyl beta cyclodextrin was more effective than the sulfobutyl ether derivative in solubilizing both racIB and SIB. The tendency of HPCD to form more stable complexes with these compounds which was possibly related to its hydroxypropyl side chain which might have expanded over the hydrophobic cyclodextrin cavity

by capping it and increased substrate binding via a hydrophobic effect. In the case of CDSB there was possibly an obstruction to the substrate molecule from entering into the hydrophobic cavity which resulted in the formation of comparatively weaker inclusion complexes as discussed previously. [21] Also, even though SIB and racIB have the same molecular weight, they could have different degrees of penetration into the cyclodextrin cavity as well as different orientations of the phenyl groups in the cavity. The predominant mechanisms for the formation of inclusion complexes between the ibuprofen isomers and derviatized cyclodextrins were dipole or induced dipole-dipole interactions or van der Waals type of associations when the aromatic rings fit in the hydrophobic cavity of the beta cyclodextrin molecule. [21] A reverse phenomenon was observed with the addition of increased concentration of underivatized beta cyclodextrin. The equilibrium phase solubility diagram was the B_s type with the drug-ligand complex precipitating out of the solution at increased ligand concentrations. A similar case of B_s type of phase solubility diagram where the drug-ligand separated out was observed in an earlier study. [21] CD exists as a crystalline solid and has a limited aqueous solubility while both HPCD and CDSB are more soluble in water due to their amorphous nature. This partly explained the deficiency of CD to solubilize racIB and SIB.

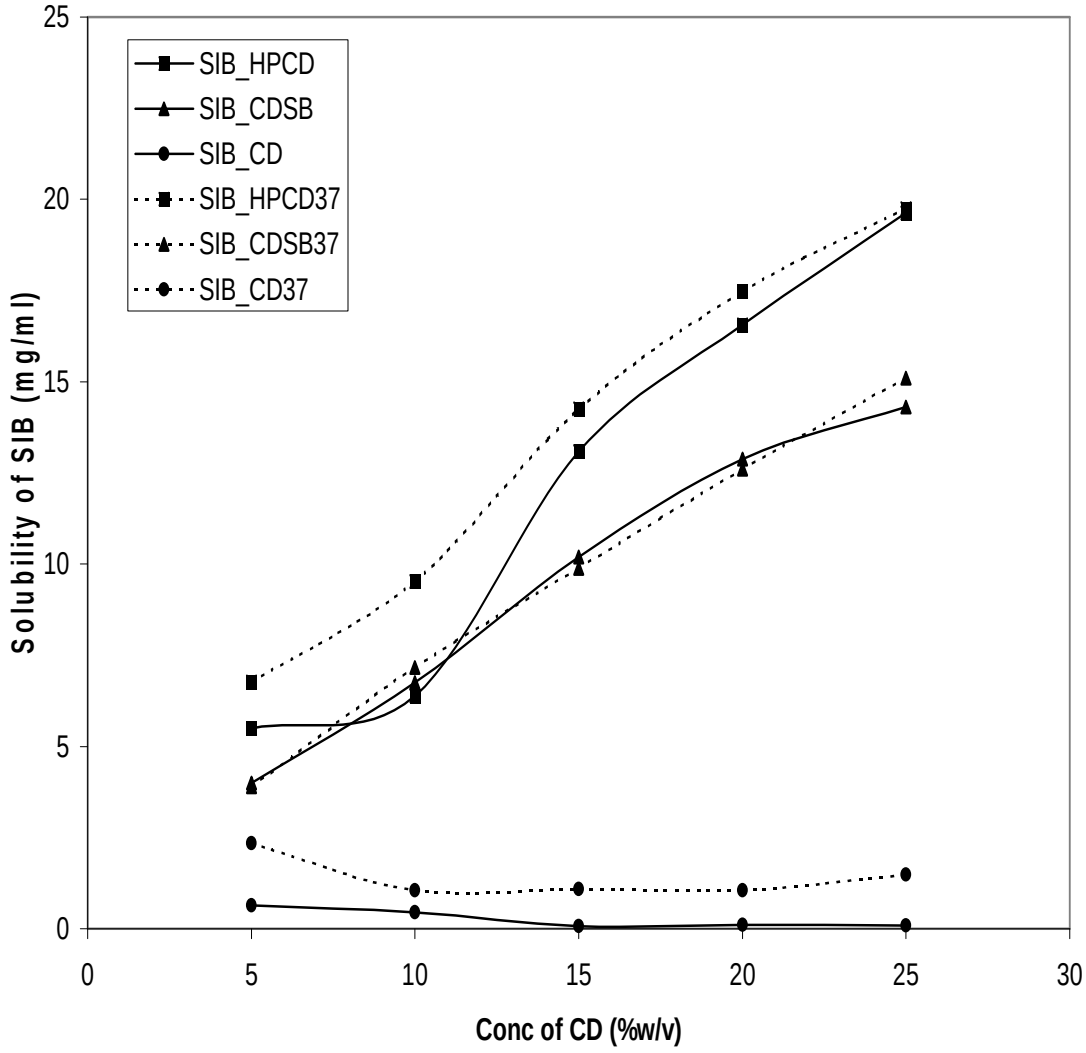


Figure 4.3.A. Solubility of SIB in the presence of various cyclodextrins at 25 and 37 deg. C

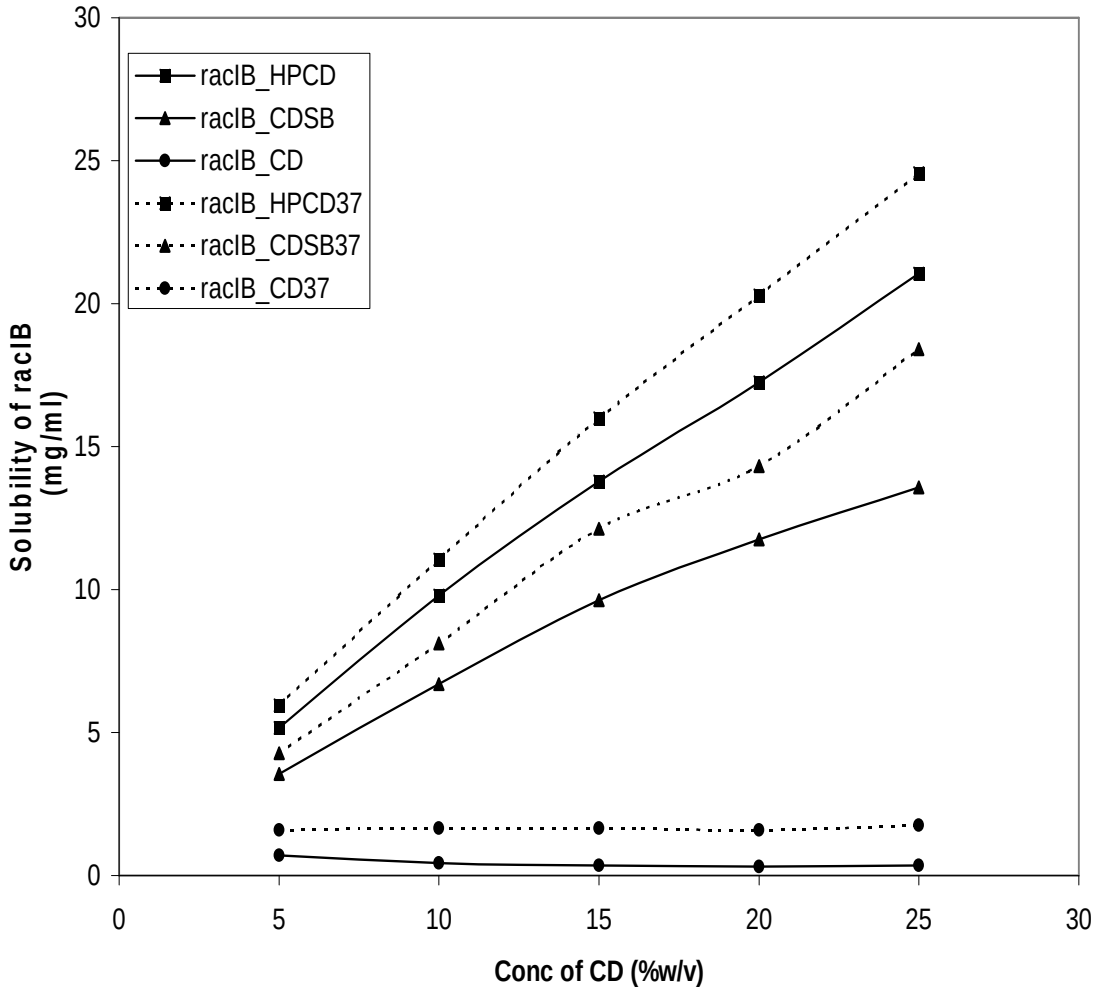


Figure 4.3.B. Solubility of racIB in the presence of various cyclodextrins at 25 and 37 deg. C

Note: Legends used in all the figures are as follows

HPCD: Hydroxypropyl beta cyclodextrin at 25 ^{0} C

CDSB: Beta cyclodextrin sulfobutyl ether sodium salt at 25 ^{0} C

CD: Beta cyclodextrin at 25 ^{0} C

HPCD37: Hydroxypropyl beta cyclodextrin at 37 ^{0} C

CDSB37: Beta cyclodextrin sulfobutyl ether sodium salt at 37 ^{0} C

CD37: Beta cyclodextrin at 37 ^{0} C

Table 4.4. ANOVA of the solubility data for SIB and racIB in HPCD and CDSB systems at 25 deg C

Source	DF	Sum of squares	Mean squares	F value	Pr > F
SIB-HPCD	1	295.6	295.6	173.02	<.0001
Error	8	13.668	1.7085		
Total	9	309.27			
SIB-CDSB	1	143.27	143.27	347.67	<.0001
Error	8	3.2968	0.4121		
Total	9	146.57			
racIB-HPCD	1	307.96	307.96	1582.7	<.0001
Error	8	1.5566	0.1946		
Total	9	309.51			
racIB-CDSB	1	126.05	126.05	561.67	<.0001
Error	8	1.7954	0.2244		
Total	9	127.85			

Note: DF is degrees of freedom

SIB-HPCD is SIB in hydroxypropyl beta cyclodextrin at 25 ^{0} C

SIB-CDSB is SIB in beta cyclodextrin sulfobutyl ether sodium salt at 25 ^{0} C

racIB-HPCD is racIB in hydroxypropyl beta cyclodextrin at 25 ^{0} C

racIB-CDSB is racIB in beta cyclodextrin sulfobutyl ether sodium salt at 25 ^{0} C

Table 4.5. Solubility and stability constants of cyclodextrin complexes at 25 and 37 deg C

	Solubility at 25% w/w		Stability constant K(mM^{-1})	
Derivative	CDSB 25 ^{0} C	CDSB 37 ^{0}C	25 ^{0} C	37 ^{0} C
racIB	65.83	89.24	1.91	3.73
SIB	69.37	73.19	3.26	2.63
	HPCD 25 ^{0} C	HPCD 37 ^{0} C	25 ^{0} C	37 ^{0} C
racIB	102.08	119.1	2.07	2.63
SIB	95.1	95.73	2.94	1.68

Note: HPCD is hydroxypropyl beta cyclodextrin.

CDSB is beta cyclodextrin sulfobutyl ether sodium salt.

Thermodynamic Considerations

The thermodynamic parameters associated with the solubilization of both racIB and SIB in the aqueous cosolvent systems were obtained by calculating the standard free energy changes associated with the process which is given by the third law of thermodynamics described by the following equation. [13]

$$\Delta G^0 = \Delta H^0 - T\,\Delta S^0 \qquad \text{Eqn. (3)}$$

The change in enthalpy (ΔH^0) was calculated using the integrated form of the van't Hoff equation:

$$\Delta H^0 = 2.303 \log \{ (S_a/S_w)_{37^o\,C} / (S_a/S_w)_{25^o\,C} \} . \{(RT_2\,T_1) / T_2 - T_1\} \qquad \text{Eqn. (4)}$$

where S_a is the solubility of the drug in the presence of additive and S_w is its solubility in pure water, respectively. R is the gas constant at 1.987 cal $mol^{-1}\,K^{-1}$ and T_2 and T_1 are 310.15 ^{0}K and 298.15 ^{0}K, respectively. An indication of the type of reaction occurring between the solute and the solvents or the additives can be obtained from the standard free energy changes associated with the process. The changes in the system or the solubilization of the drug is said to be spontaneous when the free energy of the system decreases as indicated by negative ΔG^0. The free energy of the system, in turn, depends on the enthalpy (change in heat content), the entropy (change in randomness) and the temperature at which the process occurs. Hence, at a constant temperature the free energy will be determined by the change in heat content and the degree of randomness. The thermodynamic parameters associated with the solubilization of racIB and SIB by cosolvents, and CD, HPCD and CDSB were calculated. Results indicated that the free energy changes associated with solubilization of SIB by glycerol, propylene glycol and PEG 300 at 25^0 C were negative values which indicated the spontaneity of the process. In case of sorbitol systems, the solubilization of SIB at low volume fractions of sorbitol (20% v/v) was a

spontaneous process, but became increasingly nonspontaneous with increasing concentration of sorbitol in the system. The changes in free energy were higher at 37^0 C than at 25^0 C ($\Delta G_{25}^{\ 0} << \Delta G_{37}^{\ 0}$) due to temperature effects i.e. whenever energy is supplied to a system from an external source, there is higher degree of randomness of the molecules and hence entropy increases leading to larger values of free energy change. Increasing the cosolvent fractions lead to higher negative values of ΔG^0 which indicated a thermodynamically more favorable environment for SIB and racIB to go into solution which led to higher $\Delta H^{\ 0}$ and thus negative values of ΔG^0.

Examination of the enthalpic and entropic changes associated with the solubilization of racIB and SIB by cosolvents and cyclodextrins indicated essentially differing thermodynamic mechanisms for the drugs to go into solution. For the solubilization of the drugs using cosolvents, it was observed that the entropic changes associated with solubilization were large positive values which overrode the positive enthalpy changes resulting in negative free energy changes and thus a spontaneous solubilization process was obtained. This was in accordance with classical hydrophobic interactions which are predominantly entropically driven mechanisms. The solubilization of the S-isomer and the racemic form of ibuprofen by HPCD and CDSB, on the other hand were enthalpically driven processes, which were characterized by large negative values of ΔH^0 and small positive or negative values of ΔS^0. The complexation specifically by HPCD with racIB and SIB over the entire concentration range studied, resulted in large negative enthalpies of formation. [22] This indicated that the complexation of racIB and SIB with HPCD was predominantly driven by the release of enthalpy-rich water molecules from the hydrophobic cyclodextrin cavity and its subsequent replacement by the less polar racIB and SIB molecules. [23]

Conclusions

The study showed that glycerol, propylene glycol and PEG 300 had very different solubilizing effects on the racemic form and the S-form of ibuprofen. The cosolvency approach to increasing solubility was much more effective than molecular inclusion complexation. Further, the differential solubility behavior of racIB and SIB observed was explained on the basis of their solid-structure, melting points and thermodynamic parameters obtained. Formulation of liquid dosage forms, both oral as well as parenteral, of the drugs may require the incorporation of water miscible solvents or cyclodextrins to increase the solubility as well as the stability of the dosage form. Specific solubility behaviors of the chiral isomers and racemic forms of the same compound under similar environments need to be carefully considered during the formulation of liquid dosage forms for such drugs.

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CHAPTER 5

FORMULATION AND CHARACTERIZATION OF FAST RELEASE BINARY AND TERNARY SOLID DISPERSIONS OF DEXIBUPROFEN USING POLYETHYLENE GLYCOL 8000 AS A DISPERSION CARRIER[1]

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[1] Jayanti Nerurkar, J. C. Price and H. W. Jun. Submitted to *Drug Development and Industrial Pharmacy*, 07/07/2004.

Abstract

Solid dispersions of dexibuprofen (dexIB) were prepared by the hot melt/fusion technique using polyethylene glycol 8000 (PEG) as a dispersion carrier. The solid dispersion systems were classified as, either binary for those containing varying amounts of drug and PEG 8000, or ternary for those containing 25% of either anionic surfactant ((sodium lauryl sulfate (SLS)) or nonionic surfactant (Pluronic ® (PL-F68)) in addition to the drug and PEG 8000. The binary systems had up to 25% drug loading while the ternary systems contained up to 10% drug. Physicochemical characterization of the systems was done by differential scanning calorimetric (DSC) and X-ray powder diffraction (XRPD) techniques. Solubility studies were conducted in pH = 2 buffer system.

The solubility studies showed that PEG 8000 effectively increased the initial drug dissolution rates of dexibuprofen via the formation of solid dispersion systems for both the binary and ternary systems. The solid dispersion systems showed higher rates of drug dissolution compared to the pure drug and the physical mixtures. Binary systems containing higher drug loading (25%) did not show a marked improvement in the rate of dissolution. The ternary systems fared better than the binary systems in improving drug dissolution rates. Ternary systems containing anionic SLS imparted quick dissolving properties to the dispersions while nonionic surfactant (PL-F68) gave the highest release at the end of 2 hrs. Systems containing 5% drug and 25% nonionic PL-F68 increased the amount of dexibuprofen dissolved by about 70% at the end of 2 hrs. The SLS containing systems were characterized by “quick releasing” properties with more than 50% dexIB released within 10 min for systems containing 5% dexIB and SLS. At drug concentrations higher than 5%, both the surfactant systems were comparable in their improvement in the solubility of dexIB and were not markedly different from each other. The

PL-F68 ternary dispersion systems were similar in their release profiles and dissolved about 40% of dexibuprofen in 20 min. Similarly, the ternary systems that contained SLS with 7.5% and 10% of drug showed similar release patterns, which were consistently lower than the systems containing 5% of drug and surfactant.

The physicochemical characterization of the systems by examination of DSC endotherms and XRPD diffraction patterns of the dispersions detected no chemical interaction between the various components. However, the formation of an interstitial solid at low drug loadings was noticed. Surfactants contributed to increased dissolution rates as a result of increased wetting and micelle formation. PEG as the dispersion carrier was successful in increasing the dissolution rate of a water insoluble drug (dexibuprofen) via solid dispersion formulation and the presence of surfactants augmented to give a faster release.

Keywords: Dexibuprofen; Binary solid dispersions; Ternary solid dispersions; Sodium lauryl sulfate; Pluronic ® PL-F68; XRPD; DSC

Introduction

Poorly water-soluble drugs often have problems of low oral bioavailability as a result of their limited dissolution rates. Focus on improving the dissolution profiles of such rate limited drugs has increased in recent times due to the vast number of hydrophobic moieties entering the market as potential drug candidates. Numerous approaches have been sought to improve the dissolution characteristics of such water insoluble drugs. Techniques that improve drug dissolution rates such as micronization to increase surface area or use of surfactants to optimize wetting characteristics or complexation with solubilizers such as cyclodextrins, etc. have been extensively used in the past for active ingredients that have very low water solubility. [1]

Amongst the various approaches that are available for improving drug dissolution characteristics, the presentation of the drug as a molecular dispersion in an inert water soluble carrier matrix called a solid dispersion system seems the most attractive method as it performs dual functions of combining an increase in surface area with improved drug wetting characteristics. [2] The use of solid dispersions to improve the dissolution of poorly water soluble drugs has been documented in the past. [3-6] Solid dispersion systems were initially defined by Chiou and Riegelman (1971) as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method, while Corrigan (1985) defined this system as a product formed by converting a fluid drug-carrier combination to a solid state. [7] Primarily hydrosoluble polymers such as poly (ethylene glycol) (PEG) or poly (vinyl pyrrolidone) (PVP) are used as the dispersion carriers to enhance the dissolution of hydrophobic drug moieties.

Recently, solid dispersion systems have not just been limited to binary systems of drug and a polymer carrier. Ternary systems are gaining popularity with many studies reporting the advantage of including a surfactant in the drug-polymer matrix to promote higher dissolution rates. [8-11]

The current study was done with the objective of increasing the dissolution rate of dexibuprofen (dexIB), a drug of low water solubility, via the formation of binary and ternary solid dispersion systems using PEG 8000 as the primary dispersion carrier. Ibuprofen [(±) – (α-methyl - 4 (2 –methyl-propyl) benzeneacetic acid] is a poorly water-soluble drug which has a chiral center with the dex form (S (+)-ibuprofen) being the active enantiomer. [12] Dosage recommendations of currently used racemic ibuprofen for arthritic patients range up to 3,200 mg per day. It has been reported that the S (+)/dex form which is the biologically active isomer primarily responsible for the anti-inflammatory action is about 160 times more potent than the R-(-) form. Studies that were undertaken to compare the pharmacological profile of dexibuprofen to racemic ibuprofen found that the dose ratio was 0.5 to 0.75. [13-15] These studies suggest the administration of dexibuprofen alone at a lower dose rather than as a racemic mixture to reduce the metabolic load. Enhancement of dissolution rate could further reduce the dose requirement. Hence dexibuprofen was chosen as the model drug. A number of studies have dealt with the improvement of solubility of racemic ibuprofen via the formation of solid dispersions using either PEG or PVP as the primary dispersion carrier. [4, 16-18]

The aim of the present study was primarily focused on investigating the effect of varying amounts of PEG 8000 as a dispersion carrier on the dissolution rates of dexIB. After initial optimization of the dexIB/PEG 8000 binary systems, the effect of incorporating a surfactant in the systems was studied. Two types of surfactants, non-ionic (Pluronic ® F68 (PL-F68)) and

anionic (sodium lauryl sulfate (SLS)) were used for this purpose and their effects on the dissolution of dexIB from the dispersion systems were studied. Finally both the binary (dexIB/PEG 8000) and the ternary systems (dexIB/surfactant/PEG 8000) were characterized by dissolution tests for release and solubility characteristics, X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) for possible solid-state interactions between the various components. All the solid dispersion systems were compared with their physical mixtures for more accurate interpretations.

Materials and Methods

Materials

Dexibuprofen was a gift from Albemarle Co. (Baton Rouge, LA). PEG 8000 (Union Carbide Co., Danbury, CT), sodium lauryl sulfate (Fisher Scientific Co., NJ), Pluronic ® F68 (BASF Wyandotte Co., NJ) were used as obtained from the suppliers. Sodium lauryl sulfate was used as the anionic surfactant while Pluronic ® F68 was the nonionic surfactant. All reagents used were of analytical grade and used as received.

Methods

Preparation of binary and ternary solid dispersions and physical mixtures

Solid dispersions

The binary (5%, 10% and 25% dexIB) and ternary (5%, 7.5% and 10% dexIB with 25% surfactant) solid dispersion systems of dexIB were prepared by the hot melt/fusion technique. A

broader range of dexIB concentrations (5 - 25% w/w) was used for the binary systems. The range of dexIB concentration in the ternary systems was reduced to 5 -10%w/w after observing the release characteristics of the binary systems. The ternary dispersion systems contained either SLS or PL-F68 in addition to dexIB and PEG, the concentration of which was fixed at 25% w/w. The concentration of the surfactant in the ternary systems was maintained constant at 25% to ensure the detection of the pure surfactant phase during solid-state characterization by the DSC and XRPD methods.

An accurately weighed quantity of PEG 8000 was first melted at about 70 ^{0}C. This was followed by the addition of dexIB to the molten carrier with constant stirring until it completely dissolved to form one phase. In case of the ternary systems, the surfactants were incorporated in molten PEG prior to the addition of dexIB. These melts were then rapidly quenched on an ice bath that was maintained at 0 ^{0}C until the mass solidified. The rapid quenching of the melt ensured the entrapment of the drug as either fine crystals/amorphous particles in the dispersion carriers. These solidified systems were then dried under vacuum for 24 hrs in a desiccator that was maintained at 25 ^{0}C. The dried solid dispersions were further pulverized in a ceramic mortar and pestle and stored for future analysis.

Physical mixtures

Accurately weighed quantities of dexIB and PEG 8000 or dexIB, surfactant and PEG 8000, were pulverized and mixed intimately in a ceramic mortar and pestle until a homogenous mixture was obtained. The physical mixtures of the binary and the ternary systems were used for comparison with the solid dispersion systems.

Evaluation and Characterization

Solubility studies

The dissolution of dexIB alone or from the various binary and ternary preparations was carried out in a Distek Premiere 5100 Dissolution System using the USP XXV paddle method. The dissolution medium was 500 ml of standard buffer solution (pH=2) maintained at 37 ± 0.5^0C with a paddle rotation speed of 100 rpm. Each powdered sample containing 50 mg of dexIB or dexIB equivalent was introduced in the dissolution medium. Samples (5 ml) were withdrawn at suitable time intervals and immediately replaced with an equal volume of fresh medium maintained at 37 ± 0.5^0C. The withdrawn samples were then filtered through a Millipore® filter (0.45μm pore size) and assayed spectrophotometrically for dexIB content at 221 nm. Readings were obtained in duplicate.

X-Ray diffractometry

X-Ray powder diffraction patterns for all the dispersion systems as well as their physical mixtures were done on Scintag XDS 2000 using Cu Kα radiation (1.78892 ^{0}A) with divergence slits of $1^0/2^0$, and receiving slits of $0.5^0/0.3^0$. The operating voltage and current were 40 KV and 35 mA, respectively. The samples were scanned from start angle 5^0 2θ and stop angle 40 ^{0} 2θ at a continuous scan rate of 1^0/min.

Differential scanning calorimetry

Thermal analysis of the various dispersion systems and their physical mixtures were done on a Perkin-Elmer Differential Scanning Calorimeter DSC-7 (Perkin-Elmer, Norwalk, CT).

Approximately 1 mg of the sample was weighed in aluminum pans, which were hermetically sealed, and the samples scanned from 25 to 150 ^{0}C at a scan rate of 2 ^{0}C per min. The thermograms were analyzed for changes in the melting point of dexIB using DSC-7 program.

Drug loading

The influence of the dexIB concentration in the dispersion system on its dissolution rate from the solid dispersion systems was first optimized using the fused systems with binary components. The initial ratios of dexIB to PEG 8000 were fixed on a weight basis at 5:95, 10:90 and 25:75. The concentration ranges for the ternary systems were decided on the basis of binary systems that showed the highest release profiles. As previously mentioned, all the ternary systems contained the same amount of surfactant, which was constant at 25%. After optimization, the ternary systems had the following ratios of dexIB: surfactant: PEG 8000: 5:25:70, 7.5:25:67.5 and 10:25:65. The quantities of dexIB, PEG and surfactant are reported in Table 5.1. The same ratios of dexIB, PEG and SLS or PL-F68 were used in the physical mixtures for comparison with the dispersion systems.

Table 5.1. Composition of the binary and ternary systems

Formulation	dexIB (g)	PEG 8000 (g)	Surfactant (g)	dexIB/Surfactant	dexIB (%)	Type of dispersion
1	0.1	1.9	0	0	5	binary
2	0.2	1.8	0	0	10	binary
3	0.5	1.5	0	0	25	binary
4	0.1	1.4	0.5	0.2	5	ternary
5	0.15	1.35	0.5	0.3	7.5	ternary
6	0.2	1.3	0.5	0.4	10	ternary

Results and Discussion

Solubility of the binary and ternary solid dispersion and physical mixture systems

The dissolution of dexIB from the binary solid dispersion systems is given in Figure 5.1. The dissolution rate of pure dexIB was used as the reference. It can be seen from Figure 5.1 that the binary solid dispersions were effective in achieving a rapid dissolution of the drug up to 1 hr, as compared to the drug alone. Amongst the various binary systems formulated, the 5% binary system containing only PEG 8000 as the dispersion carrier, gave the highest amount of dexIB that dissolved in 30 min, which was about 2 fold higher than the reference which was dexIB alone, while release from the 10% binary systems was 1.5 times greater than that of pure dexIB. The binary system that contained 25% drug did not show any significant increase in initial drug dissolution rates compared to the drug alone. At the end of 2 hrs, the 5% binary system gave the highest dissolution, followed by pure drug, which in turn was followed by the 10% and 25% systems. This is consistent with earlier findings that the drug/PEG ratio is one of the prominent influencing factors on the performance of solid dispersion systems with low drug loadings facilitating the formation of amorphous systems and thereby vastly increasing drug solubility and rate of dissolution. [1, 6] Figure 5.2 shows the dissolution profiles of the binary solid dispersions while comparing them with their corresponding physical mixtures. It is seen that while the solid dispersion containing 5% of drug and PEG 8000 gave the fastest release and highest rate of dexIB dissolution, its comparable physical mixture wasn't as effective in dissolving dexIB. In general, the physical mixtures gave lower rates of drug dissolution when compared to the solid dispersion systems. Furthermore, it was noted that as the percent of the drug in the binary solid dispersion systems increased, the dissolution rate decreased. The dexIB dissolution rates were

rank ordered as 5%>10%>25%. This is in accordance with earlier reports on nifedipine solid dispersions formulated with hydroxypropyl methylcellulose (HPMC). It was observed that the concentration of nifedipine in the dissolution medium increased with decreasing content (or increasing HPMC content) in the dispersion systems, which was attributed to possible mechanistic changes in the drug-polymer system. [19] Drug dissolution rates for the dexIB dispersions increased up to 10% of drug loadings. Binary solid dispersions containing 25% by weight of dexIB did not show any significant improvement in the dissolution rate over drug alone, hence was eliminated during the formulation of ternary systems. Therefore, the concentration ranges of the drug in the ternary systems that additionally contained a surfactant were limited to 5%, 7.5% and 10% of dexIB.

PEG 8000 greatly improved the rate and extent of dexIB dissolution and was thus very efficient as a primary dispersion carrier. The enhancement of dexIB dissolution from the binary fused systems can be explained on the basis of its improved solubilization by PEG. Additionally, PEG is also known to reduce aggregation/agglomeration between hydrophobic drug molecules/particles thus increasing drug dissolution rates. Other factors could include possible solid-state interactions leading to the formation of interstitial solids when dexIB was quench cooled with PEG 8000 (as seen from the XRD scans) that helped in enhancing the solubility of dexIB from the fused binary systems.

PEG is a semi-crystalline polymer (in the molecular range of 3000 to 20,000) containing both ordered and amorphous components. Depending on various factors such as method of preparation, relative size of the drug to PEG, solubility/miscibility of the drug in the PEG chains, PEG has favored the formation of interstitial solid solutions whereby the drug dissolves in the amorphous/unordered fraction of PEG at solid state. [20]

It was observed that during the preparation of these systems both the drug and carrier were completely miscible with each other in the molten state. The complete miscibility of dexIB in molten PEG can be hypothesized to be a predictor of its partial miscibility in the high molecular weight PEG complex at the solid state. This was further confirmed from the XRD scans. Further, quenching of the molten system allowed for the entrapment of the drug in its finest subdivided or its amorphous form in the dispersion carriers. Primarily, the inherent miscibility of dexIB in PEG and secondarily, the method of preparation were both thought to be responsible for the formation of an interstitial solid especially at low drug concentrations (5% systems). Comparable physical mixtures were not as effective as the fused systems in increasing the dissolution of dexIB especially in case of binary mixtures.

The dissolution profiles of the ternary solid dispersion systems are shown in Figure 5.3. The ternary systems showed a much faster release as compared to the binary systems as well as the pure drug. All the ternary systems (both fused and physical mixes) gave a considerably faster release of dexIB releasing more than 40% within 20 minutes, independent of the drug concentration. As observed in binary systems, the ternary fused systems also exhibited similar dependence of dissolution rate on dexIB concentration in the system with 5% drug systems giving the best release profiles. Molten/fused systems containing 7.5% drug or 10% of the drug did not appear significantly different in their dissolution profiles.

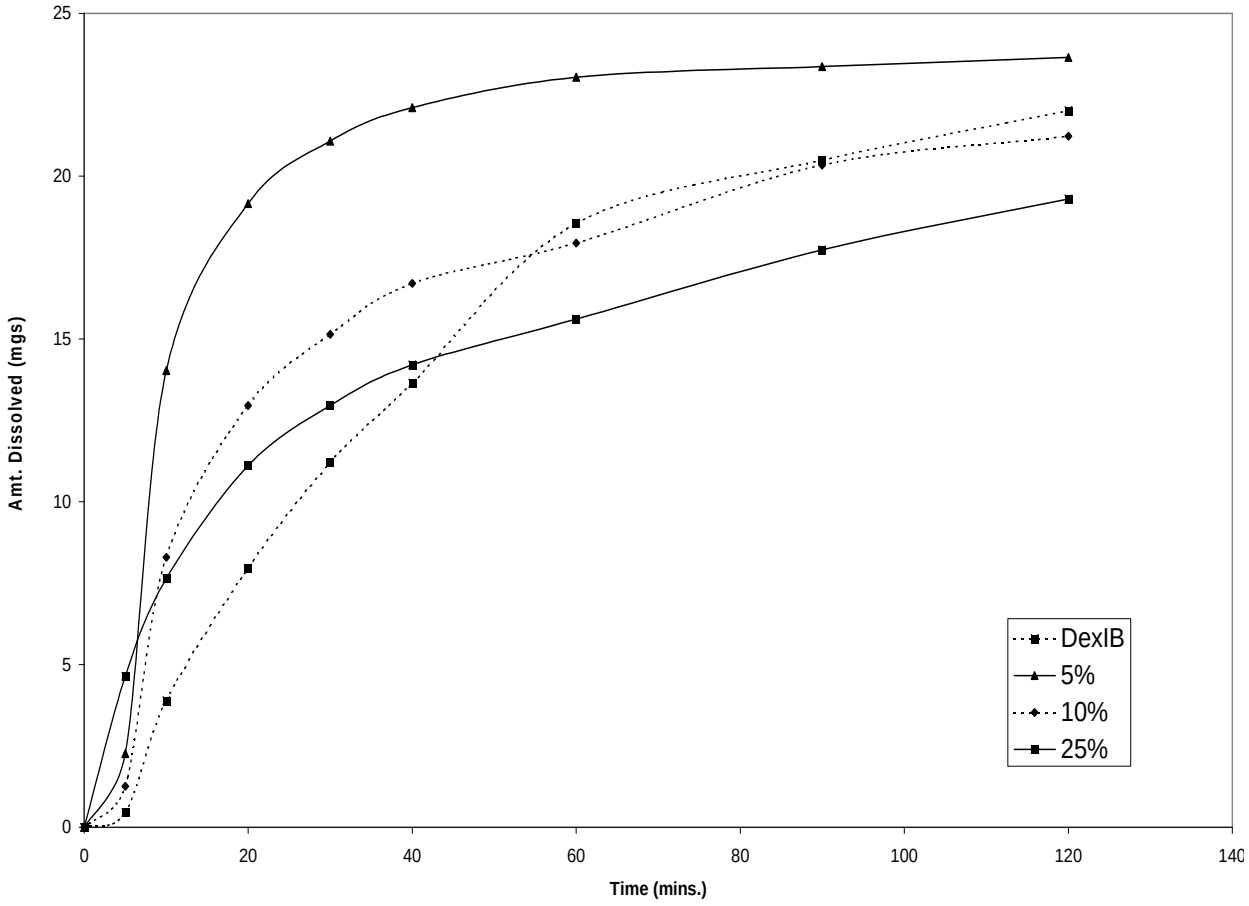

Figure 5.1. Dissolution of dexIB from binary solid dispersion systems

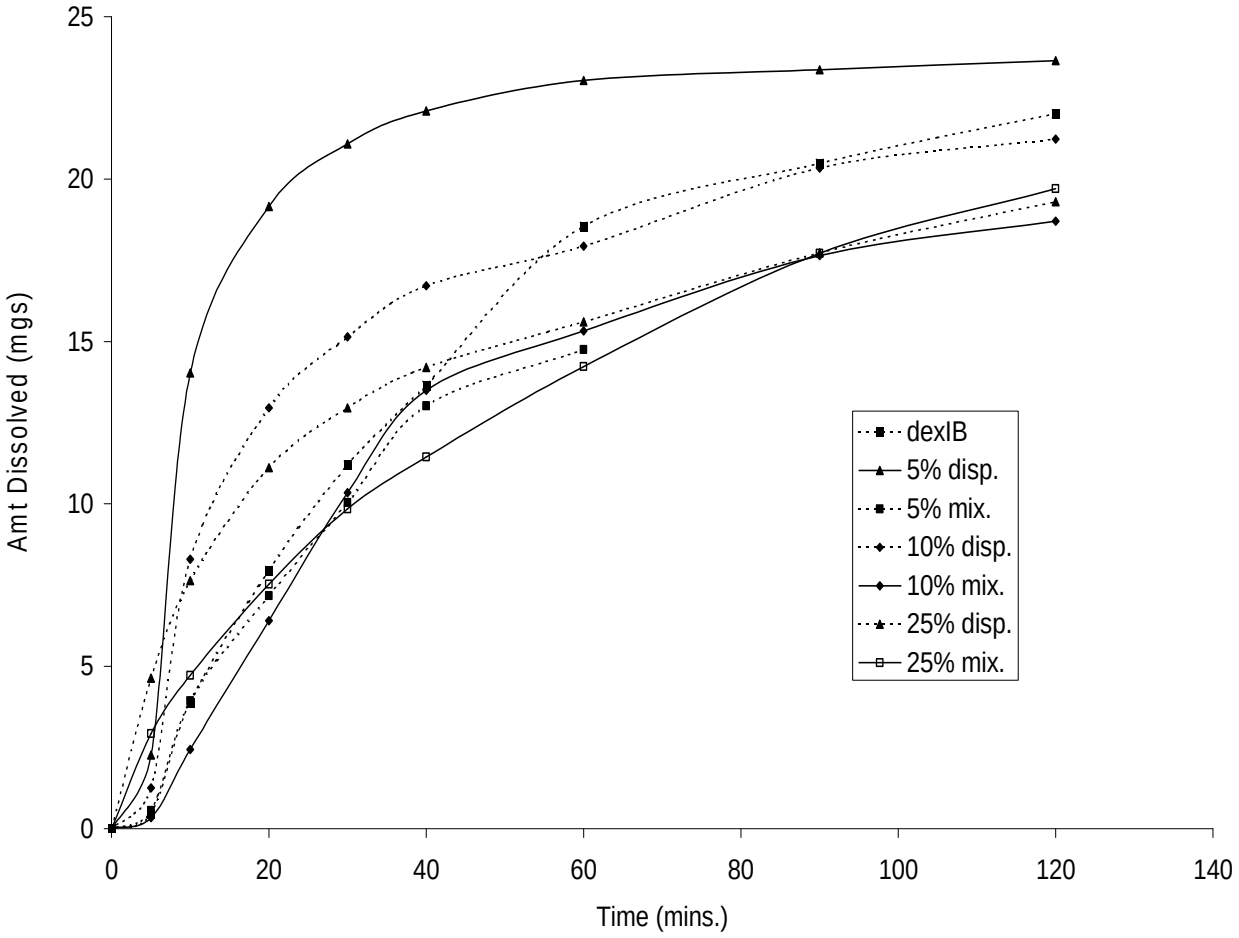

Figure 5.2. Comparison of binary dispersions with their physical mixtures

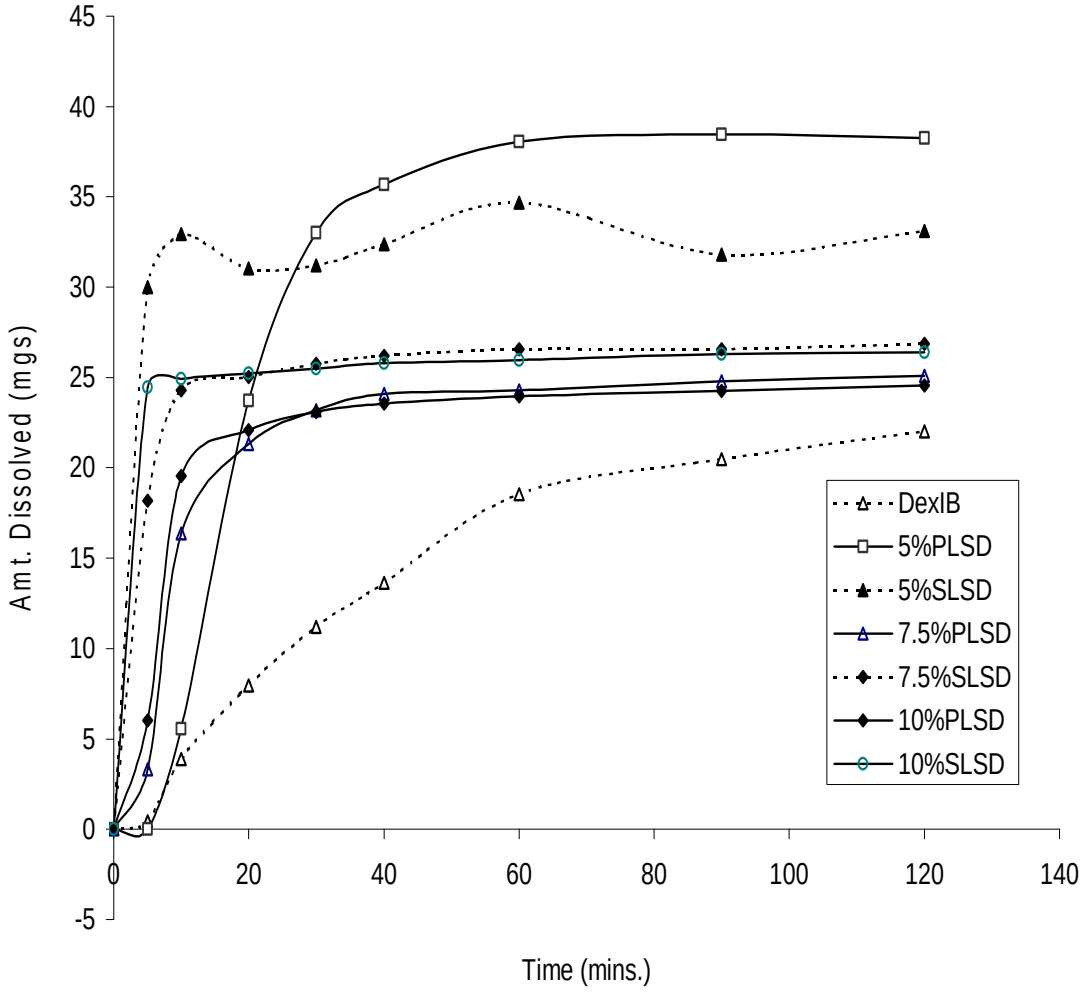

Figure 5.3. Dissolution of dexIB from ternary solid dispersion systems

Note: Legends used in Figure 5.3 are as follows

PLSD is dexIB solid dispersion with Pluronic ® F68

SLSD is dexIB solid dispersion with SLS

Initial dissolution profiles of the ternary fused systems show surfactant based differences. The SLS (anionic) system containing 5% of dexIB was a fast dissolving system releasing about 60% of the drug in 5 minutes much higher than any of the other ternary systems. After a quick release of the drug, the profile leveled off due to the attainment of saturation conditions in the dissolution vessel with the drug precipitating out. In contrast, the 5% ternary system containing PL-F68 showed a slower rate of dissolution but gave a higher cumulative percent of drug dissolving at the end of 2 hrs. The 7.5% and 10% surfactant-based systems for both the types, exhibited a biphasic release characterized by an initial rapid release of the drug followed by a plateauing effect attributable to the attainment of saturation conditions in the dissolution vessel and subsequent precipitation of dexIB. Although the SLS system was a quick dissolving matrix, the highest drug concentration was obtained from the 5% PL-F68 system which was about 70% higher compared to the drug alone. A comparison of the physical mixtures of the ternary systems also showed an increase in the rate of dissolution of dexIB. However, these rates were much lower than those obtained from the corresponding fused systems. The increase in dissolution rates from the physical mixtures could be due to improved wetting of the drug as a result of the incorporation of a surfactant in the system. Figure 5.4 gives a comparable graph of the performance of the various solid dispersion systems at the end of 30 mins. It is seen that the three component solid dispersion systems containing 5% of dexIB and PL-F68 dissolved 33mgs of dexIB from the total of 50 mgs that were introduced in the dissolution vessel. It was followed by the 5% three component system containing SLS which dissolved 31 mgs of dexIB which was about 1.5 fold greater than that dissolved by the binary solid dispersion system containing the same amount of dexIB. Table 5.2 gives the relative dissolution rates of the various systems as compared to dexIB alone. Since the drug reached a saturation level in the dissolution medium at

the end of 2 hours, the relative rate of dissolution of dexIB from the various binary and ternary dispersion systems as well as the physical mixtures was determined to give a more accurate interpretation of the rate of solubilization of the various systems. The relative dissolution rate was calculated as:

$$\text{Relative dissolution rate} = \frac{\text{Amount of drug dissolved (mg) in 30 min from system}}{\text{Amount of pure drug dissolved (mg) in 30 min.}}$$

The highest relative dissolution rates were obtained by the ternary systems. Physical mixtures of the three component systems that contained SLS also had high relative dissolution rates compared to the PL-F68 physical mixture systems. The binary physical mixtures fared poorly in comparison to all the systems. It was interesting to note that the surfactant containing systems had higher relative dissolution rates compared to the binary solid dispersions. This observation shows the importance of wetting by the surfactants.

Overall, the ternary systems were more effective in attaining quicker dissolution and greater solubility of dexIB in comparison to the binary systems. One of the primary reasons for such behavior is notably due to increased wetting of drug particles by the dissolution fluid caused by the surfactant molecules. Many reports are available in the literature that emphasizes the importance of wetting during drug dissolution, particularly for hydrophobic drugs. [8-10] Surfactant concentrations in the ternary systems were fixed at 25% w/w, which is much higher than their critical micelle concentration. SLS seemed to indicate a favorable interaction between the anionic surfactant and the weakly acidic drug dexIB as seen from the rapid dissolution of dexIB from the SLS based systems. [6, 18] The dominant mechanism for the better performance of surfactant-based systems was improved wettability, but PL-F68 actually increased the total amount of drug dissolved.

Other contributing mechanisms that result in faster dissolution of a poorly soluble drug such as dexIB from the drug/ surfactant/polymer fused three component system is the formation of a solid solution whereby the drug is completely soluble in the polymer structure aided by the addition of surfactant molecules. [8,10] This type of mechanism was evident for the fused ternary system wherein the miscibility of dexIB in PEG 8000 was greatly aided by the addition of surfactant to the system.

Table 5.2. Relative dissolution and T40% of all the systems

System	Type	RDD [a]	T40% [b]
5% drug + PEG	Fused	1.89	30
5% drug + PEG	Mixed	0.9	>120
10% drug +PEG	Fused	1.35	90
10% drug +PEG	Mixed	0.92	>120
25% drug +PEG	Fused	1.16	>120
25% drug +PEG	Mixed	0.88	>120
5% drug + PEG+ PL-F68	Fused	2.95	15
5% drug + PEG+ PL-F68	Mixed	1.81	30
5% drug + PEG+ SLS	Fused	2.79	<5
5% drug + PEG+ SLS	Mixed	2.22	<5
7.5% drug + PEG+ PL-F68	Fused	2.07	20
7.5% drug + PEG+ PL-F68	Mixed	1.43	>120
7.5% drug + PEG+ SLS	Fused	2.3	<10
7.5% drug + PEG+ SLS	Mixed	2.29	<20
10% drug + PEG+ PL-F68	Fused	2.06	10
10% drug + PEG+ PL-F68	Mixed	1.89	20
10% drug + PEG+ SLS	Fused	2.28	<5
10% drug + PEG+ SLS	Mixed	2.1	<20
dexIB		None	90

Note: a: Relative dissolution rate = Amount of drug dissolved (mg) in 30 min from dispersion system/ Amount of pure drug dissolved (mg) in 30 min.; b: The time required to dissolve 40% of the drug in min.

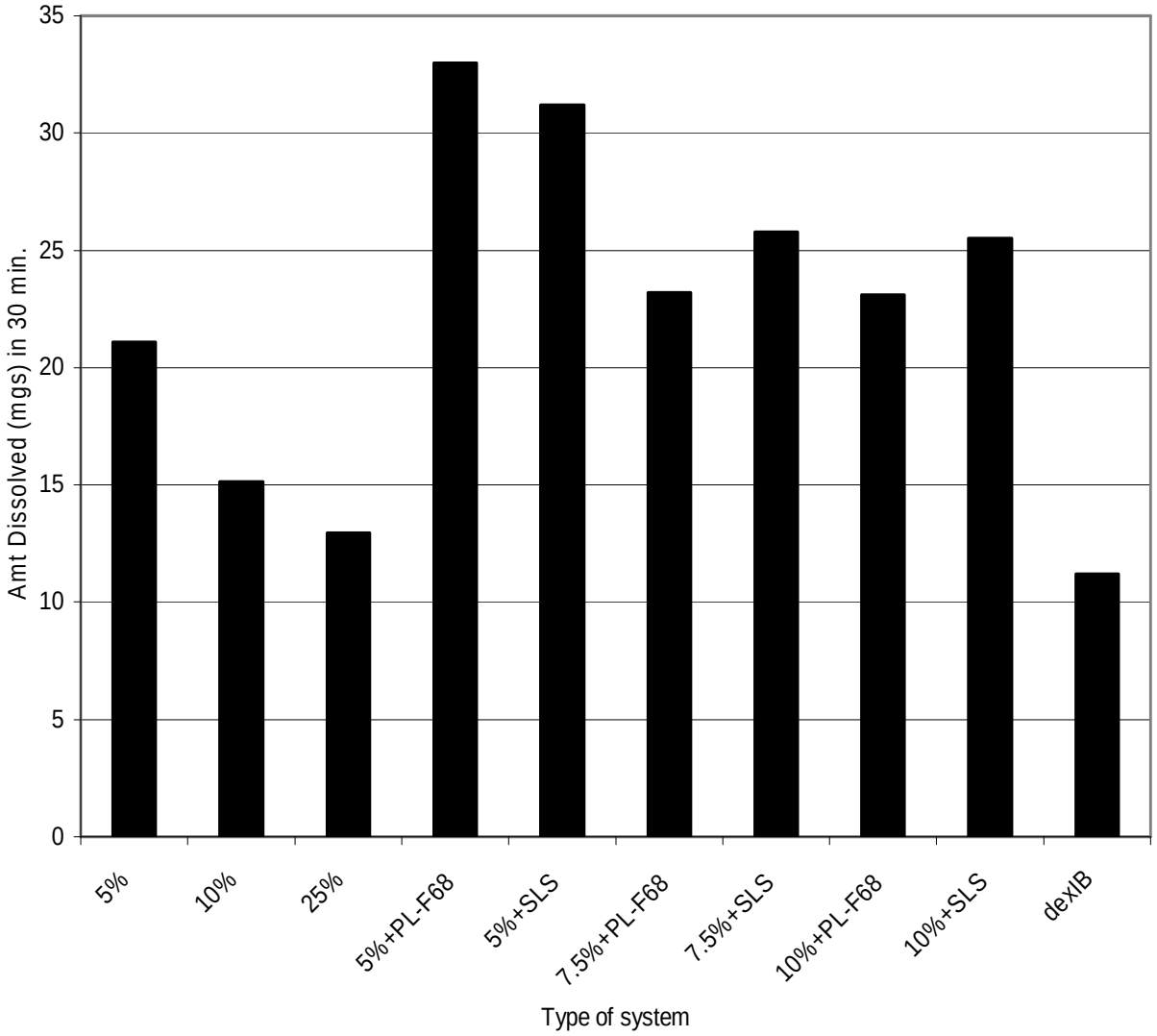

Figure 5.4. Amount of dexibuprofen dissolved in 30 min from the binary and ternary dispersion systems

X-Ray diffractometry

The X-ray powder diffraction patterns of pure dexIB and the different solid dispersion (SD) systems and their corresponding physical mixtures (PM) are shown in Figures 5.5-5.7. Characteristic peaks of dexIB appeared at a diffraction angle of 2θ, at 8.94, 14.36, 21.98, 23.02, 24.92 and 25.62^0. These were in accordance with those reported in earlier by Dwivedi *et al*. [21]

The XRD patterns of binary solid dispersions and the corresponding physical mixes of dexIB in PEG 8000 of the same composition were comparable. In all the samples, it was observed that the dexIB spectrum was progressively masked by the signals from PEG 8000. Further, as the concentration of dexIB increased its characteristic peaks started appearing in the spectrum. For the binary systems, the XRD patterns suggested a formation of an interstitial solid that is commonly found when a high molecular weight carrier such as PEG is used with a low concentration of a low molecular weight drug such as dexibuprofen. [22]

For the ternary systems of dexIB, the addition of a surfactant did not change the diffraction patterns of the dispersion and the physical mixtures very much as they were also comparable when the compositions were the same. Similar to the binary system, the dexIB spectrum was almost completely masked by the PEG signals in the ternary systems. Furthermore, as the percent of dexIB in the systems increased, the number of peaks characteristic to the drug also started to increase, thus suggesting the solubility of dexIB in the primary and secondary dispersion carriers and the formation of interstitial solid solutions.

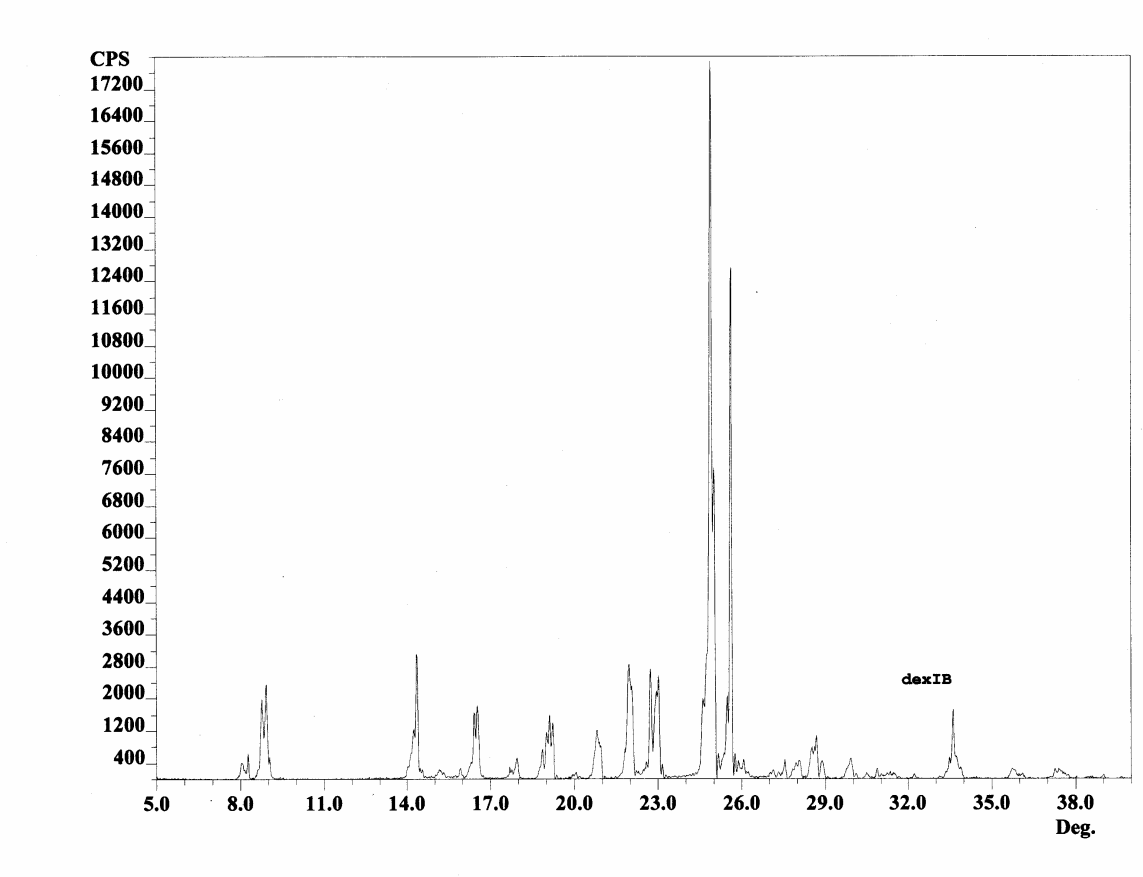

Figure 5.5. XRD scan of dexIB

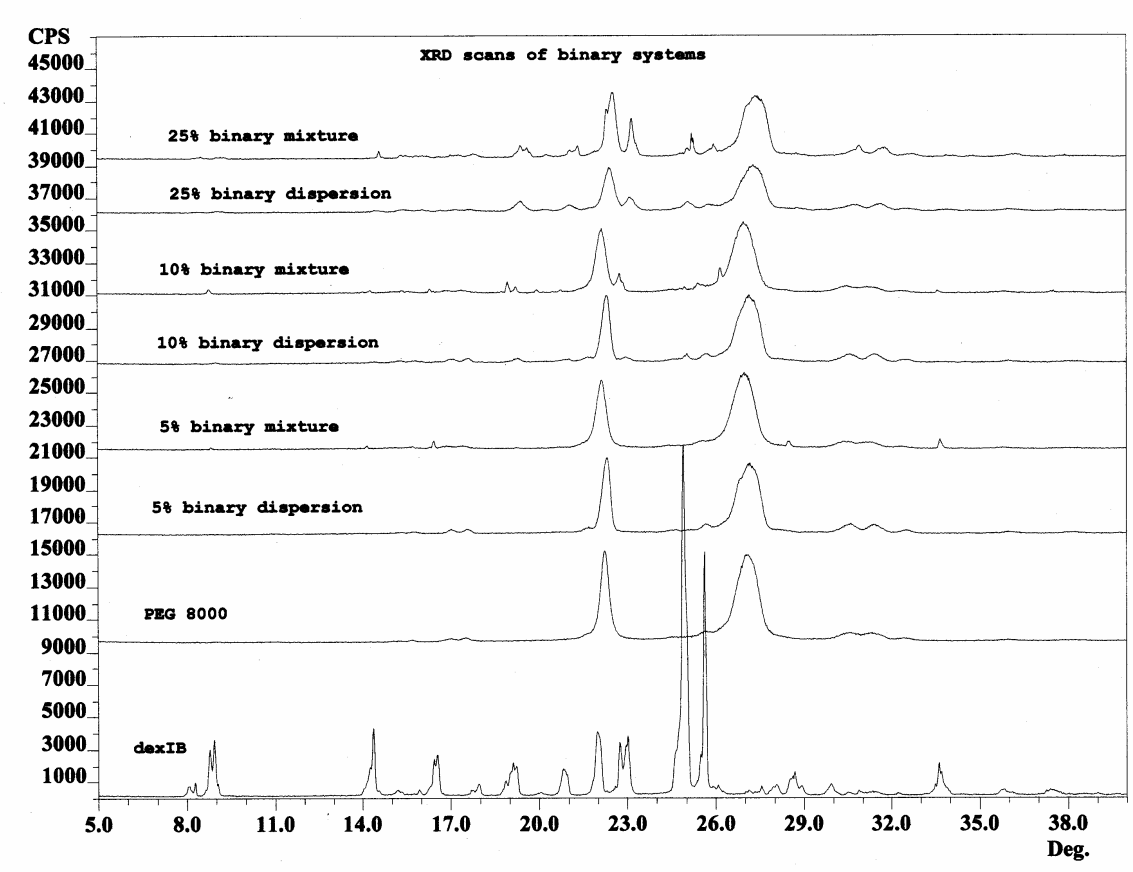

Figure 5.6. XRD scans of binary systems

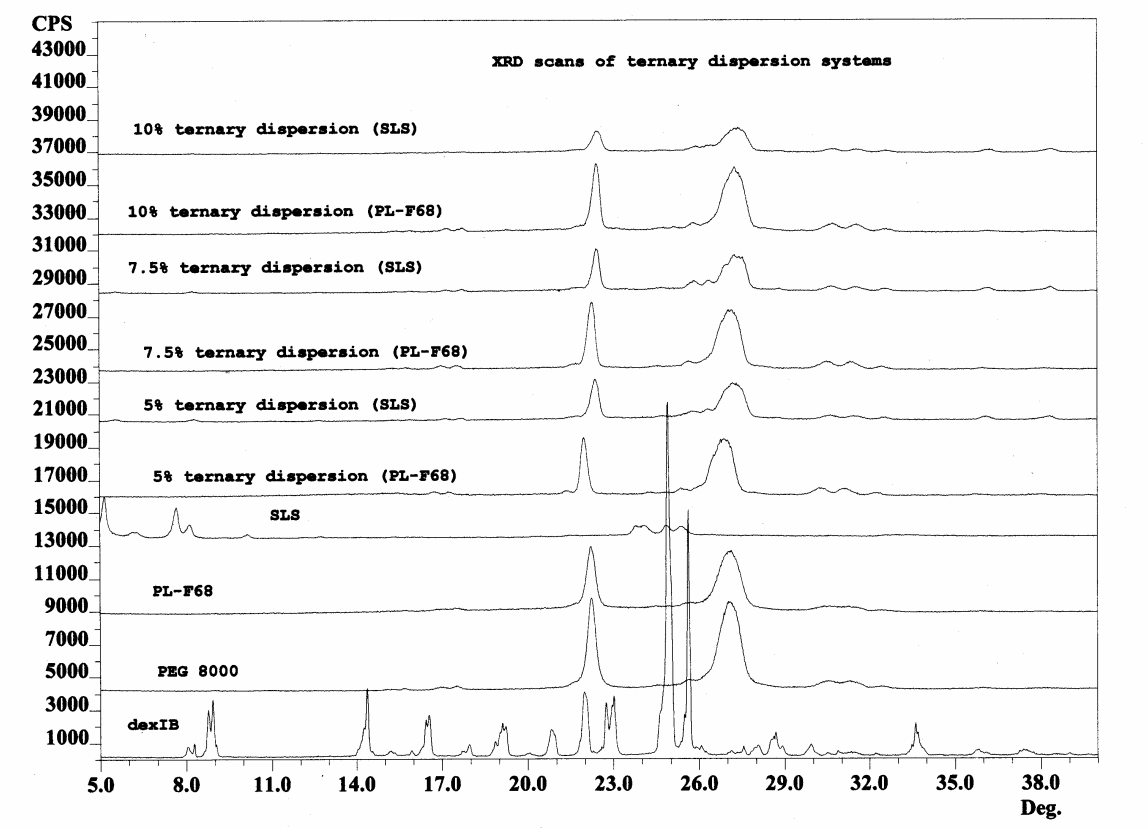

Figure 5.7. XRD scans of ternary systems

Differential scanning calorimetry

The DSC scans of the solid dispersions of dexIB with PEG 8000 and with SLS/PL-F68 and PEG 8000 are given in Figure 5.8. The scans of pure drug and the components as well as the physical mixtures are also given for comparison purposes. It was observed from the DSC curve of pure drug that dexIB melted at 55.5^0 C, which is exhibited by a sharp endothermic peak (Figure 5.9). PEG as stated previously has a semi-crystalline nature and melted at 53.05^0 C (Figure 5.10) while PL-F68 showed an endothermal peak at 44.09^0 C (Figure 5.11). The SLS thermal curve (Figure 5.12) showed 3 characteristic endothermal effects, a short broad peak appearing at around 59.96^0 C, a relatively sharper and larger peak at around 94.229^0 C and another broad peak at around 120^0 C.

The DCS endotherms of the binary dispersions and physical mixtures of dexIB with PEG 8000 showed broadening of the peaks of dexIB and PEG 8000. Shifts in characteristic endotherms were seen as the percent of dexIB decreased in the dispersion systems. For the ternary systems, a similar pattern was observed with peak broadening for the ternary systems. The fusion peaks for the ternary solid dispersions were much lower than for the corresponding physical mixtures, which showed a higher fusion temperature. Also as the amount of drug in the system decreased, the fusion temperatures started becoming lower than the pure drug. In general, the ternary systems showed lower fusion temperatures compared to binary systems which were both higher than the pure drug. The type of surfactant did not have any effect the fusion temperature as both the surfactant containing systems gave a typical hump at the fusion temperature.

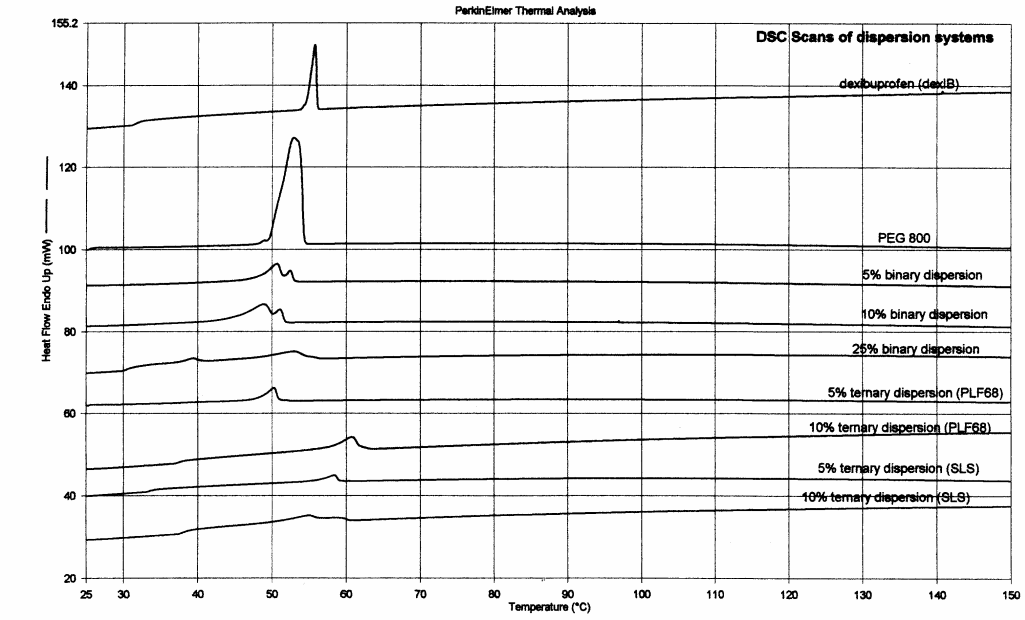

Figure 5.8. DSC endotherms of the binary and ternary systems

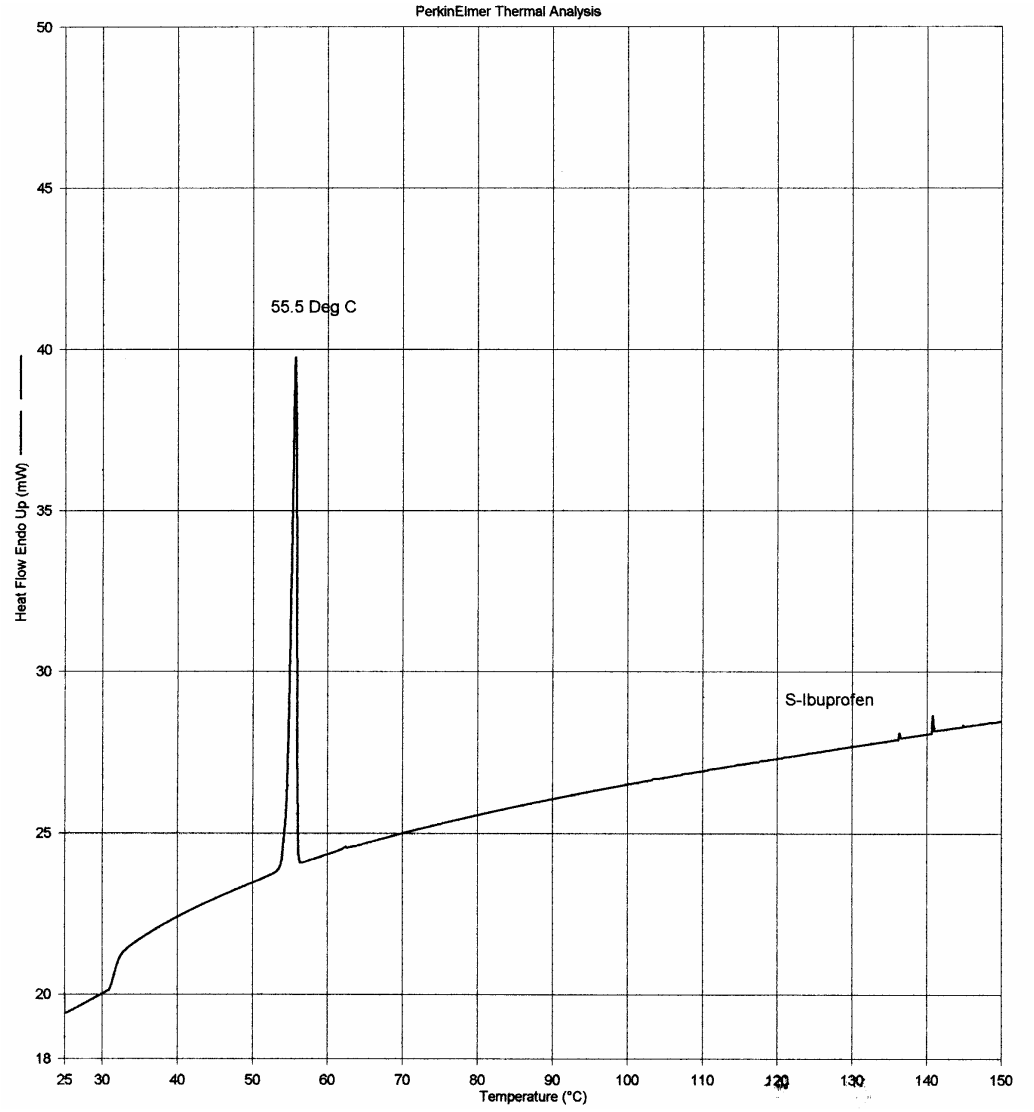

Figure 5.9. DSC endotherm of dexIB

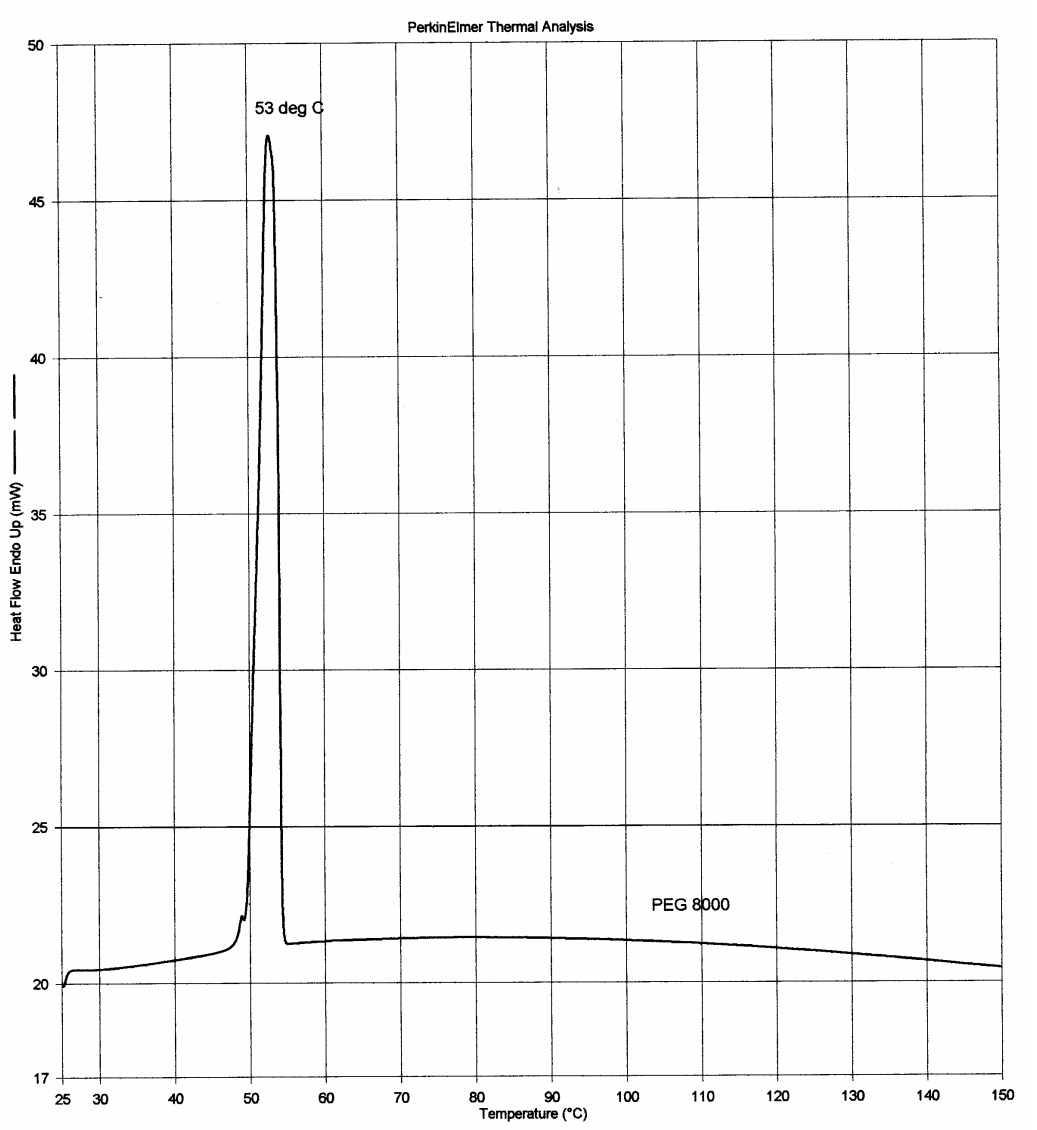

Figure 5.10. DSC endotherm of PEG 8000

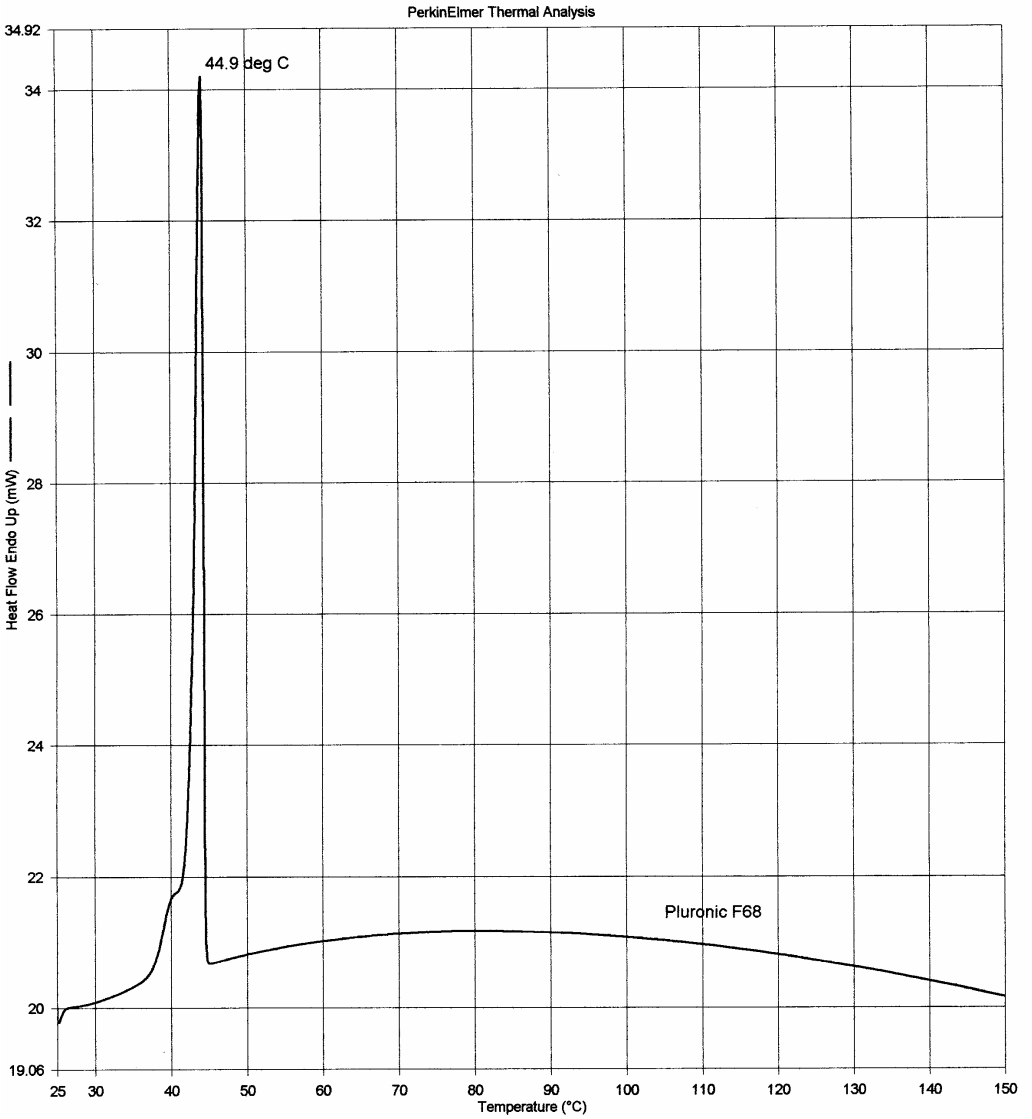

Figure 5.11. DSC endotherm of PL-F68

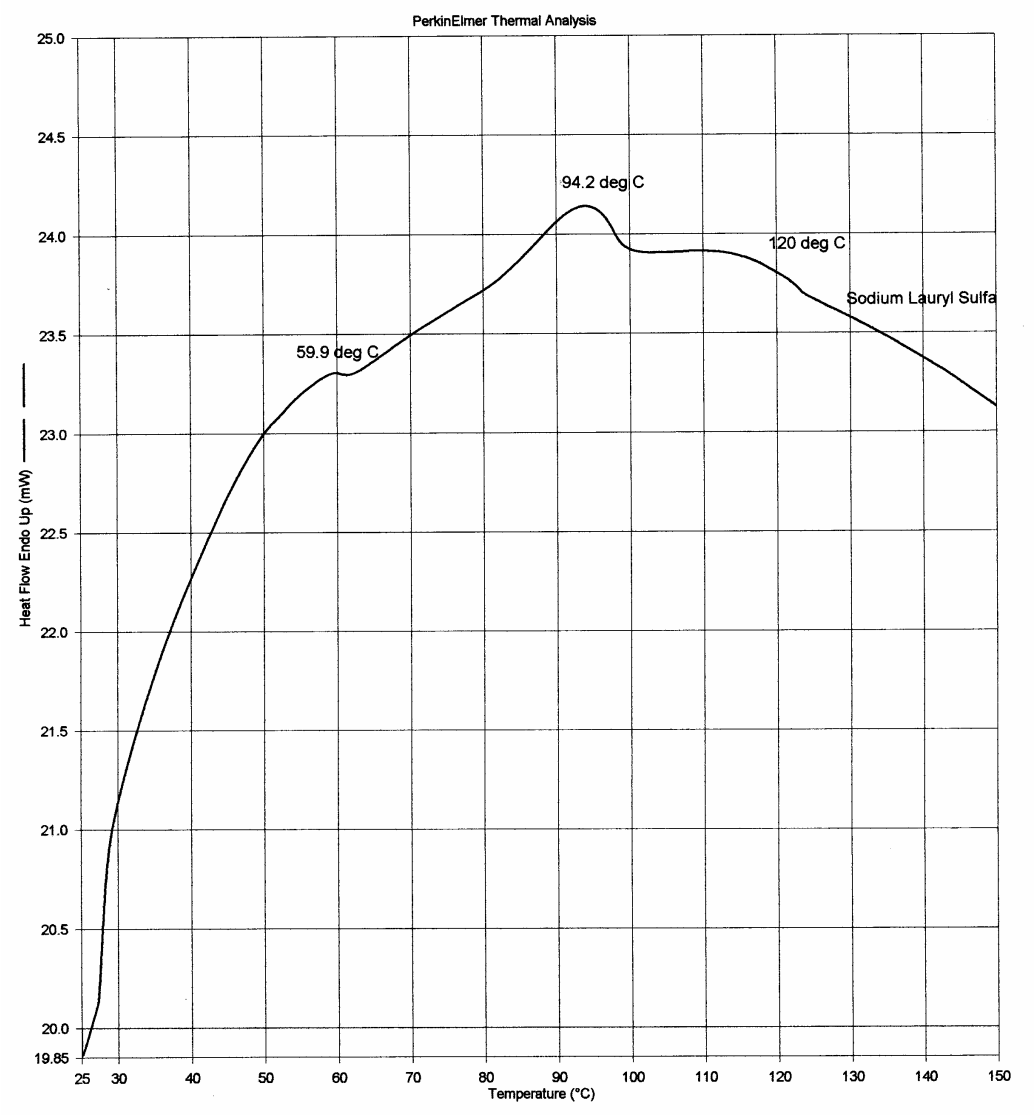

Figure 5.12. DSC endotherm of SLS

Conclusions

PEG 8000 was found to be an effective dispersion carrier for increasing the solubility of a water insoluble drug such as dexIB. The model drug was found to be totally miscible in PEG 8000 in the molten form and partially miscible in the solid state upon quench cooling. This indicated the formation of an interstitial solid (for parts of dexIB that did not crystallize out), which commonly occurs with PEG due to its molecular size. The interstitial solids were more commonly found at lower concentrations of dexIB.

Drug-polymer interactions and associated solid-state changes were observed. A great improvement in the solubility characteristics of the drug was found by the incorporation of a surfactant to the system, in addition to the PEG. Thus an improved solubilization, increase in the wettability, a reduction of particle size (due to partial crystallization of dexIB in the PEG matrix) and drug-polymer interactions dominated the mechanisms responsible for the improvement in the dissolution of dexIB from the dispersion systems.

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CHAPTER 6

CONTROLLED-RELEASE MATRIX TABLETS OF IBUPROFEN USING CELLULOSE ETHERS AND CARRAGEENANS: EFFECT OF FORMULATION FACTORS ON DISSOLUTION RATES[1]

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[1]Jayanti Nerurkar, H.W. Jun and J.C. Price. Submitted to *European Journal of Pharmaceutics and Biopharmaceutics*, 07/06/2004

Abstract

The study was conducted to investigate the effects of carrageenans, and cellulose ethers on the drug release rates of ibuprofen controlled-release tablet matrices prepared by direct compression. Polymer blends containing carrageenans or cellulose ethers were used for the formulation and the effect of varying the polymer concentration on the release of the drug was studied. Other factors such as changes in surface topography of the matrices due to hydration were observed using a cryogenic scanning electron microscopy technique. Multiple regression analysis was used to predict the time for 50% release (t_{50}) as a function of the concentration of the polymers used. Most of the formulations showed linear release profiles (r^2 > = 0.96 - 0.99) and sustained the release of ibuprofen over 12-16 hrs. The highest t_{50} (9.3 hr) was for the formulation that contained a blend of 1:2 ratio of Viscarin and HPMC, while the lowest (3 hr) was for the matrices that contained a 2:1 ratio of methylcellulose and Gelcarin. The majority of the matrix tablets that contained 10% polymer disintegrated prematurely. Of all the polymer blends that were investigated, the combination of Viscarin and HPMC gave almost linear release profiles over the entire range of concentration that was studied. The least effective combination was methylcellulose in combination with HPMC. Most of the formulations released ibuprofen by an anomalous (non-Fickian) transport mechanism, except those matrices that contained methylcellulose and Gelcarin (in a 1:1 and 1:2 ratio), which showed zero-order release.

Keywords: Ibuprofen; Controlled-release; Zero-order; Carrageenans; Hydroxypropyl methylcellulose; Matrix tablets

1. Introduction

Hydrophilic swellable polymers are widely used to control the release of drugs from matrix formulations [1, 2]. Cellulose ethers such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxylpropylcellulose (HPC) and sodium carboxymethylcellulose (NaCMC) have gained popularity in the formulation of oral hydrophilic matrices due to their swelling properties. Additionally, cellulose ethers have good compression characteristics such that they can be directly compressed to form sustained release swellable matrices [3]. In addition to synthetic cellulose ethers, naturally occurring polymers such as carrageenans, xanthan and guar gums have been utilized to effectively control the release of drugs from swellable matrix tablets [4-6]. Carrageenans are naturally occurring high molecular weight sulfated polysaccharides extracted from marine plants belonging to class *Rhodophyceae*. They are widely used in the food industry as viscosity enhancing, gelling and stabilizing agents. There are three main types of carrageenans, the first is lambda (λ-carrageenan) which gives viscous solutions but does not gel, the second is iota (ι-carrageenan) and the third is kappa (κ-carrageenan). Kappa and iota carrageenans do not dissolve in water, but form gels [7].

The key element to drug release from swellable polymers is the use of polymers that will undergo transition from the glassy to the rubbery state which is characterized by a gel-like layer, on hydration by water. This transition should occur fairly rapidly so that the drug has to pass through the viscous gel layer to be released [1]. The rate at which the drug is released from the swellable hydrophilic matrices is determined by numerous processes such as hydration of the polymer that leads to swelling, diffusion of the drug through the hydrated polymer, drug dissolution and polymer erosion. Many of these processes occur simultaneously to release the drug.

Mathematical models describing drug release mechanisms through hydrophilic matrices have been reviewed previously. [3, 8]. These reviews indicate the role of polymer swelling and erosion which play an influential role in determining the kinetics of release. Previous studies which were conducted by Hariharan (1997) and Gupta (2001) indicated the feasibility of using a blend of iota-carrageenan and lambda-carrageenan in the formulation of oral controlled-release tablet matrices to give zero-order release [6, 9]. Both water soluble and insoluble drugs were used to prepare the matrix tablets and found to give linear release profiles for about 70% of the drug release [9]. Hariharan et al (1997) used a specialized type of statistical design, the mixture experiment to optimize the formulation. The current study was undertaken to further analyze whether various cellulose ethers combined with carrageenans in different proportions could also result in zero-order or near zero-order release profiles as observed previously with carrageenans alone.

Many studies have explained the release characteristics of water soluble drugs from HPMC based matrices. They have concluded that the polymer content, which is related to swelling behavior, and the viscosity grade are the determining factors in predicting the release of drugs from the matrices [2, 10-13]. In our study the polymers were combined in such a manner that the tablet matrices contained an active ingredient (ibuprofen) and at least one gel forming polymer. Also very few studies have noted the possibility of combining cellulose ethers with carrageenans to give swellable matrix tablets. The feasibility of using these polymers for sustaining the release of ibuprofen from matrix tablets was investigated.

Mixture experiments, which are statistical experimental designs, are commonly used for the optimization of pharmaceutical formulations. Mixture designs allow the formulator to study the effects of the variables on the response systematically over a narrow range [14]. The current

investigation dealt with the optimization of the hydrophilic matrices for ibuprofen (water-insoluble drug) containing a blend of one or more gel forming polymers using a mixture experiment. The limits of the formulation were also studied to determine the highest and lowest concentration of the polymers which could give linear release. Five such polymer combinations were identified and tested.

2. Materials and Methods

2.1. Materials

Ibuprofen USP was a kind donation from Albemarle Co. (Baton Rouge, LA). The two grades of carrageenan used, Gelcarin GP-379 (ι-carrageenan, GC) and Viscarin GP-209 (λ-carrageenan, VC) and microcrystalline cellulose (Avicel PH 101, MCC) were gifts from the FMC Corporation (Princeton, NJ). Hydroxypropyl methylcellulose (Methocel® K4M Premium, HPMC) was a gift from The Dow Chemical Company (Midland, MI). Sodium carboxymethylcellulose (Na CMC), methylcellulose (MC) (4000 cps) and magnesium stearate were purchased from Sigma Chemicals (St. Louis, MO). Hydroxypropyl cellulose (HPC) was purchased from Spectrum Chemicals (New Brunswick, NJ).

2.2. Micromeritic properties

True densities of all the powder samples (except the drug and the lubricant) were measured using the Accupyc gas comparison pycnometer from Micromeritics (Norcross, GA) using helium as the displacement gas.

Bulk density was determined by carefully pouring pre-weighed amounts of powders into a 100-ml graduated cylinder and measuring the volume occupied by the powders. The tapped

bulk density was determined by the volume of the powder bed after tapping the cylinder onto a hard wood surface three times from a height of approximately 2.5 cm at 2 second intervals, and the ultimate tapped density was calculated after continued tapping caused no further reduction in volume. The compressibility index was calculated using the bulk and ultimate tapped bulk density.

2.3. Tablet preparation

The tablets were made by using a combination of two hydrophilic polymers. Microcrystalline cellulose was used as the filler. Magnesium stearate was used as the lubricant. Tablets weighed 500 mg (± 25mg) and measured 1.27 cm in diameter. All the formulation ingredients, except the lubricant, were mixed in a plastic container and shaken by hand for about 15 to 20 min. The lubricant was added to the powder mixture and mixed for another 2-3 min by hand. The tablets were compressed on a Model B Carver laboratory press from Fred S Carver Inc, (Summit, NJ) fitted with flat faced 1.27 cm punch and die sets and compressed at a force of 2000 lbs.

2.4. Experimental design

The tablets were formulated using a simplex experimental design which is frequently used for optimization in mixture experiments. The compositions of the formulations are shown in Table 6.1. The concentration of ibuprofen was kept constant at 20% of tablet weight and Avicel PH 101 was used as the filler. Five sets of formulations were prepared. Set A contained a combination of MC and Gelcarin. Set B contained Na CMC and HPMC while Set C contained Viscarin and HPMC. Set D contained MC and HPMC while, Set E contained HPC and HPMC.

The total amount of polymer content in the tablet was varied from 16% to 64% of the total tablet weight, while the percent of the two polymers used in each set was varied from 10% to 40%. Within each set, the concentration of the polymers was varied such that 5 levels were obtained (25 formulations were prepared). The combination of polymers was such that each set contained one gelling and one viscosity increasing polymer. Preliminary experiments were done to obtain the feasible range of the polymer concentration that could sustain the release of the drug.

Table 6.1. Composition of formulations prepared for 500mg tablet matrices of ibuprofen.

Numbers represent the proportion of the excipients which totals 400 mg

Set A	MC[a]	GC[b]	MCC[c]
1a	0.3	0.3	0.4
2a	0.2	0.2	0.6
3a	0.1	0.1	0.8
4a	0.4	0.2	0.4
5a	0.2	0.4	0.4
Set B	NaCMC[d]	HPMC[e]	MCC
1b	0.3	0.3	0.4
2b	0.2	0.2	0.6
3b	0.1	0.1	0.8
4b	0.4	0.2	0.4
5b	0.2	0.4	0.4
Set C	VC[f]	HPMC	MCC
1c	0.3	0.3	0.4
2c	0.2	0.2	0.6
3c	0.1	0.1	0.8
4c	0.4	0.2	0.4
5c	0.2	0.4	0.4
Set D	MC	HPMC	MCC
1d	0.3	0.3	0.4
2d	0.2	0.2	0.6
3d	0.1	0.1	0.8
4d	0.4	0.2	0.4
5d	0.2	0.4	0.4
Set E	HPC[g]	HPMC	MCC
1e	0.3	0.3	0.4
2e	0.2	0.2	0.6
3e	0.1	0.1	0.8
4e	0.4	0.2	0.4
5e	0.2	0.4	0.4

[a] MC: Methylcellulose

[b] GC: Gelcarin (GP-379) (iota-carrageenan)

[c]MCC: Microcrystalline cellulose (Avicel PH 101)

[d]NaCMC: Sodium carboxy methylcellulose

[e]HPMC: Hydroxypropyl methylcellulose (HPMC K4M Premium)

[f]VC: Viscarin (GP-209) (lambda-carrageenan)

[g]HPC: Hydroxypropyl cellulose

2.5. Dissolution studies

Dissolution studies were performed in 900 ml of simulated intestinal fluid (SIF, USP 25) without enzymes, using the paddle method (USP 25), at 100 rpm and 37^0C ±0.5^0C. The amount of ibuprofen released over time was determined by withdrawing 5 ml samples at various time intervals and replacing them with equal amounts of dissolution media. The concentration of ibuprofen was obtained by measuring its absorbance at 263nm in a Spectronic 2000 ultraviolet spectrophotometer by Bausch and Lomb (Rochester, NY). The excipients and polymers used in the tablets did not interfere with the sample absorption at the wavelength used. Since the tablet matrices that were being tested swelled and tended to adhere to the dissolution vessel on hydration, the tablets were placed in spiral cages made of stainless steel wire. Four replicates for each experiment were obtained.

2.6. Water uptake studies

The swelling of the polymers upon hydration by the test medium was determined by the equilibrium weight gain method as reported earlier [15]. Representative formulations from each set were analyzed for swelling behavior. These were formulations 1a, 1b, 1c, 1d and 1e. The matrix tablets were weighed and placed in tared metallic baskets. These baskets were then immersed in 900 ml of simulated intestinal fluid (SIF, USP 25) without enzymes, at 100 rpm and 37^0C ±0.5^0C (USP 25 basket method). At specified time intervals, the baskets containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent water uptake was calculated as follows:

$$\text{Percent water uptake} = [(W_s - W_d) / W_d] \times 100 \quad (1)$$

where W_s is the weight of the swollen matrix at time t and W_d is the weight of the dry matrix. The swelling study was done in triplicate for all samples tested.

2.7. Scanning electron microscopy

Scanning electron microscopy (SEM) studies were performed using the LEO 982 Field emission scanning electron microscope FE-SEM, LEO Electron Microscopy, Inc. (Thornwood, NY) on representative samples from each set. The raw materials were coated with a gold palladium mixture and mounted on a sample holder. All the samples were examined with a SEM at an accelerating voltage of 5-15kV depending on the sample at different magnifications. Cryogenic SEM was performed on hydrated tablets to observe the changes in surface topography due to swelling and hydration. The tablets were allowed to hydrate overnight or for 24 hr in water and rapidly plunged in liquid nitrogen slush and then transferred to the cryoprep chamber by Gatan Alto 2500 Cryostage and cryoprep chamber (Gatan, UK). They were then etched with liquid nitrogen under vacuum for about 2 hr to remove traces of surface moisture. A dry tablet which was etched with liquid nitrogen for 5 to 15 min to remove moisture traces was also observed using the cryogenic SEM technique and used for comparison.

3. Results and discussion

3.1. Micromeritics

The micromeritic properties of the polymers used are given in Table 6.2. The true density measurements of the carrageenans (Gelcarin and Viscarin) were found to be comparatively higher than those of the cellulose ethers (MC, HPMC, NaCMC and HPC). Among the polymers, HPC had the lowest true density value indicating the presence of comparatively higher number of possible enclosed voids. The compressibility index is an indication of changes that occur in the packing arrangement while tapping the powder and is a direct measure of the propensity of a powder to consolidate when undergoing vibration, shipping and handling [16]. Direct compression technology, which eliminates granulation procedures for the processing of tablet formulations, requires the use of excipients that have very good flow and compaction properties. Table 6.2 shows that the compressibility index was the highest for MC which had poor, flow qualities since higher values tend to indicate poor flowability of powders [17]. The lowest compressibility index is 5-15% which indicates excellent flow properties.

Table 6.2. Micromeritic properties of polymers used

Sample	Helium Displacement Density (g/cm3)	Bulk Density (g/cm3)	Tapped Bulk Density (g/cm3)	Ultimate Tapped Density (g/cm3)	Compress-ibility Index (%)
Gelcarin	1.73	0.61	0.69	0.85	28
Viscarin	1.69	0.59	0.64	0.79	26
MC	1.34	0.24	0.26	0.39	40
HPMC	1.32	0.36	0.38	0.50	28
Na CMC	1.55	0.53	0.58	0.70	24
HPC	1.22	0.31	0.35	0.43	28

3.2. Dissolution studies

All the powder blends were successfully compressed into tablets and their dissolution profiles analyzed to study the effect of varying concentrations of polymers and the effect of a blend of polymers on the kinetics of ibuprofen release. Preliminary experiments were done prior to the selection of the polymer combinations such that the tablet maintained its integrity without premature disintegration for at least 30 min. As stated previously, five sets of tablet matrices were formulated with different types of polymer blends and each set contained five levels of polymer concentrations. An earlier study showed that Gelcarin , Viscarin, and Avicel in the ratio of 30:30:40 gave zero-order release of a highly water soluble drug, tripelennamine HCl over a 12 hr period and hence this was used as the base level around which the polymer concentrations were varied from 10% to 40% [6]. Although the previous study investigated the use of lambda and iota carrageenans as release controlling polymers, this investigation studied the feasibility of using various cellulose ethers in combination with the carrageenans to achieve zero-order release of ibuprofen.

A general observation that occurred during dissolution testing of the matrix tablets was the rapid surface hydration of the matrix which resulted in its swelling and the consequent formation of a gel layer. The hydration progressed from the surface to the core of the tablet over time. On sufficient hydration, the gel layer slowly dissolved and eroded away exposing a new gel layer as is commonly observed with swellable controlled-release tablets [10]. The use of water insoluble microcrystalline cellulose as the tablet excipient also partly contributed to the prevention of the tablet matrix from disintegrating. Microcrystalline cellulose has crystalline (70%) and amorphous regions. On contacting water, the amorphous regions swell, while the

denser crystalline domains prevent the dissolution of the matrix due to its limited interaction with water [4, 7].

3.3. Release kinetics

The kinetics of ibuprofen release from the various hydrophilic matrices was analyzed using the Peppas and Korsmeyer model given by the following equation [18]:

$$M_t / M_\infty = kt^n \qquad (2)$$

where M_t / M_∞ is the fraction of drug released at time t, k is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and n is the diffusional exponent which characterizes the transport mechanism of the drug. The release data was fitted into the above model to determine the time at which 50% of the drug is released (t_{50}) and the n values. The transport mechanisms were classified based on the values that n assumes. For a cylinder, the drug transport mechanism is by Fickian diffusion when n=0.45, if $0.45 < n < 0.89$, it indicated Anomalous (non-Fickian) transport and for values of n = 0.89, Case II or zero-order release kinetics was indicated [18]. Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms, the coupling of drug diffusion and polymer relaxation [19]. Table 6.3 gives the t_{50} and the n values for all the formulations that were tested. These were obtained by fitting the initial 60% of the release data in the logarithmic form of the Peppas equation. Table 6.3 shows that release of ibuprofen from the majority of the matrix tablets that were formulated was by anomalous (non-Fickian) mechanisms. Matrices that contained MC and Gelcarin in 1:1 and 1:2 ratios (Formulations 1a and 5a) showed zero-order or Case II release with values of n close to 1, while formulations containing a blend of MC and HPMC in the exact same ratios (Formulations 1d and 5d) released the drug by Fickian diffusion.

Further, it was also observed that MC and HPMC in combination were primarily ineffective in sustaining the release of ibuprofen as only 2 of the set of 5 matrix tablets prepared controlled the release of ibuprofen up to a 12 hr period. The values of the kinetic constant k were in accordance with the values of n, the diffusional exponent, with k having lower values when the transport mechanism was Case II and higher values for formulations that released the drug by Fickian diffusion. The Peppas model gave a good fit to most of the dissolution data of the swellable matrix tablets as shown by the R^2 values ($0.95 > R^2 > 0.99$). The t_{50} values of the formulations tested were in the range of 6 to 8 hr, indicating a 12-16 hr time range for completely releasing the drug from the matrices. The t_{50} value was the shortest for formulation 4a (MC and Gelcarin in a 2:1 ratio) with the matrix releasing 50% of ibuprofen in about 3 hr, while it was the highest (9.3 hr) for formulation 5c containing a 1:2 ratio of Viscarin and HPMC blend, amongst all the tablet matrices tested.

Table 6.3. Release rates and diffusional constants for the release of ibuprofen from the hydrophilic matrices

Formulation Number	n	k (h-1)	T50 (hr)	R2	Transport mechanism
1a	1.10	0.07	6.15	0.99	**Case II**
2a	0.65	0.25	2.86	0.96	Anomalous
4a	0.52	0.3	2.72	0.97	Anomalous
5a	1.12	0.07	5.52	0.99	**Case II**
1b	0.55	0.18	6.24	0.98	Anomalous
2b	0.46	0.24	4.85	0.99	***Fickian***
4b	0.68	0.17	5.1	0.99	Anomalous
5b	0.74	0.10	8.42	0.99	Anomalous
1c	0.81	0.09	8.14	0.99	Anomalous
2c	0.74	0.12	6.9	0.99	Anomalous
3c	0.46	0.26	4.16	0.98	***Fickian***
4c	0.83	0.09	7.2	0.99	Anomalous
5c	0.78	0.09	9.3	0.99	Anomalous
1d	0.39	0.24	6.7	0.99	***Fickian***
5d	0.41	0.22	7.58	0.99	***Fickian***
1e	0.56	0.16	7.44	0.99	Anomalous
4e	0.62	0.16	6.21	0.99	Anomalous
5e	0.61	0.13	8.77	0.99	Anomalous

3.4. Effect of polymer concentration and type of polymer:

The dissolution profiles of matrices from Set A that contained a combination of MC and Gelcarin released ibuprofen from the matrix tablets as shown in Fig. 6.1. The release of ibuprofen from HPMC based matrices namely Sets B to E are given in Fig. 6.2-6.5.

All the tablet matrices that were tested in the study indicated that increasing the concentration of the gelling polymer such as Gelcarin or HPMC, in the matrix led to slower drug release. This observation was in accordance with previous studies which have underscored the importance of such swellable polymers and their concentrations on the release of the drug from the matrix [10, 20-22]. Matrices that contained lower concentrations of either Gelcarin or HPMC tended to release the drug in shorter time periods, while release slowed as the concentration of the gelling polymer increased, thus confirming the dominant role played by the swellable hydrophilic polymer in the release of ibuprofen from these tablets. The viscosity increasing polymers such as MC, Na CMC, Viscarin and HPC were also deemed to be essential for maintaining tablet integrity and their role was complementary to the predominant gel forming polymers (HPMC or Gelcarin) and helped to retain the integrity of the matrix. At the least polymer concentration studied (10% each of the polymers); it was observed that only matrices that contained a blend of Viscarin and HPMC (Formulation 3c) could sustain the release of ibuprofen up to 10 hr (Fig. 6.3). This is possibly due to slower erosion of HPMC, as the viscosity increasing Viscarin helped to keep the hydrated gel layer intact thus releasing the drug for 10 hr. This mechanism was hypothesized based on earlier published reports of tablet matrices which were made with predominantly either Viscarin or Gelcarin (80% of the carrageenan) using tripelennamine HCl as the drug. Such matrices were essentially ineffective in maintaining the integrity of the matrix as well as sustaining the release of the drug. For example, the tablets that

contained predominantly Gelcarin disintegrated after hydration while those matrices containing Viscarin dissolved very rapidly [6]. Hence a combination of the polymers was used in this study and proved to be more effective.

Formulations that contained the lowest concentration of each polymer i.e. 10% (3a-3e) failed to control the release of ibuprofen and disintegrated prematurely within 2 hr. Formulations that contained MC in combination with either Gelcarin or HPMC (3a and 3d) as well as HPC and HPMC in combination (Formulation 3e), were ineffective in controlling the release of ibuprofen at concentrations below or at 20% (combined) tablet weight. Tablets that contained a mixture of Na CMC and HPMC at 10% polymer level each (Formulation 3b) fared better than MC containing matrices; they disintegrated in about 4 hr as opposed to 2 hr. The premature disintegration of matrices (3a-3e) that contained 10% of HPMC or Gelcarin was due to very rapid hydration of the gelling polymer particles. This consequently led to them behaving as disintegrants rather than as release controlling polymers. The isolated pockets of these polymer aggregates could have assisted the disintegration of the tablets due to localized wetting and the formation of a discontinuous gel layer [10].

Increasing the concentration of the blends from 20% to 40% each showed a sustaining effect on ibuprofen release. Fig. 6.1-6.5 showed almost linear release profiles of ibuprofen from matrices that contained varying proportions of the polymer blends (Formulations 1a-5e). As stated previously, the rapidly hydrating polymer (HPMC or Gelcarin) dominated in controlling the release of ibuprofen from the matrix tablets as seen from the dissolution profiles and the swelling data. Release rates slowed when the concentration of Gelcarin or HPMC increased from 20% to 40% (Figure 6.2-6.5). This is because as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater

swelling leading to a thicker gel layer. Simultaneous surface erosion could have also helped in controlling the release process. Addition of viscosity enhancers such as MC, HPC, Viscarin and Na CMC also contributed to interference in the water penetration rates, water absorption and polymer swelling [23]. Formulations 1a and 5a showed a zero-order release rate, based on fitting the dissolution data to the Peppas and Korsmeyer model. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional pathlengths. When the thickness of the gelled layer and thus the diffusional pathlengths remain constant, zero-order release can be expected, as seen for formulations 1a and 5a. In contrast, the majority of formulations that showed non-Fickian release must have had a progressively thickening gel layer due to slower erosion thus creating a zone of drug depletion that moved inwards as time progressed. This led to increased diffusional pathlengths and a decrease in the drug release rate with time [24-26]. At higher concentrations, the viscosity enhancing polymers contributed by keeping the hydrated layers intact, thus maintaining the integrity of the matrix and slowing the erosion process.

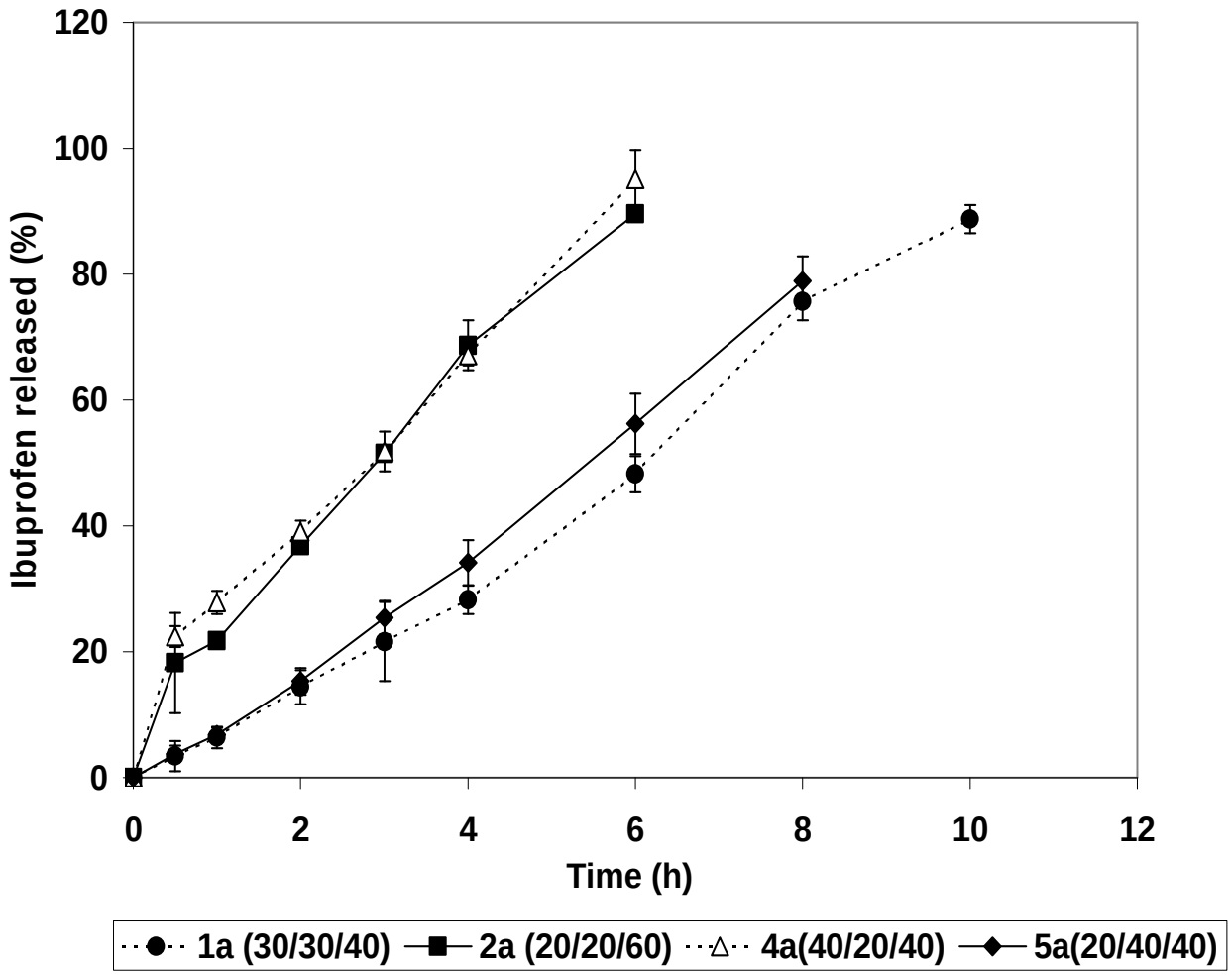

Figure 6.1. Release profiles of ibuprofen from tablet matrices of Set A (1a-5a) containing MC/Gelcarin/Avicel PH 101

3.4.1. HPMC based matrices:

Sets B to E were formulated using HPMC blended with MC, Viscarin, Na CMC and HPC (Fig. 6.2-6.5). For all these matrices, especially those containing cellulose ethers such as MC and HPC, a rapid burst effect releasing up to 50% of the drug was observed. A similar but much smaller burst effect was seen from matrices with low HPC/HPMC loadings and was attributed to disaggregation of the matrix or erosion of the tablet surface prior to gelation as previously shown [23]. For cellulose ethers, the degree of substitution plays an influential role in its water solubility. Both methylcellulose and hydroxypropylcellulose are characterized by lower hydrophilicity as compared to HPMC [3]. This difference in the hydrophilicity explained the lower rates of absorption of water by the HPC/HPMC and MC/HPMC based matrices consequently leading to the initial rapid release. The dissolution profiles for the latter time periods of these matrices showed significantly slower rates of release which was probably due to an increase in the diffusional pathlength of the drug over time and stabilization of the gel barrier.

The presence of anionic polymers such as Viscarin and Na CMC on the other hand had a beneficial effect on the viscosity and gave almost linear release of ibuprofen over a 10-12 hr period. Since the sulfated groups containing carrageenans and carboxyl groups containing Na CMC are anionic in nature, they have a tendency to interact with nonionic hydrocolloids, resulting in an increase in the gel viscosity. Studies have reported such ionic interactions between Na CMC and HPMC as well as Carbopol® and HPMC [27, 28]. The capacity of Viscarin and Na CMC to form hydrogen bonds with the hydroxyl groups of HPMC led to a synergistic effect on gel viscosity that explains the better control these polymers had on the release of ibuprofen. A similar explanation is also valid for MC-Gelcarin (Set A) matrices that gave zero-order release profiles, since higher the viscosity of the gel layer, the greater is its

resistance to erosion [1]. It has been reported that gel erosion plays an important role in the release of drugs with low water solubility such as ibuprofen [1].

Fig. 6.6 shows a comparison between the dissolution profiles of representative formulations (1a, 1b, 1c, 1d and 1e) from the various sets that were prepared. These formulations contained 30:30:40 mix of the polymer blends studied. It was seen that formulation 1c containing a blend of Viscarin and HPMC gave the slowest release throughout the 12 hr test period, followed by HPC/HPMC matrices. Tablets containing a blend of MC and Gelcarin gave the slowest release in the first 3 hr, followed by a quick release which was probably due to rapid erosion of the gelled matrix. A similar trend was also observed for the Na CMC/HPMC tablets where the release quickened after 8 hr of linearity. Formulations that contained MC/HPMC on the other hand showed a reverse trend with a quick initial release followed by a slower release as time progressed that was possibly due to a slower eroding complex that resulted in a longer diffusional pathlength for the drug molecules.

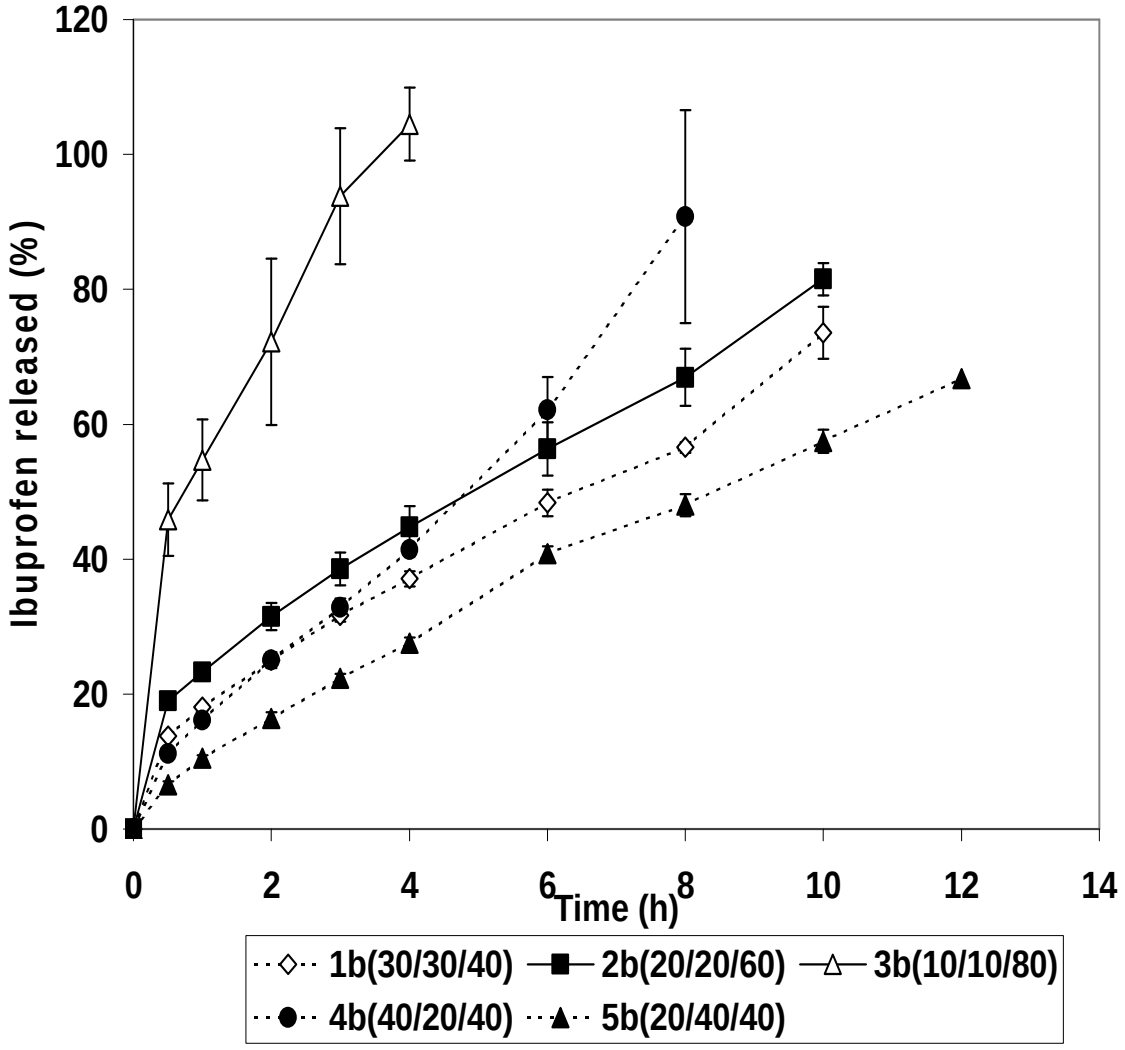

Figure 6.2. Release profiles of ibuprofen from tablet matrices of Set B (1b-5b) containing Na CMC/HPMC/Avicel PH 101

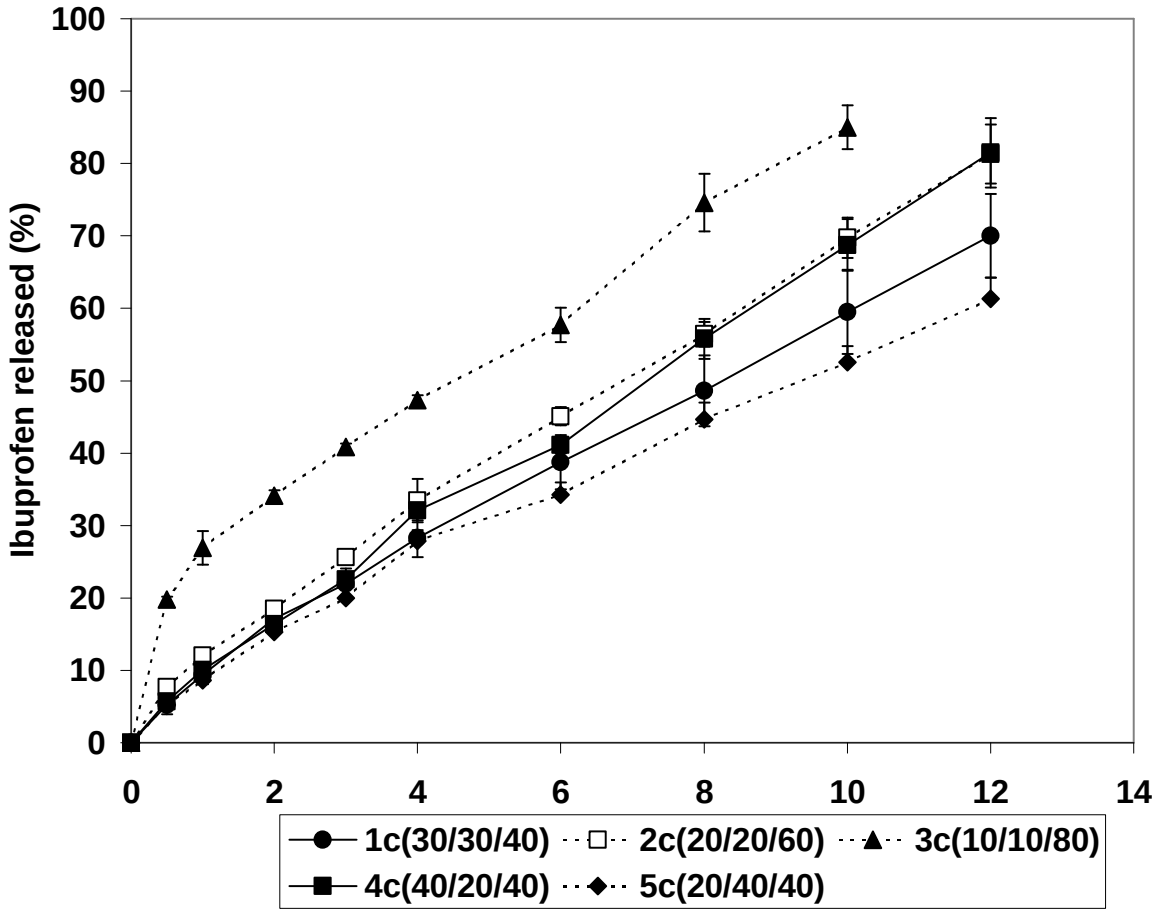

Figure 6.3. Release profiles of ibuprofen from tablet matrices of Set C (1c-5c) containing Viscarin/HPMC/Avicel PH 101

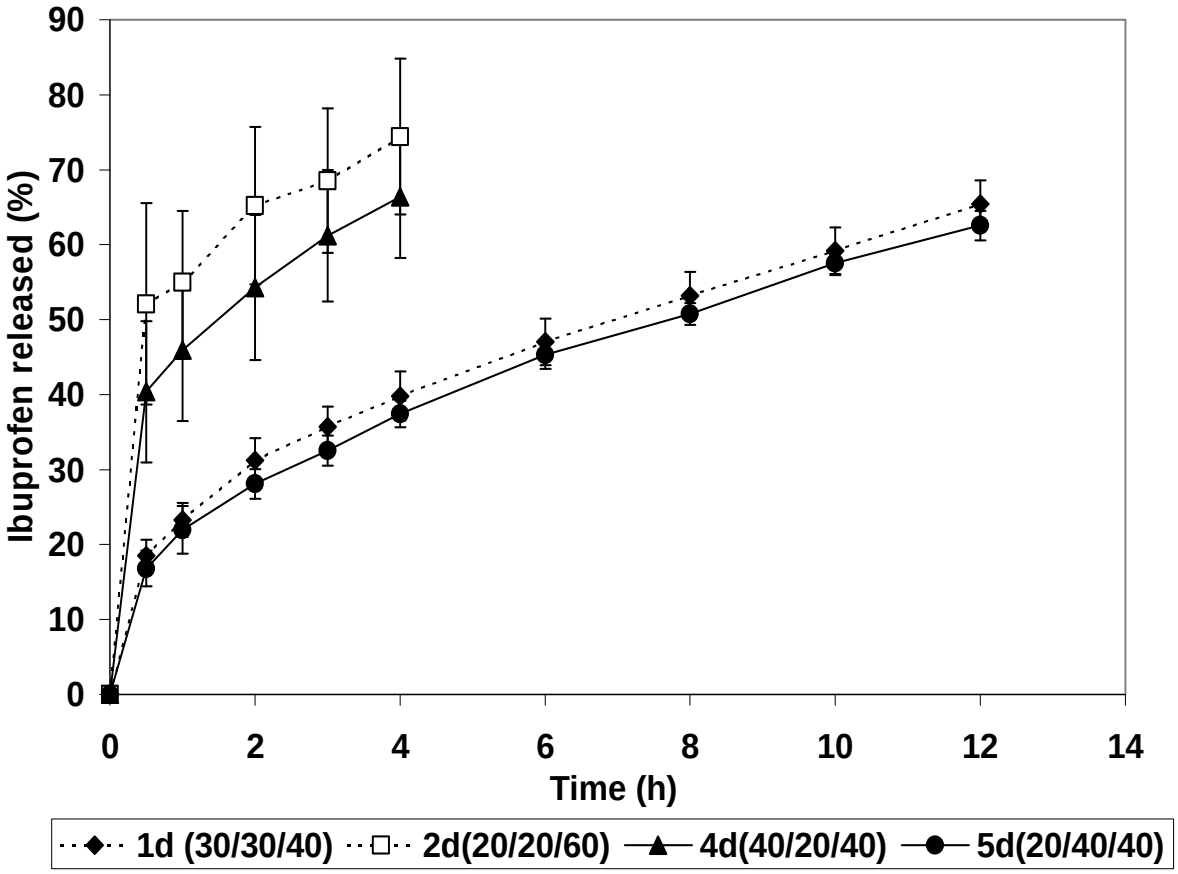

Figure 6.4. Release profiles of ibuprofen from tablet matrices of Set D (1d-5d) containing MC/HPMC/Avicel PH 101

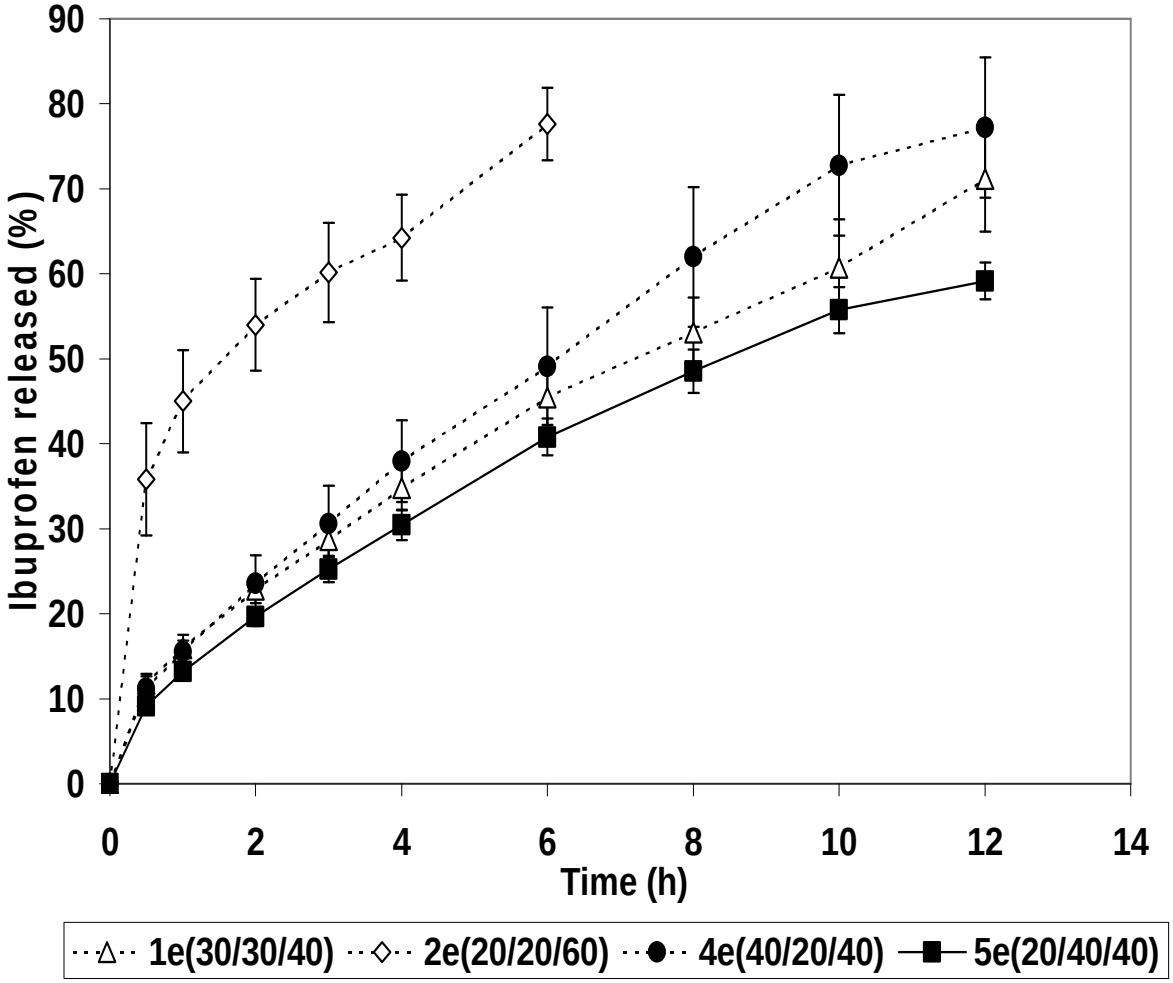

Figure 6.5. Release profiles of ibuprofen from tablet matrices of Set E (1e-5e) containing HPC/HPMC/Avicel PH 101

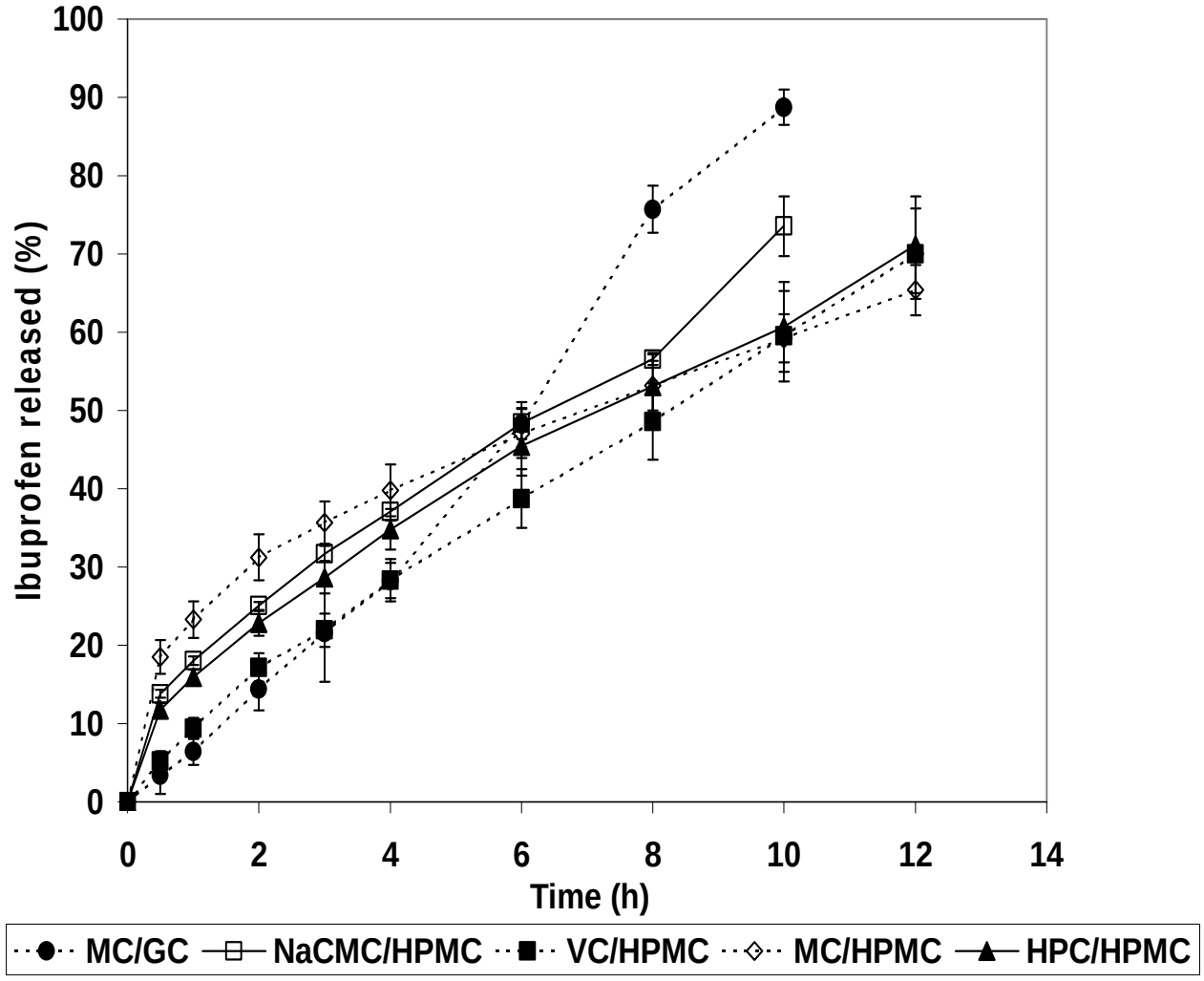

Figure 6.6. Release profiles of ibuprofen from matrix tablets containing equal amounts of both the polymers

3.5. Water uptake

The swelling behavior of various polymer blends was analyzed to compare their water uptake capacity. Fig. 6.7 shows the rate of swelling for matrix tablets that contained equal proportions of the two polymers (Formulations 1a, 1b, 1c, 1d and 1e were used for the swelling analyses). Swelling of the matrix, which is indicated by the transition of the polymer from the glassy to the rubbery state, is an important parameter in the determination of the release characteristics of the matrix system [29]. The correlation of polymer swelling to drug release can help explain why different polymer blends gave different mechanisms of release. Fig. 6.7 showed that matrices which contained Na CMC/HPMC, MC/Gelcarin and Viscarin/HPMC in combination showed significant swelling over time. The highest degree of hydration was achieved by the Na CMC/HPMC tablet, indicating that the ionic interactions between the cellulose ethers increased the water uptake capacity to a greater extent than the carrageenan-cellulose ether associations. There was about 300% to 400% weight gain at the end of 8 hr due to swelling in these matrices. On the other hand, both MC and HPC are less hydrophilic and were hydrated to a much lower extent when combined with HPMC. These matrices could hydrate only up to 6 hr after which there was no further increase in the tablet weight due to water uptake. For the HPC/HPMC matrix, there was significant erosion of the matrix after 6 hr. Similar observations were made for HPC containing matrices regarding their inability to hydrate for longer time periods [30, 31]. For matrices containing a combination of anionic and nonionic polymer, swelling was higher and more control over the release of ibuprofen was observed.

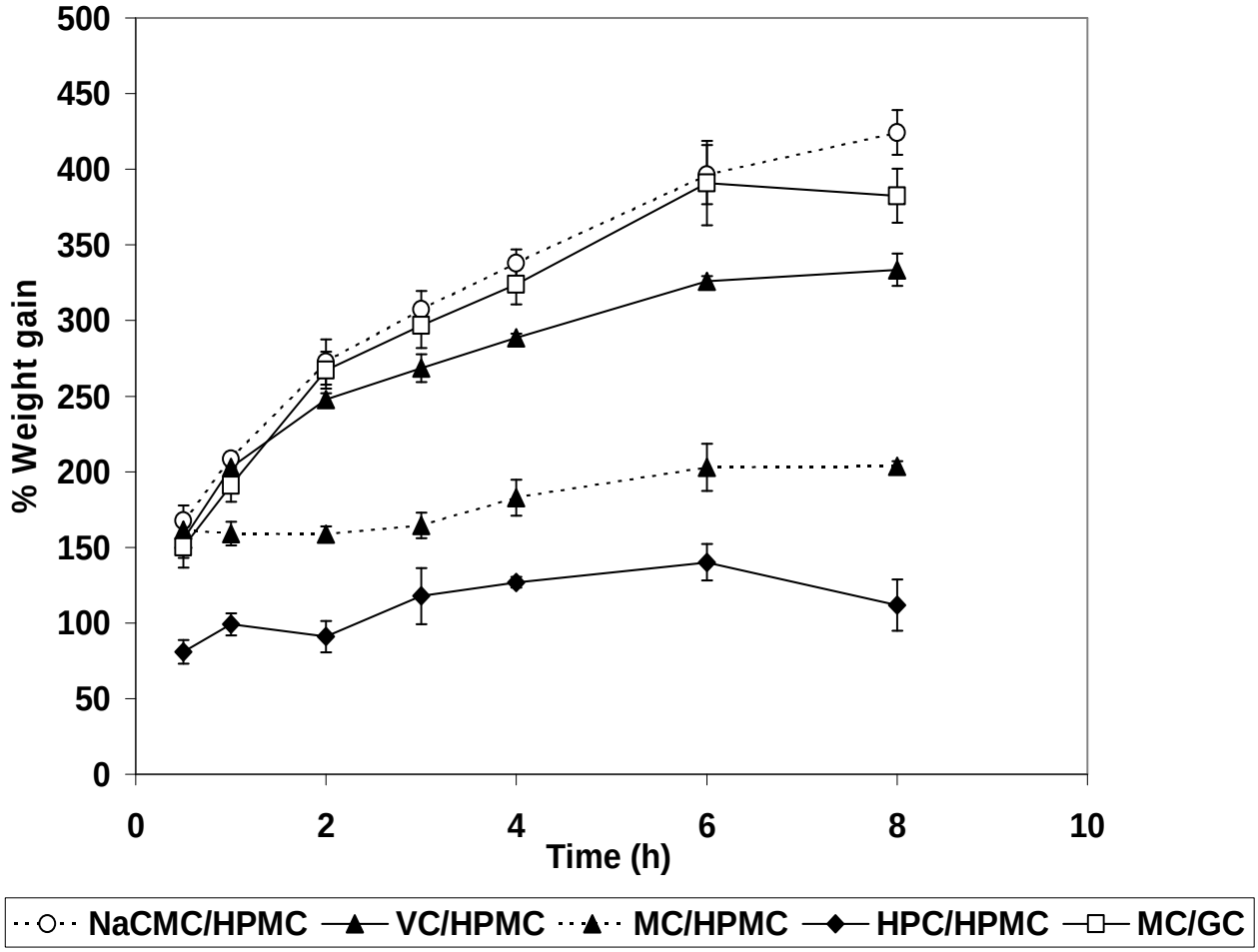

Figure 6.7. Graphical representation of percent water uptake versus time for matrices (1a, 1b, 1c, 1d, and 1e) containing 100 mg of ibuprofen

3.6. Statistical analysis:

Multiple regression analyses were done using Statistical Analysis Software (SAS®), (SAS Institute Inc., Cary, NC, USA) version 8.0. The significance level was set at 0.05. Since the independent variables add up to one, the following multiple regression model was used:

$$Y = \beta_0 + \beta_1 x1 + \beta_2 x2 + \beta_3 x1x2 + \beta_4 x1x3 + \beta_5 x2x3 + \beta_6 x1x2x3 + \epsilon \qquad (3)$$

where Y is the percent of drug released in 2 hrs,

Set A: x1= MC, x2 = Gelcarin and x3= Avicel PH 101

Set B: x1= Na CMC, x2 = HPMC and x3= Avicel PH 101

Set C: x1= Viscarin, x2= HPMC and x3= Avicel PH 101

Set D: x1= MC, x2 = HPMC and x3= Avicel PH 101

Set E: x1= HPC, x2 = HPMC and x3= Avicel PH 101

The regression statistics are given in Table 6.4. For all the formulation sets tested, the estimated regression coefficients that were significant to the model were selected, and the final model was found to have low coefficients of variance. The R^2 of the models tested were mostly above 0.9. The F-statistic was found to be highly significant for all the sets of tablets prepared.

Table 6.4. Regression model statistics for release parameters

2h%	F_{reg}	R^2	SD	Pr> F
Set A	180.61	0.98	7.55	<.0001
Set B	49.27	0.90	20.82	<.0001
Set C	226.33	0.98	5.91	<.0001
Set D	23.89	0.86	16.45	<.0001
Set E	149.77	0.96	10.71	<.0001

3.7. Scanning Electron Microscopy

The SEM images of the raw materials indicated a fibrous nature of all the cellulose derivatives as seen in Figure 6.8. The MC and HPC particles were of larger dimensions than the rest. Fig. 6.9 shows the various images of the dry tablets that were taken. All the dry tablets showed a porous surface formed by the compressed particles. The SEM images of the dry tablet surfaces showed a degree of mechanical interlocking of the tablet excipient particles without brittle fracture when compressed [7, 32]. The surface images of the tablet compacts also indicated that there was some degree of elastic deformation of the tablet excipients and polymers [7]. The hydrated tablet matrices of Formulations 2a, 1b,1c,1d and 1e were used to analyze three dimensional changes and the texture of the tablet surface on hydration. The tablets were soaked in water for either 24 hrs or overnight based on their ability to retain their integrity after soaking. The imaging technique used to observe the topographical changes due to hydration of the rapidly frozen gels was cryogenic SEM which is a highly sophisticated technique often used to observe biological samples and biomaterials in their wet state. The advantage of using cryogenic SEM was that the hydrated samples could be analyzed as such in their wet state and did not require drying to withstand the high vacuum conditions in a conventional SEM chamber. For the sample preparation the hydrated tablets were plunged into liquid nitrogen slush (approximately -206 ^{0} C) and kept frozen through out the imaging process. Plunging the samples in the liquid nitrogen slush caused the formation of amorphous vitreous/glassy ice thus preserving the native structure. Subsequently, there is no distortation of the surface morphology of the hydrated tablet due to ice crystals. A common observation of all the wet tablets was the gelation of the swollen hydrated polymers. The surface topography and the cross-sectional SEM images of the hydrated tablets are shown in Fig. 6.10. On hydration, the surfaces of the tablets showed the formation of a

membranous but porous film that was due to the gel layer formed by the polymer relaxation upon absorption of water. The cross-sectional images on the other hand indicated a highly porous honeycomb structure of the polymer network, which allows the drug to diffuse out from the core to the surface. Further, the outer surface showed smaller pores, while the cross-section showed a network of pores which would probably explain the routes for the drugs to travel within the body of the gel layer. Since the gel layer undergoes surface erosion, it is possible that the inner porous network is exposed after the dissolution of the outer film of the tablet. The inner pores were larger for the formulations that contained HPMC as compared to Gelcarin containing matrices. A similar sponge-like pore network was also reported for tablets made from cross-linked high amylase starch which similarly swells on hydration and is used for controlled-release purposes [33].

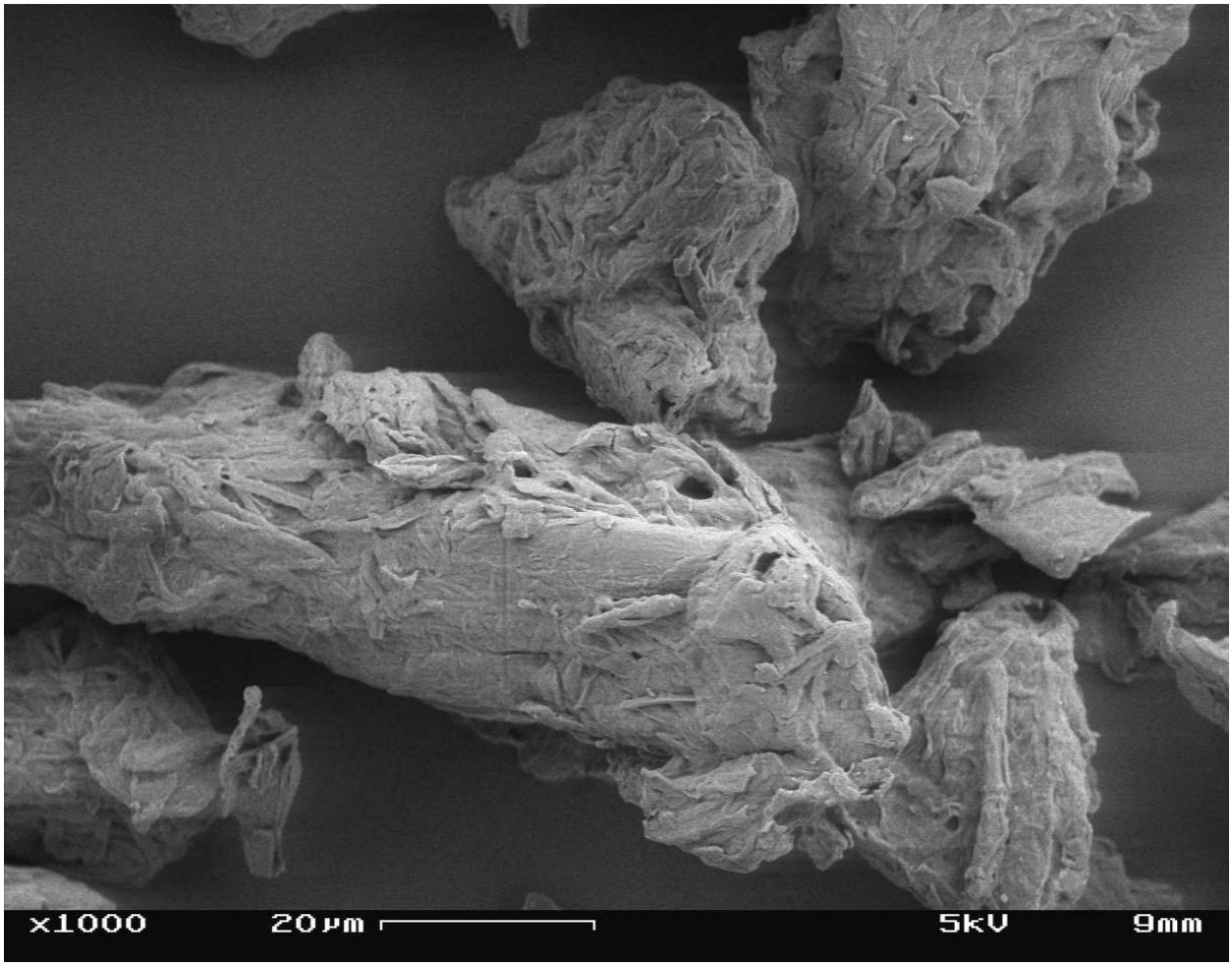

Figure 6.8. SEM images of raw materials

Figure 6.8.1. Microcrystalline cellulose

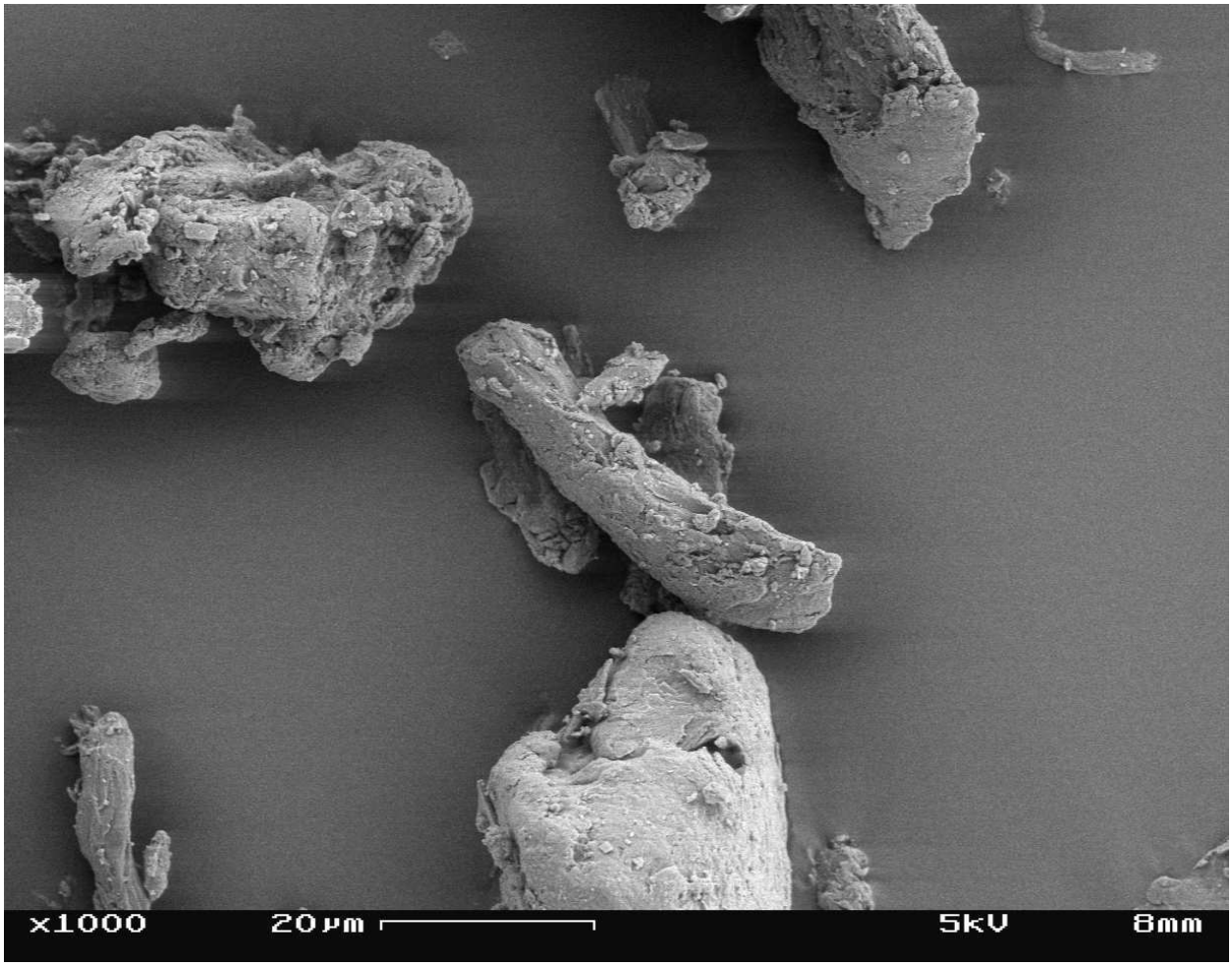

Figure 6.8.2. Gelcarin

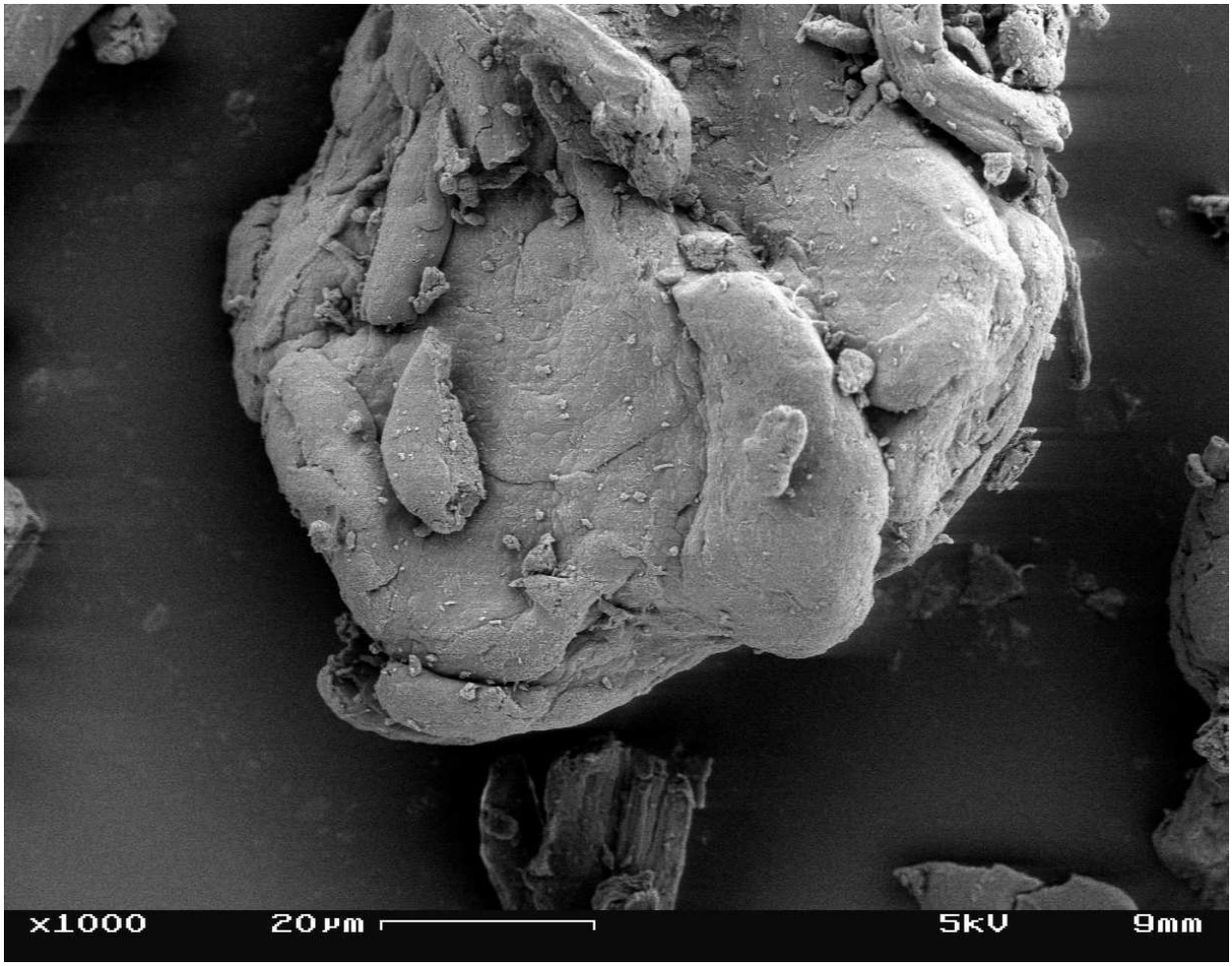

Figure 6.8.3. Viscarin

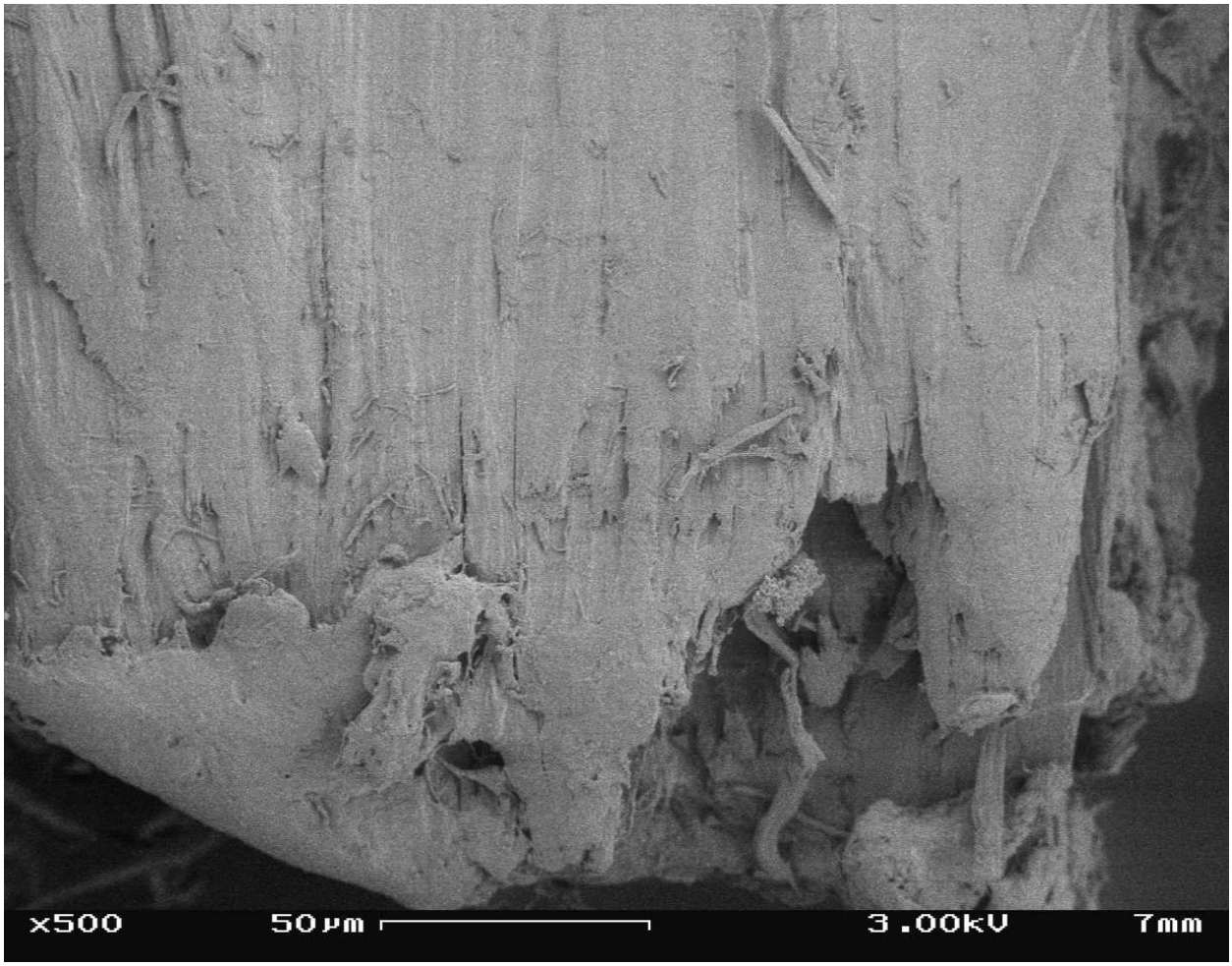

Figure 6.8.4. Methylcellulose

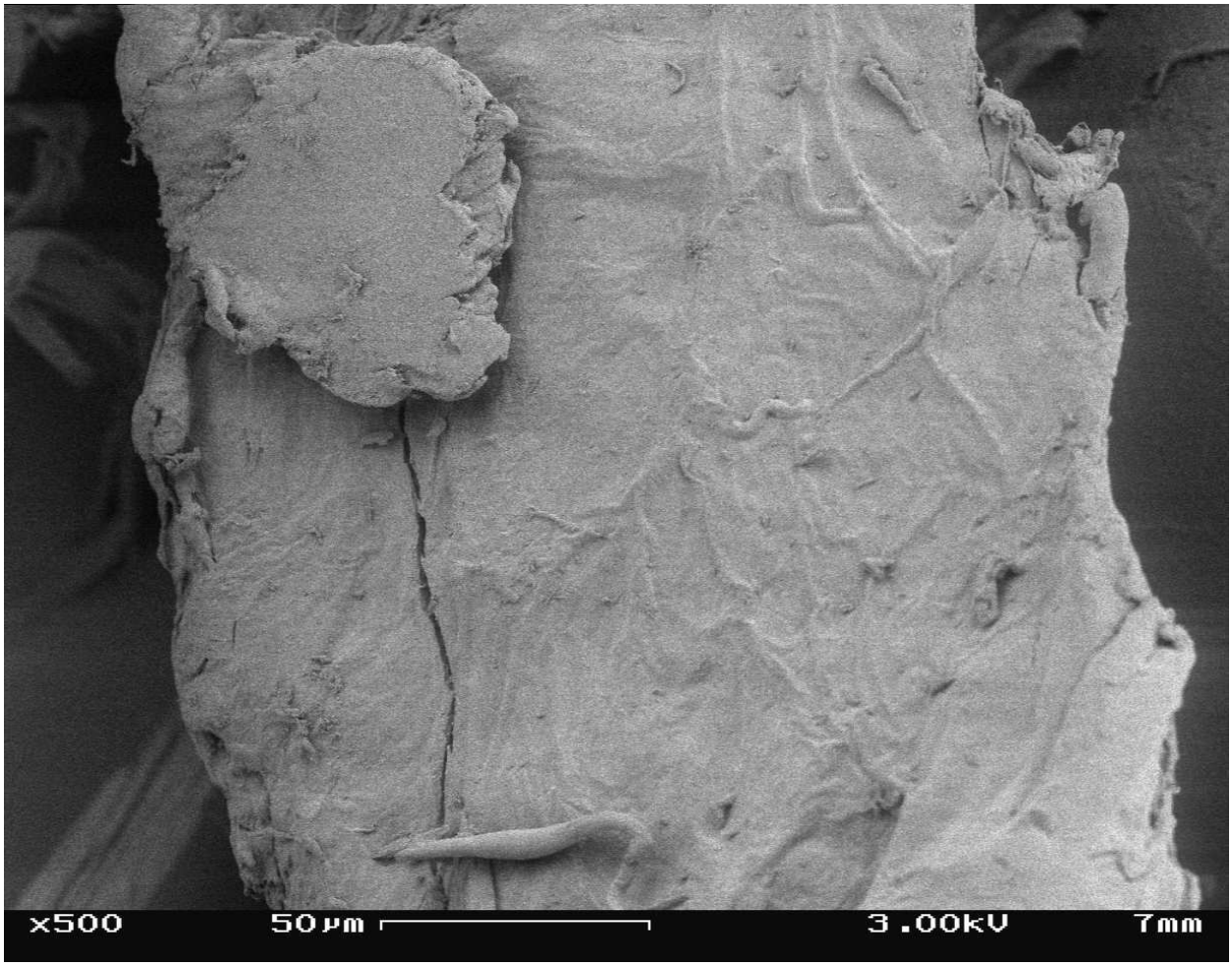

Figure 6.8.5. Hydroxypropyl cellulose

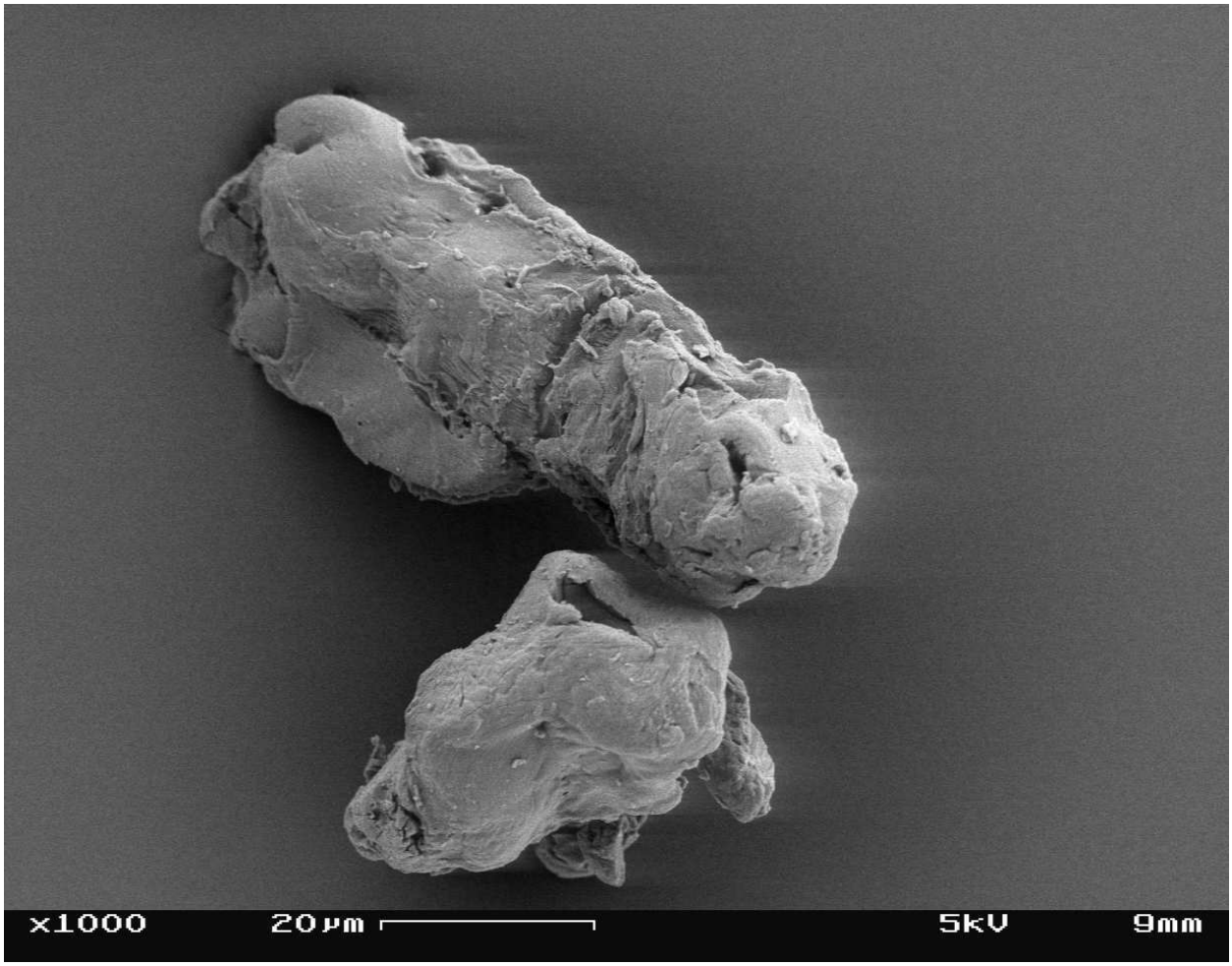

Figure 6.8.6. Sodium carboxymethylcellulose

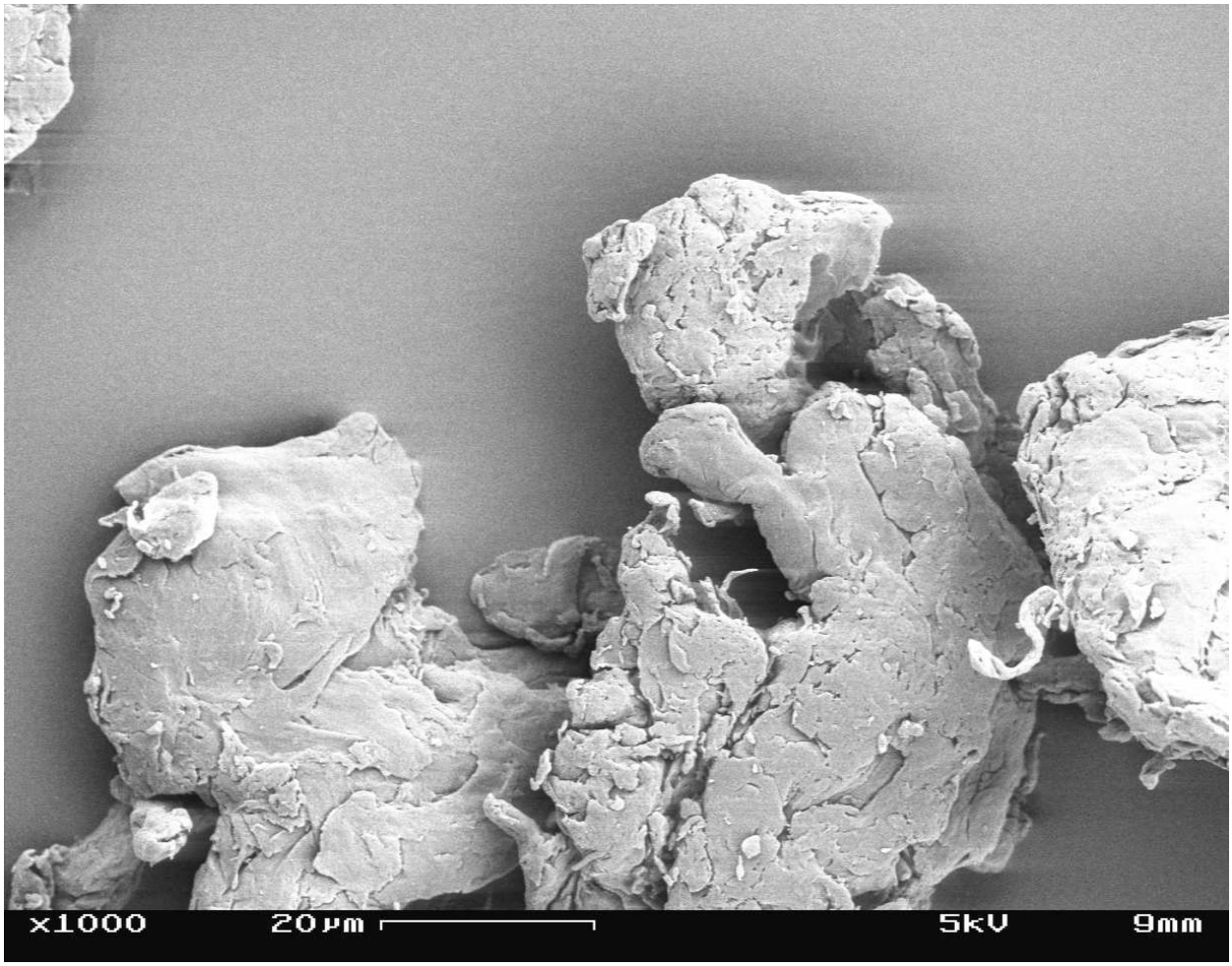

Figure 6.8.7. Hydroxypropyl methylcellulose

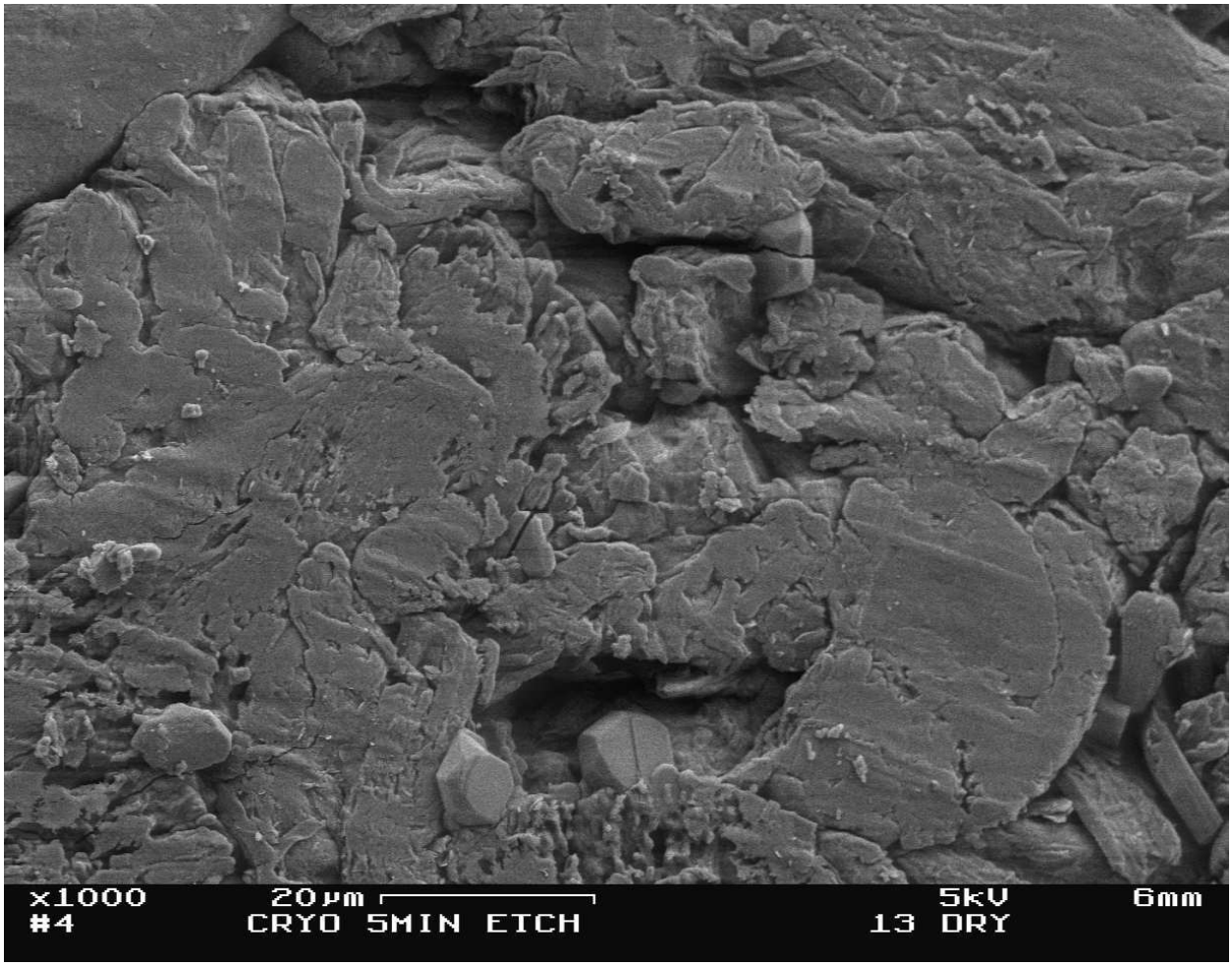

Figure 6.9. SEM images of dry tablet surfaces

Figure 6.9.1. Tablet 2a

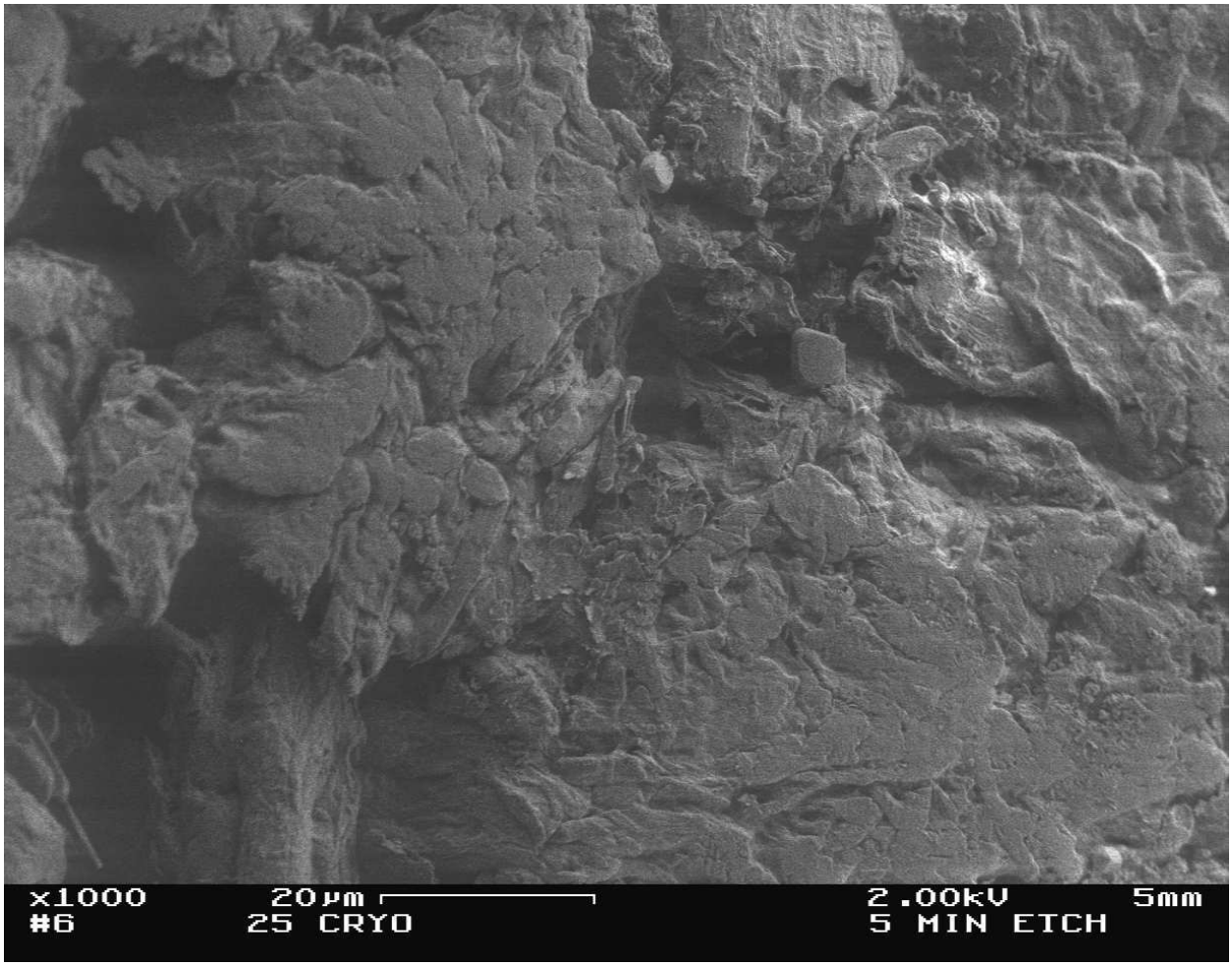

Figure 6.9.2. Tablet 1b

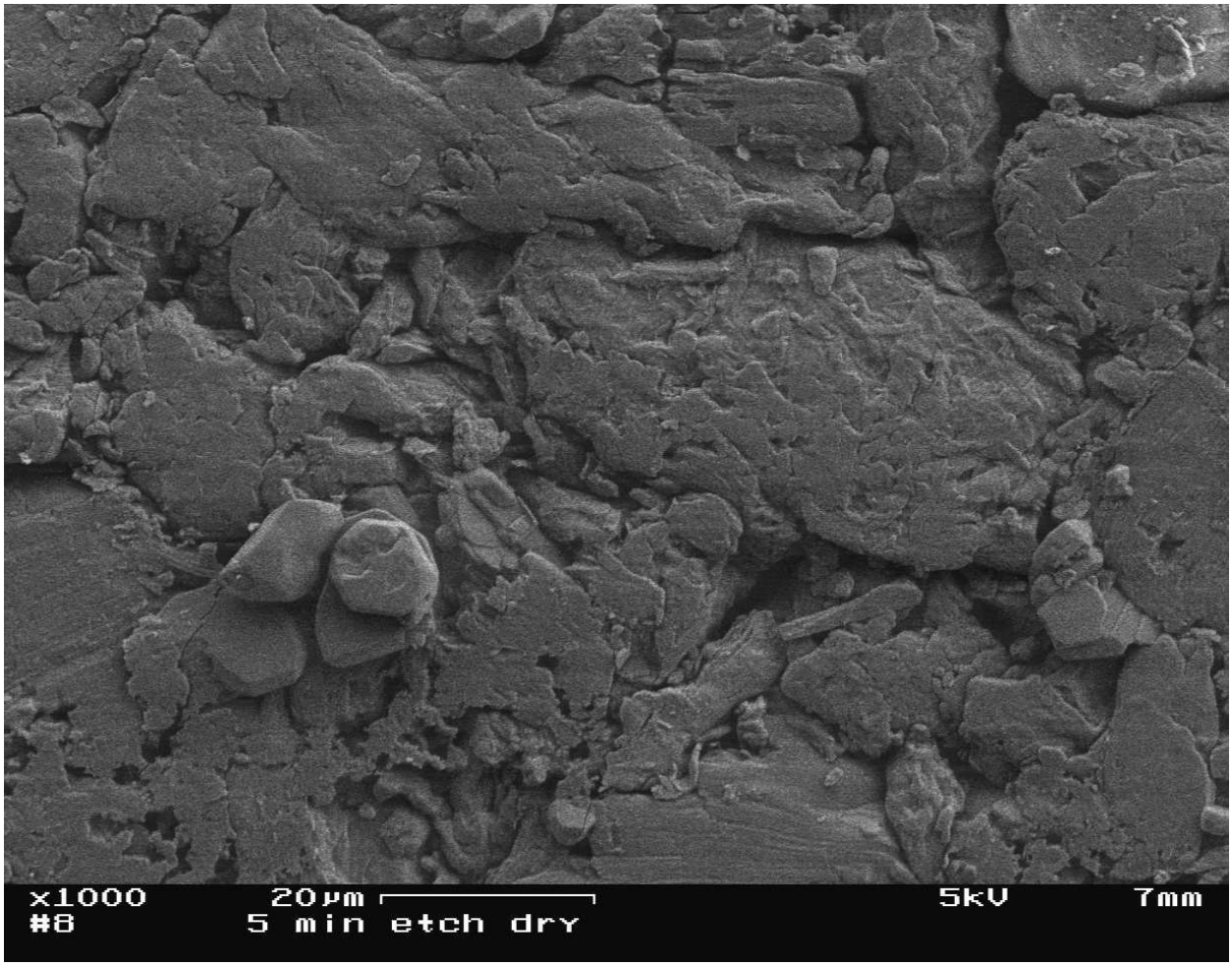

Figure 6.9. 3. Tablet 1c

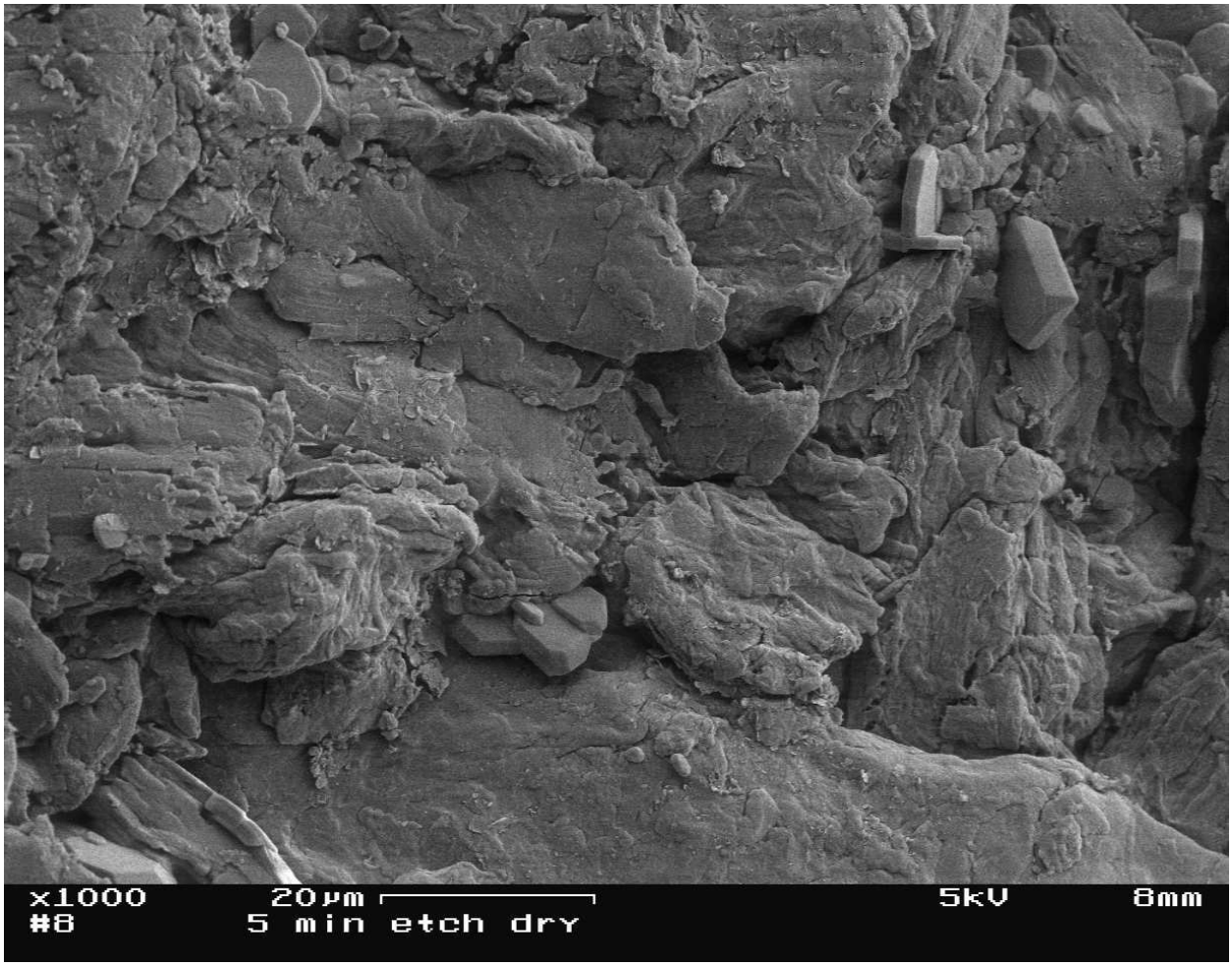

Figure 6.9.4. Tablet 1d

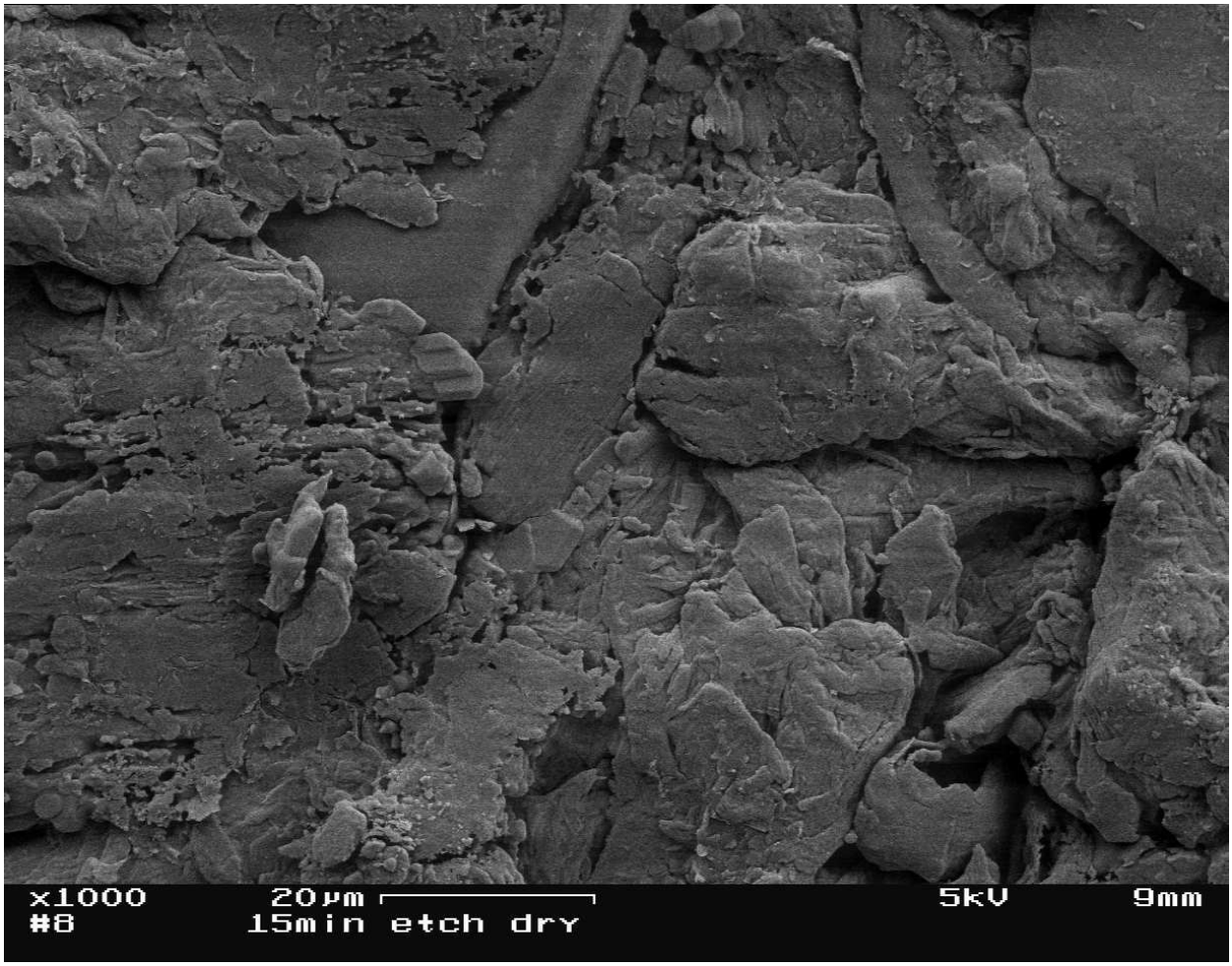

Figure 6.9.5. Tablet 1e

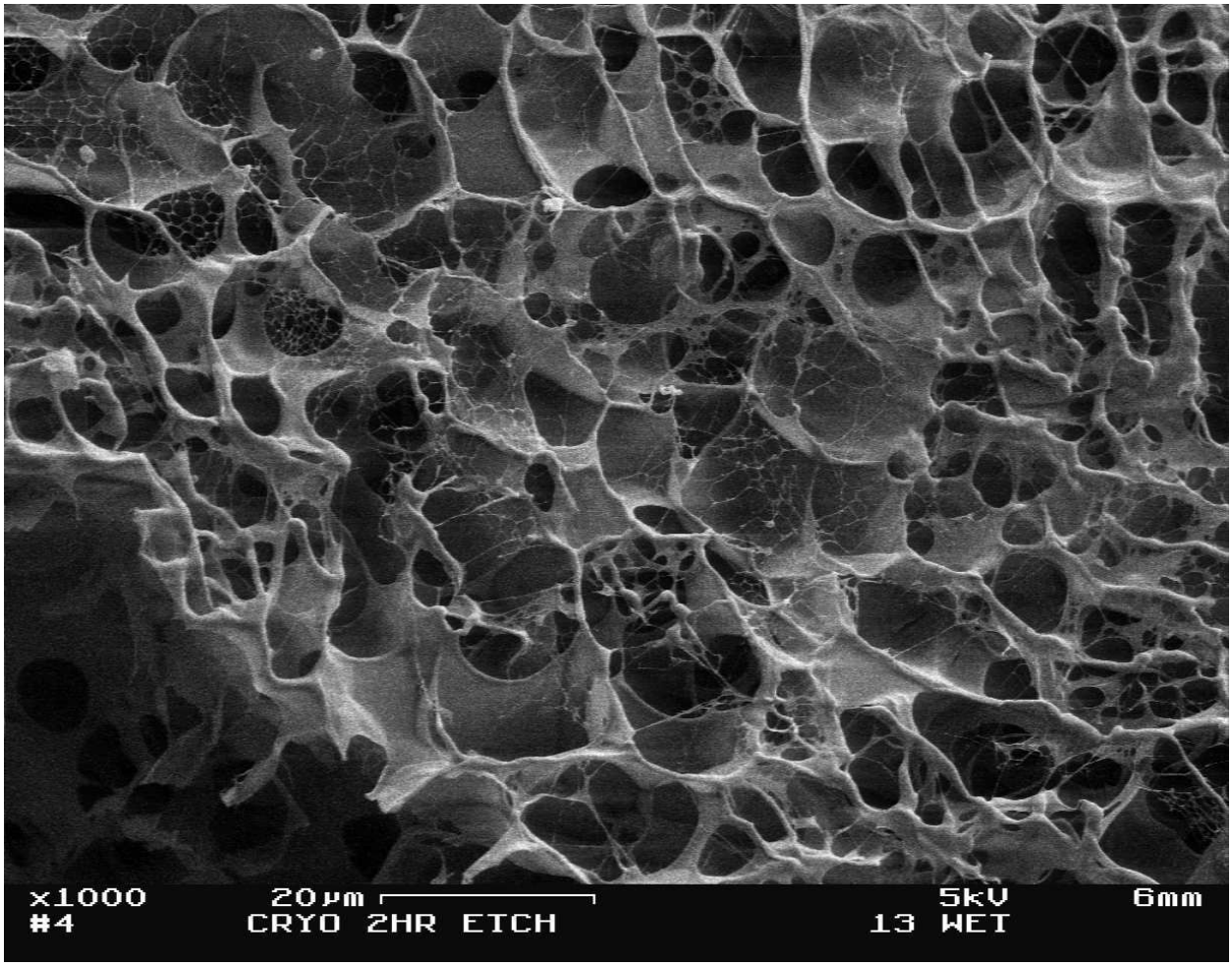

Figure 6.10. Cross-sectional views and surface topography of hydrated matrices using cryogenic SEM technique

Figure 6.10.1. Cross-sectional view of tablet 2a

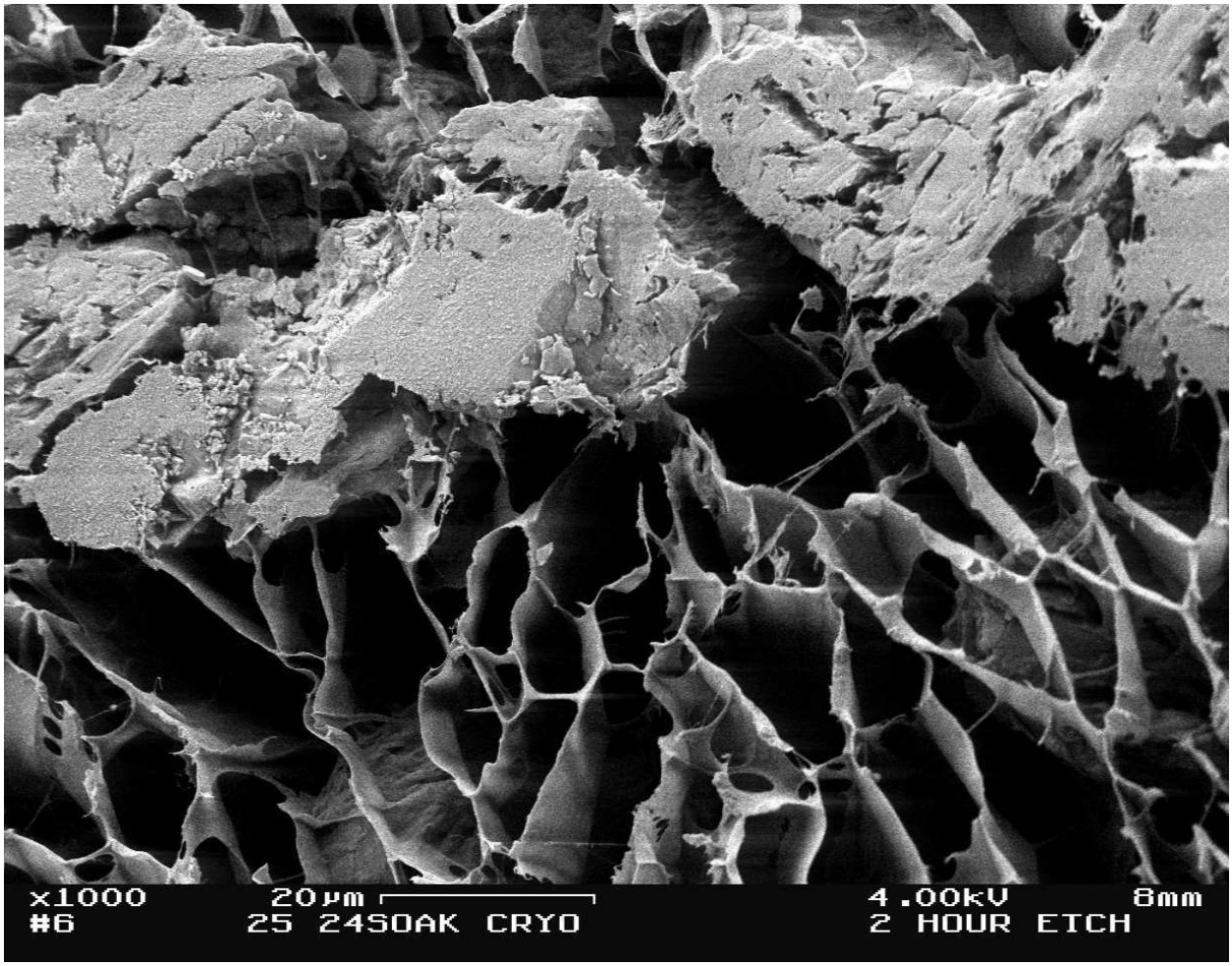

Figure 6.10.2. Cross-sectional view of tablet 1b

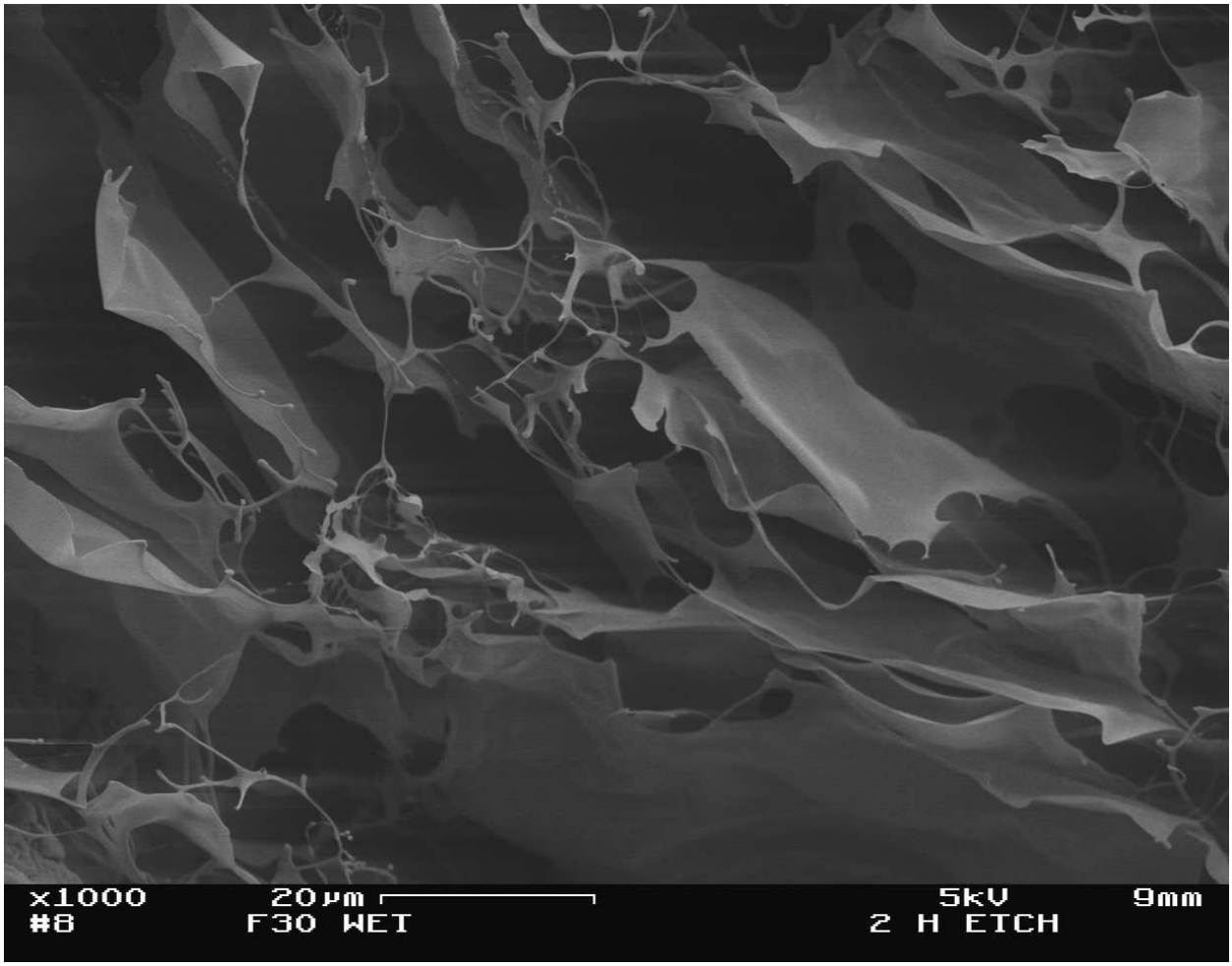

Figure 6.10.3. Cross-sectional view of tablet 1c

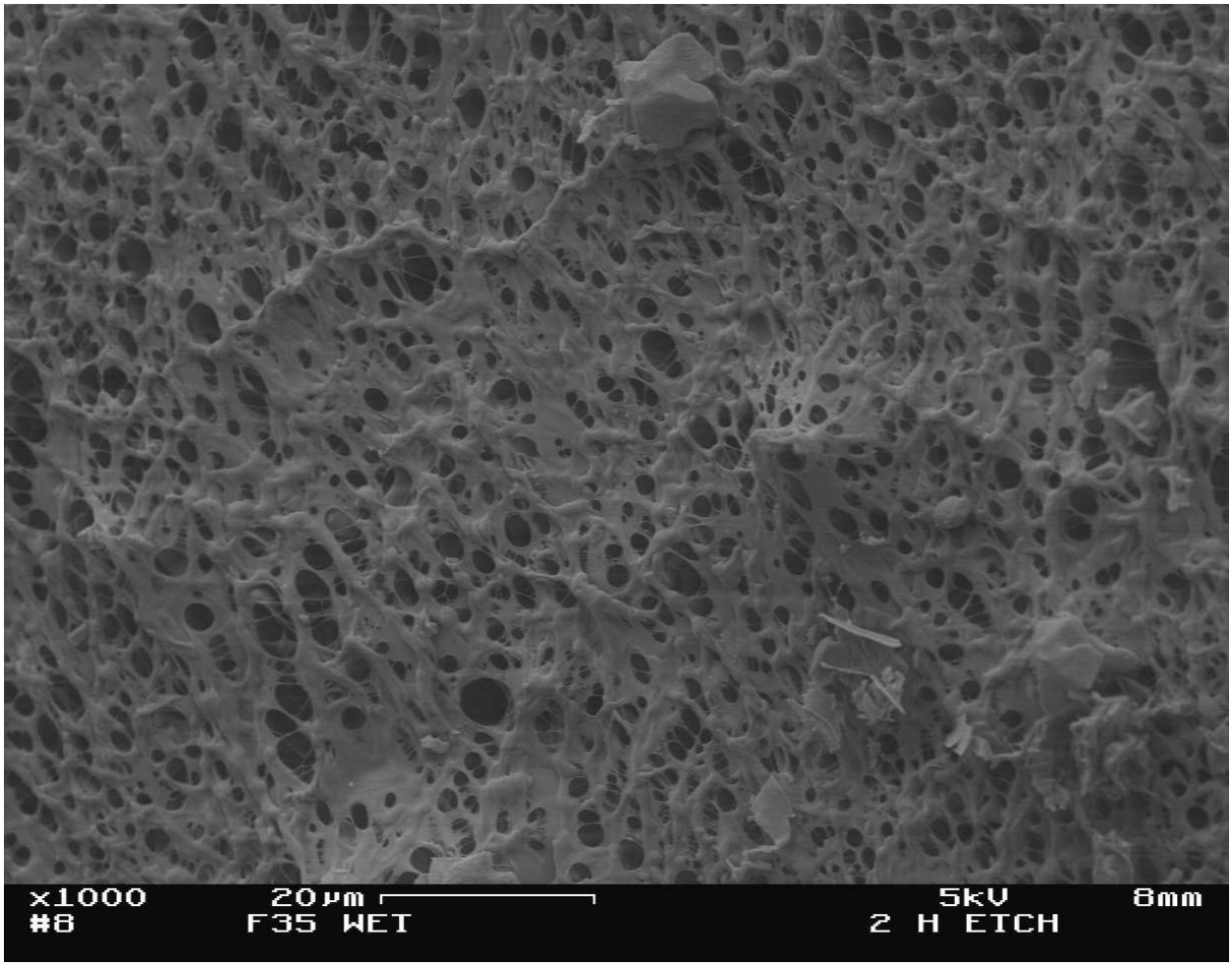

Figure 6.10.4. Cross-sectional view of tablet 1d

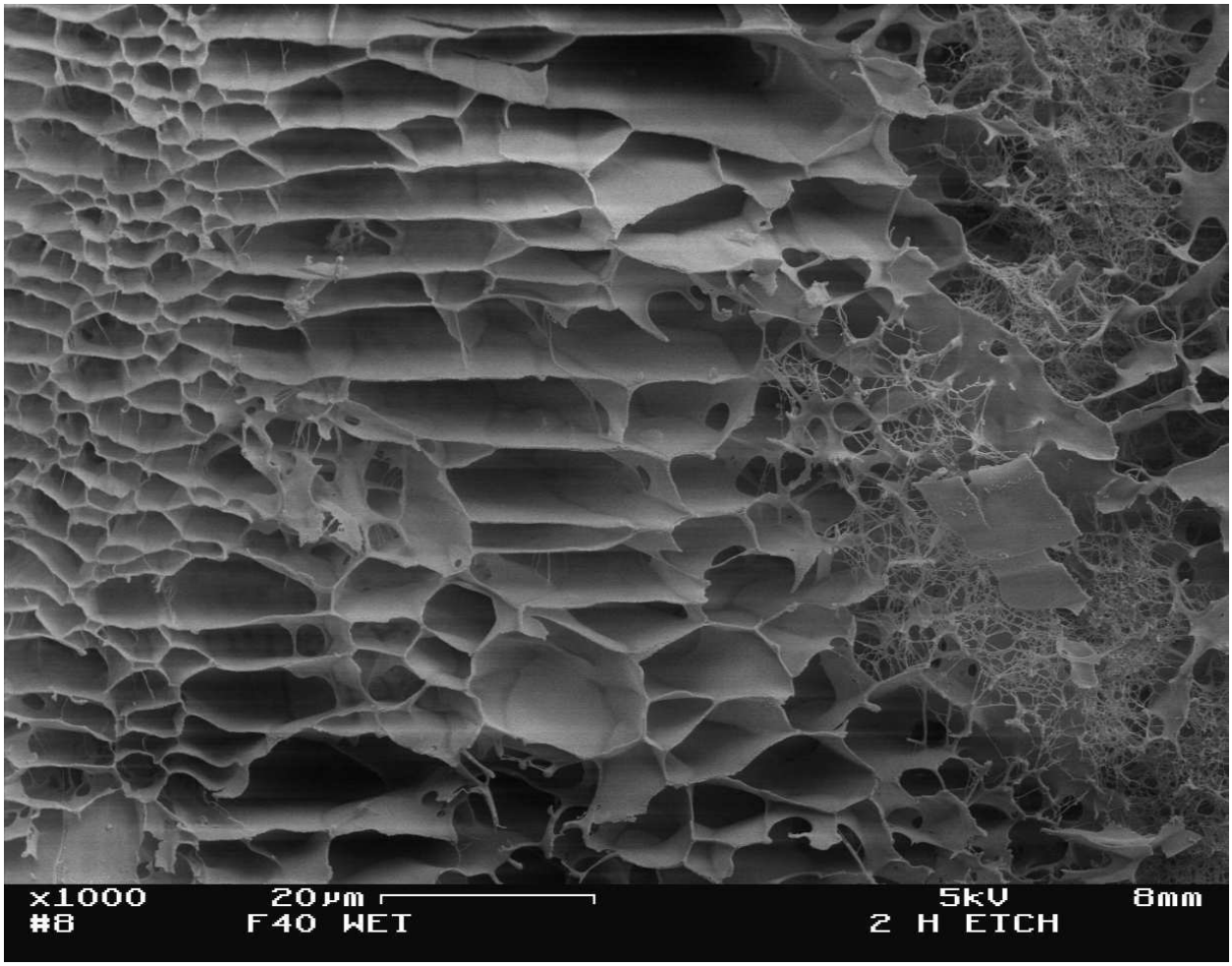

Figure 6.10.5. Cross-sectional view of tablet 1e

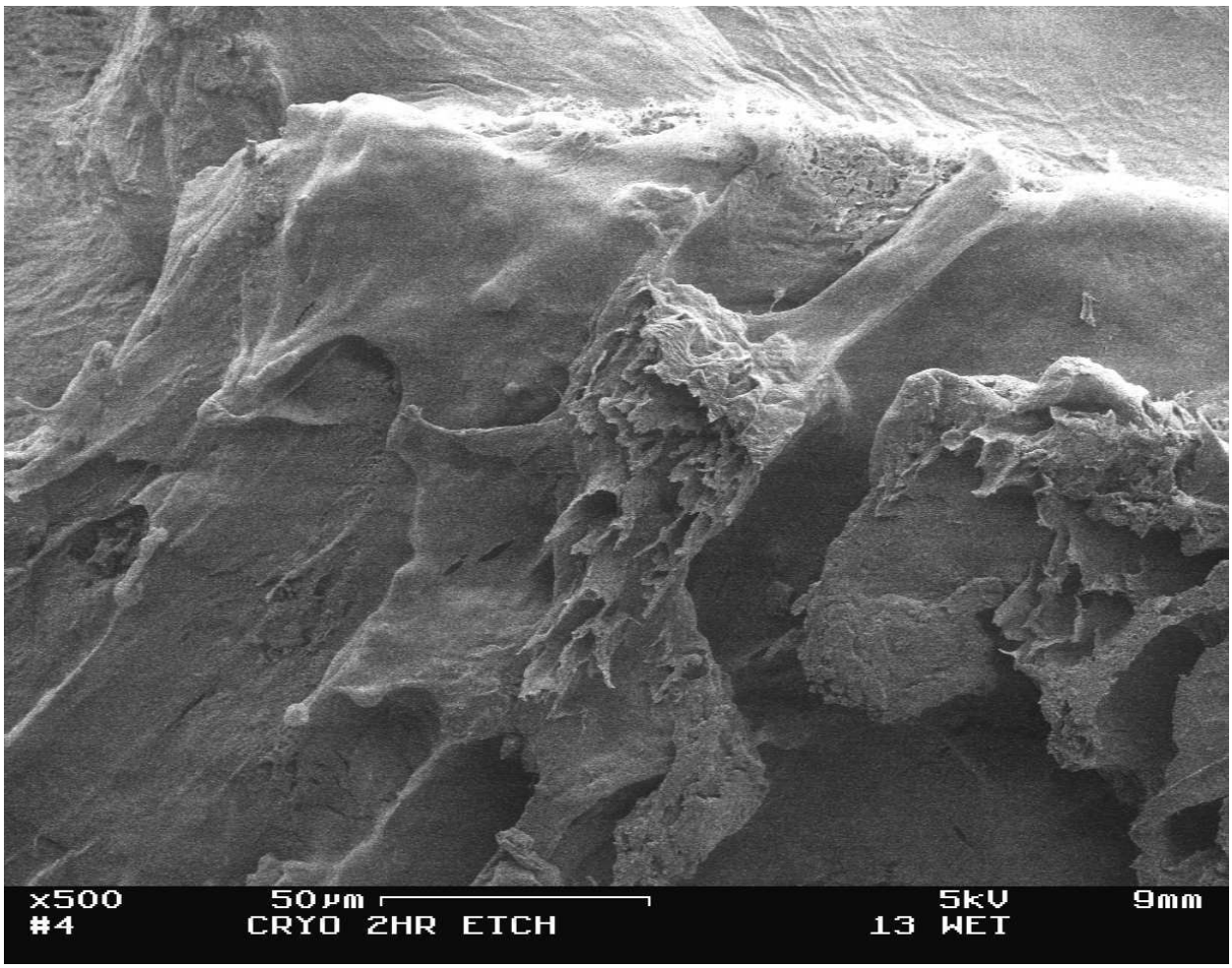

Figure 6.10.6. Surface topography of tablet 2a

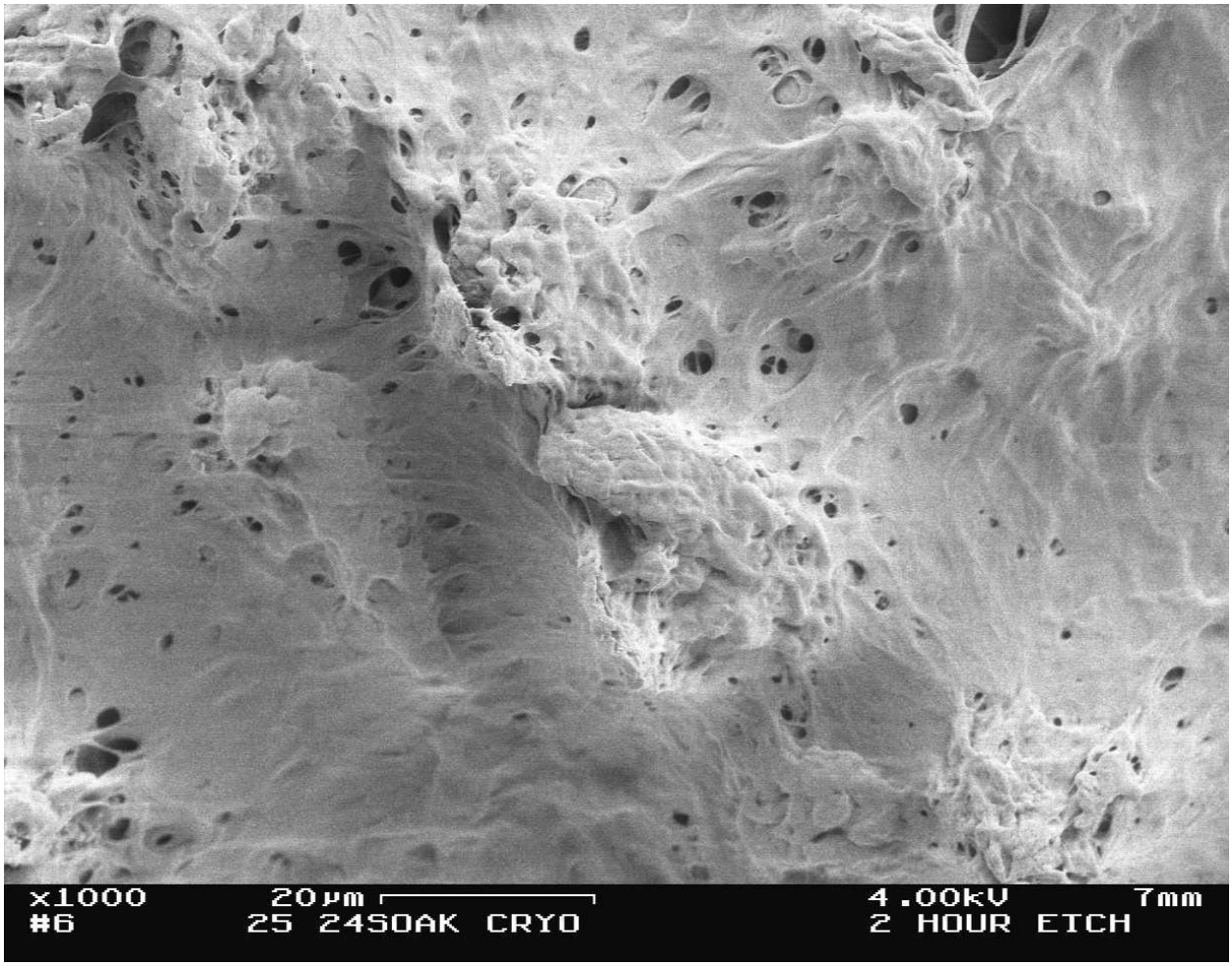

Figure 6.10.7. Surface topography of tablet 1b

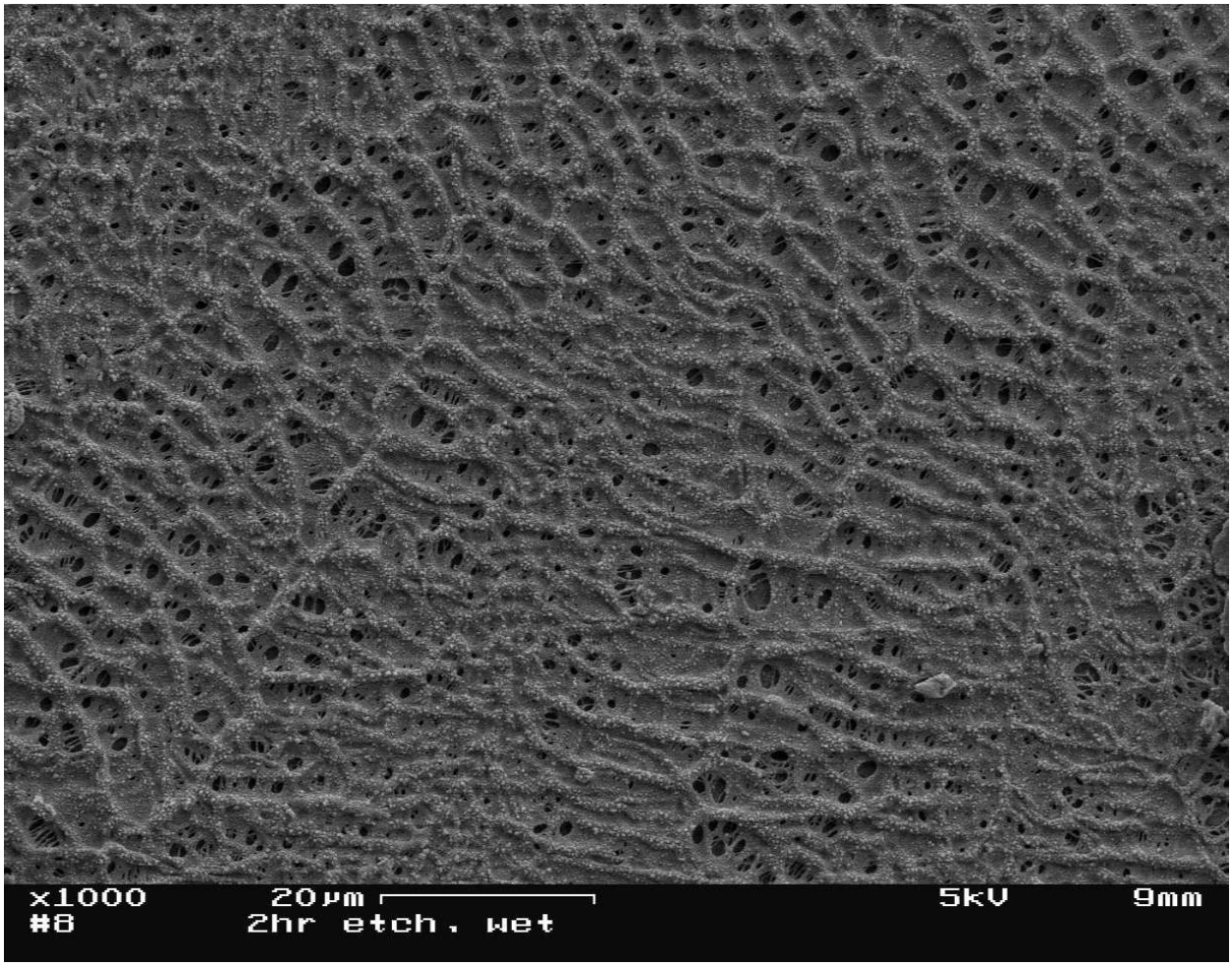

Figure 6.10.8. Surface topography of tablet 1c

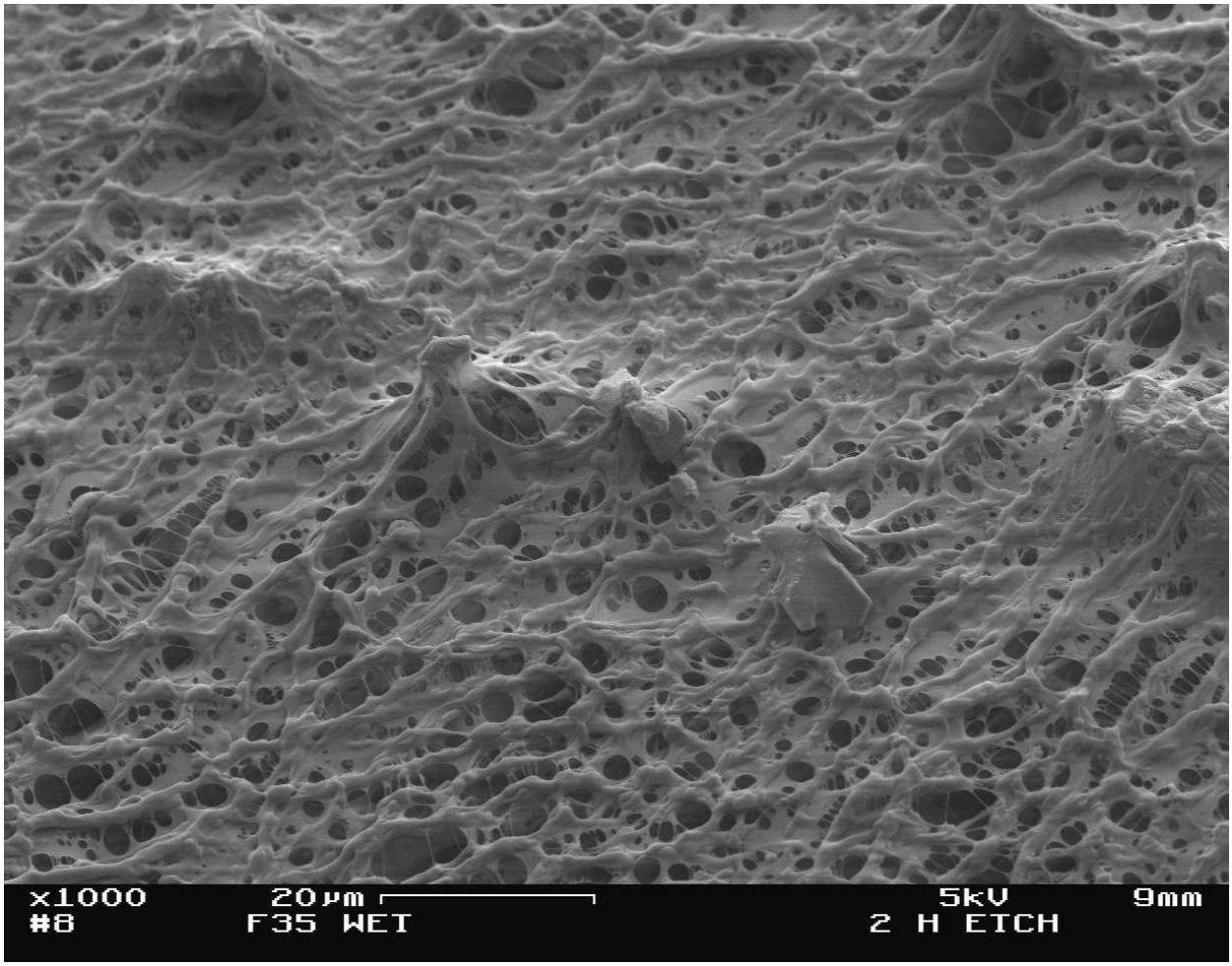

Figure 6.10.9. Surface topography of tablet 1d

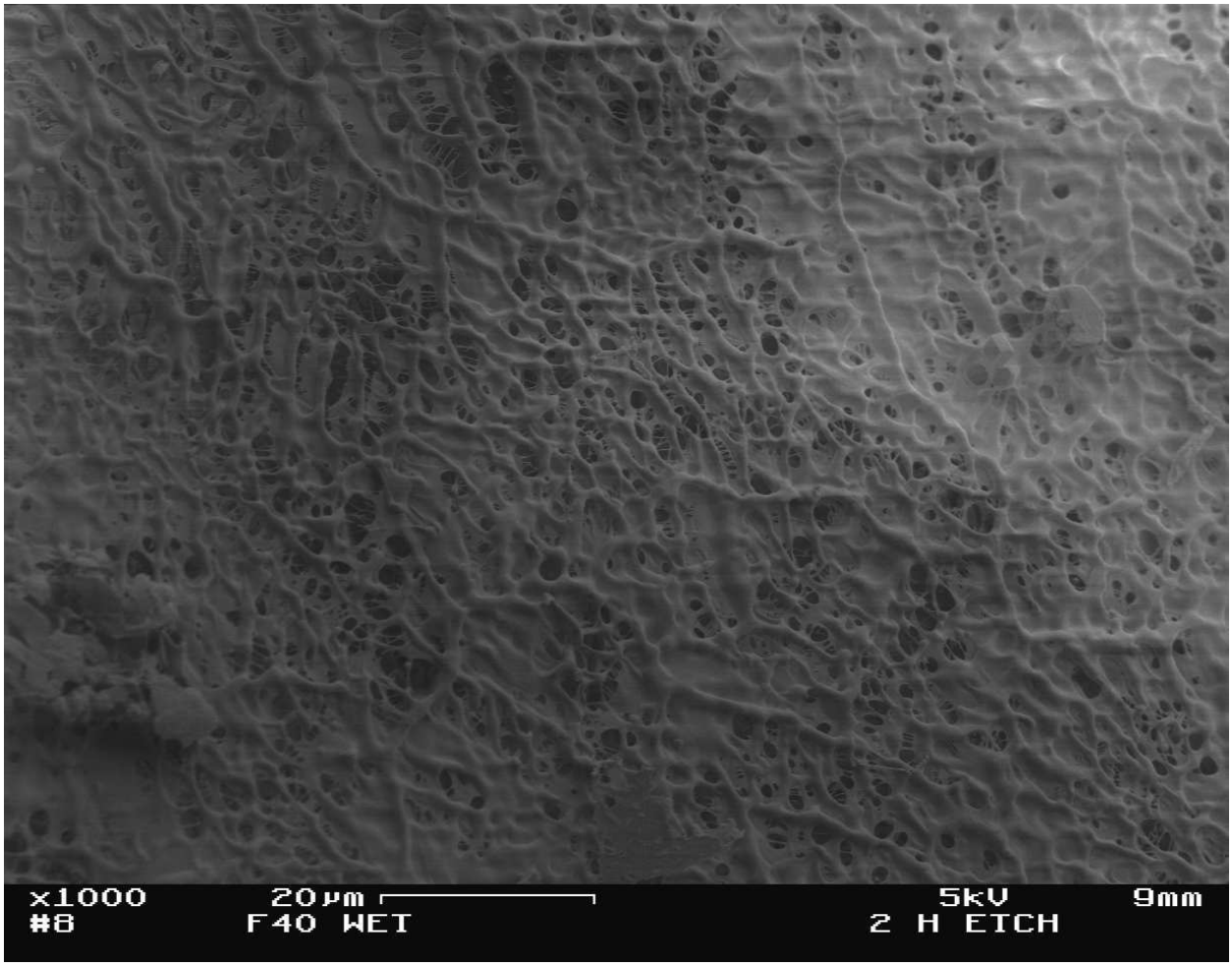

Figure 6.10.10. Surface topography of tablet 1e

4. Conclusions

Matrix tablets that contained a blend of carrageenans and cellulose ethers successfully sustained the release of ibuprofen for a period of 10 to 12 hrs. The release of the drug was primarily controlled by the amount of the gelling polymers, except that a minimum amount of viscosity increasing polymer was necessary to hold the matrix together while swelling. The presence of viscosity enhancers in the polymer blend retarded matrix hydration. Anionic polymers had possible ionic interactions with the nonionic polymers which resulted in favorable increases in the water uptake capacity and gel viscosity, leading to a better control over the release of ibuprofen. Cross-sectional SEM images on hydrated tablets showed a highly porous network formed by hydration of the polymers. These pores are indicative of the possible routes of the drug to travel. Ibuprofen was predominantly released by anomalous (non-Fickian) mechanism that is diffusion through the honeycomb network and polymer relaxation. Both lambda and iota carrageenan can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets.

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CHAPTER 7

CONCLUSIONS

This study showed that the solubility of both racemic ibuprofen (IB) and S (+)-ibuprofen (SIB) was exponentially increased by non polar cosolvents such as propylene glycol (PG) and polyethylene glycol (PEG). Glycerol was not very effective in increasing the aqueous solubilities of both the compounds, while sorbitol solution had a minimal effect on their solubility. Cosolvents like PEG and PG, that are significantly less polar than water, proved to be better solubilizers for both the forms of ibuprofen. The increase in the solubility of the drugs was due to a decrease in the polarity of the system. Derivatized cyclodextrins (CDs) such as hydroxypropyl beta cyclodextrin (HPCD) and beta cyclodextrin sulfobutyl ether sodium salt (CDSB) also increased the aqueous solubility of both SIB and IB. The phase solubility diagrams indicated the formation of soluble inclusion complexes between the drugs and HPCD and CDSB which was of 1:1 stoichiometry. In contrast, the addition of underivatized beta cyclodextrin reduced the solubility of racIB and SIB via the formation of an insoluble complex. The predominant mechanisms for the formation of inclusion complexes between the ibuprofen isomers and derviatized cyclodextrins were dipole or induced dipole-dipole interactions or van der Waals type of associations. These occur when the aromatic ring of the ibuprofen molecule fits in the hydrophobic cavity of the beta cyclodextrin molecule. Overall, the cosolvency approach was much more effective in increasing the aqueous solubility of both the compounds as compared to the molecular inclusion complexation process. Differential solubility behavior of SIB and IB was

observed under similar solvent conditions. Of the two compounds studied, greater equilibrium solubilities were observed for SIB. The reasons for the observed differences in solubility were attributed to the difference in their melting points and the thermodynamic parameters associated with solubilization were discussed. Thermodynamically, cosolvency was a predominantly entropy-driven mechanism while complexation was an enthalpy-driven process. Specific solubility behaviors of the chiral and racemic forms of ibuprofen need to be carefully considered during the formulation of liquid dosage forms of the drug.

The effect of solid additives on the dissolution rate of SIB was also evaluated via the formation of solid dispersion systems. Solid dispersions of S (+)-ibuprofen which were formulated using polyethylene glycol 8000 (PEG) were successful in increasing its dissolution rate. This was evident from comparison with the corresponding physical mixtures as well as the drug alone. Further, binary systems (drug and PEG 8000) containing higher drug loading (25%) did not show a marked improvement in the rate of dissolution. This indicates the importance of the drug to polymer ratio in the formulation of solid dispersion systems. Addition of a surfactant to the system (ternary systems) had a beneficial effect on the dissolution rate of the solid dispersion systems, while the type of surfactant used (anionic versus nonionic) did not have any significant effect. Physicochemical characterization by DSC and XRD indicated no chemical interactions between the drug and the various components. DCS endotherms of the binary and ternary dispersions and physical mixtures exhibited peak broadening. The XRD characterization showed that the dexIB spectrum was progressively masked by the signals from PEG 8000 and the surfactants. Further, as the concentration of dexIB increased its characteristic peaks started appearing in the spectrum. Both the DSC and the XRD characterization indicated the formation of an interstitial solid at low drug concentrations. A greater improvement in the solubility

characteristics of the drug was found by the incorporation of a surfactant to the system, in addition to the PEG. Thus many mechanisms such as improved solubilization, increase in the wettability, a reduction of particle size (due to partial crystallization of dexIB in the PEG matrix) and drug-polymer interactions dominated the mechanisms responsible for the improvement in the dissolution of dexIB from the dispersion systems.

The release rate of ibuprofen from various controlled-release tablet matrices was also investigated. The tablets were directly compressed using a blend of carrageenans and cellulose ethers. The effect of polymer concentration on the tablet matrices was studied. Most of the formulations showed linear release profiles (r^2 > = 0.96 - 0.99) and sustained the release of ibuprofen over 12-16 hrs. Tablet matrices that contained 1:2 blend of Viscarin and HPMC could sustain the release to the greatest amount (t_{50} (9.3 hr)). The release of the drug was primarily controlled by the amount of the gelling polymers. Further, a minimum amount of viscosity increasing polymer was necessary to maintain the matrix integrity while swelling. Cross-sectional SEM images of the swollen hydrated tablets showed a highly porous network formed upon polymer hydration. These pores are indicative of the possible routes of the drug to travel. Ibuprofen was predominantly released by an anomalous (non-Fickian) mechanism that is diffusion through the honeycomb network and polymer relaxation. Both lambda and iota carrageenan are effective when combined with cellulose ethers and can be used for the formulation of controlled-release ibuprofen tablets.

APPENDIX A

SOLUBILITY DATA OF RACEMIC AND S (+)-IBUPROFEN IN THE PRESENCE OF COSOLVENTS AND CYCLODEXTRINS

Table A1: Solubility of S (+)-ibuprofen in cosolvent/water systems

		Solubility(mg/ml)	
Cosolvent	Conc. (%v/v)	25 deg C	37 deg C
Glycerin	20	0.14	0.705
	40	0.19	0.87
	60	0.3	1.205
	80	0.625	1.755
Sorbitol	20	0.11	0.6
	40	0.075	0.575
	60	0.055	0.735
	80	0.07	0.625
Propylene	20	0.16	0.31
glycol	40	0.49	1.4
	60	4.29	22.12
	80	32.41	101.265
PEG 300	20	0.42	0.52
	40	1.79	3.2
	60	29.62	62.65
	80	124.55	145.13

Table A2: Solubility of racemic ibuprofen in cosolvent/water systems

Solubility(mg/ml)			
Cosolvent	Conc. (%v/v)	25 deg C	37 deg C
Glycerin	20	0.09	0.65
	40	0.21	0.655
	60	0.465	0.605
	80	0.78	0.855
Sorbitol	20	0.1	0.17
	40	0.18	0.17
	60	0.27	0.2
	80	0.3	0.32
Propylene	20	0.19	0.36
glycol	40	0.55	1.29
	60	3.2	7.21
	80	23.16	66.27
PEG 300	20	0.49	0.6
	40	1.24	2.83
	60	13.42	17.66
	80	110.64	135.45

Note: Solubility of S (+)-Ibuprofen in water at 25^0 C and 37^0 C is 0.081mg/ml and 0.11mg/ml respectively; Solubility of (±)-ibuprofen in water at 25^0 C and 37^0 C is 0.12mg/ml and 0.144mg/ml respectively.

Table A3: Solubility of racemic and S (+)-ibuprofen in HPCD and CDSB

Conc. (mM)	racIB (mM) 25 deg C	racIB (mM) 37 deg C	SIB (mM) 25 deg C	SIB (mM) 37 deg C
HPCD				
34.8	25.06	28.84	26.61	32.82
69.59	47.46	53.56	30.97	46.15
104.38	66.8	77.51	63.45	69.07
139.18	83.66	98.3	80.32	84.73
173.97	102.08	119.1	95.1	95.73
CDSB				
23.1	17.26	20.7	19.34	18.86
46.2	32.43	39.36	32.72	34.71
69.4	46.63	58.75	49.39	47.89
92.5	56.96	69.37	62.43	61.08
115.6	65.83	89.24	69.37	73.19

Note: HPCD is hydroxypropyl beta cyclodextrin

CDSB is beta cyclodextrin sulfobutyl ether sodium salt

APPENDIX B

THERMODYNAMIC PARAMETERS ASSOCIATED WITH THE SOLUBILIZATION OF RACEMIC AND S (+)-IBUPROFEN IN THE PRESENCE OF COSOLVENTS AND CYCLODEXTRINS

Table B1: Thermodynamic data for S (+)-ibuprofen in cosolvent/water systems

S(+)-ibuprofen						
	Conc.	DH (cal/mol)	DG (cal/mol)		DS(cal /Mole K)	
Cosolvent			25 ^{0}C	37 ^{0}C	25 ^{0}C	37 ^{0}C
Glycerin	20	20059.25	-328.21	-1148.77	68.38	68.38
	40	18603.06	-509.16	-1278.39	64.1	64.1
	60	16596.61	-779.81	1479.18	58.28	58.28
	80	11114.35	-1214.71	-1710.93	41.35	41.35
Sorbitol	20	21282.78	-185.32	-1049.37	72	72
	40	26496.32	41.62	1023.14	88.73	88.73
	60	35005.88	225.39	-1174.46	116.65	116.65
	80	28829.85	82.5	-1074.53	96.42	96.42
Propylene	20	5431.54	-407.34	-642.34	19.58	19.58
Glycol	40	11380.05	-1070.52	-1571.63	41.76	41.76
	60	20421.28	-2356.09	-3272.84	76.39	76.39
	80	12749.95	-3554.3	-4210.51	54.69	54.69
PEG 300	20	-1426.64	-979.18	-961.17	-1.5	-1.5
	40	4199.29	-1838.18	-2081.18	20.25	20.25
	60	6774.86	-3500.96	-3914.54	34.47	34.47
	80	-2355.48	-4351.98	-4432.34	6.7	6.7

Table B2: Thermodynamic data for (±)-ibuprofen in cosolvent/water systems

Racemic ibuprofen						
	Conc.	DH (cal/mol)	DG (cal/mol)		DS(cal /Mole K)	
Cosolvent			25 ^{0}C	37 ^{0}C	25 ^{0}C	37 ^{0}C
Glycerin	20	27399.25	168.75	-927.23	91.33	91.33
	40	14540.7	-333.3	-931.95	49.89	49.89
	60	1150.71	-804.32	-883.01	6.56	6.56
	80	-1473.94	-1110.81	-1096.2	-1.22	-1.22
Sorbitol	20	5246.36	106.32	-100.56	17.24	17.24
	40	-3755.27	-241.96	-100.56	-11.78	-11.78
	60	-7475.85	-482.21	-200.731	-23.46	-23.46
	80	-1891.55	-544.64	-490.43	-4.52	-4.52
Propylene	20	6907.24	-273.99	-563.03	24.09	24.09
Glycol	40	10175.34	-903.8	-1349.71	37.16	37.16
	60	9560.29	-1947.24	-2410.39	38.6	38.6
	80	13220.33	-3120.02	-3777.69	54.81	54.81
PEG 300	20	221.63	-835.35	-877.89	3.55	3.55
	40	9757.04	-1385.49	-1833.96	37.37	37.37
	60	1324.76	-2796.68	-2962.57	13.82	13.82
	80	218.52	-4046.65	-4218.31	14.31	14.31

Table B3: Thermodynamic parameters of S (+)-ibuprofen cyclodextrin complexation

S(+)-ibuprofen						
	Conc.	DH(Cal/mol)	DG (cal/mol)		DS (cal/mole K)	
Type			25 deg C	37 deg C	25 deg C	37 deg C
HPCD	5	-1487.91	-2502.23	-2543.06	3.4	3.4
	10	1407.86	-2592.18	-2753.18	13.42	13.42
	15	-3397.08	-3017.1	-3001.8	-1.27	-1.27
	20	-3878.64	-3156.78	-3127.73	-2.42	-2.42
	25	-4596.27	-3256.9	-3202.99	-4.49	-4.49
CDSB	5	-5086.12	-2313.14	-2201.53	-9.3	-9.3
	10	-3794.35	-2624.66	-2577.58	-3.92	-3.92
	15	-5170.54	-2868.7	-2776.06	-7.72	-7.72
	20	-5034	-3007.51	-2925.95	-6.79	-6.79
	25	-3874.47	-3069.9	-3037.51	-2.69	-2.69
CD	5	15342.25	-1224.11	-1890.88	55.56	55.56
	10	8449.61	-1013.44	-1394.31	31.74	31.74
	15	36149.73	41.62	-1411.67	121.12	121.12
	20	31312.62	-128.84	-1394.31	105.46	105.46
	25	39986.66	3.38	-1605.88	134.11	134.11

Table B4: Thermodynamic parameters of (±)-ibuprofen cyclodextrin complexation

Racemic Ibuprofen						
	Conc.	DH(Cal/mol)	DG (cal/mol)		DS (cal/mole K)	
Type			25 deg C	37 deg C	25 deg C	37 deg C
HPCD	5	-727.95	-2231.49	-2292	5.04	5.04
	10	-1017.99	-2609.51	-2673.56	5.34	5.34
	15	-601.97	-2812.37	-2901.33	7.41	7.41
	20	-406.12	-2945.62	-3047.83	8.52	8.52
	25	-515.55	-3063.56	-3166.11	8.55	8.55
CDSB	5	-73.41	-2009.57	-2087.5	6.49	6.49
	10	98.19	-2383.76	-2483.66	8.33	8.33
	15	657.92	-2599.43	-2730.53	10.93	10.93
	20	138.64	-2717.94	-2832.91	9.58	9.58
	25	1785.85	-2803.49	-2988.2	15.39	15.39
CD	5	9466.97	-1055.1	-1478.59	35.29	35.29
	10	17893.2402	-751.02	-1501.42	62.53	62.53
	15	20959.17	-635.98	-1505.15	72.43	72.43
	20	21912.91	-573.55	-1478.59	75.42	75.42
	25	21988.1	-627.45	-1537.69	75.85	75.85

APPENDIX C

DSC ENDOTHERMS OF RACEMIC AND S (+)-IBUPROFEN

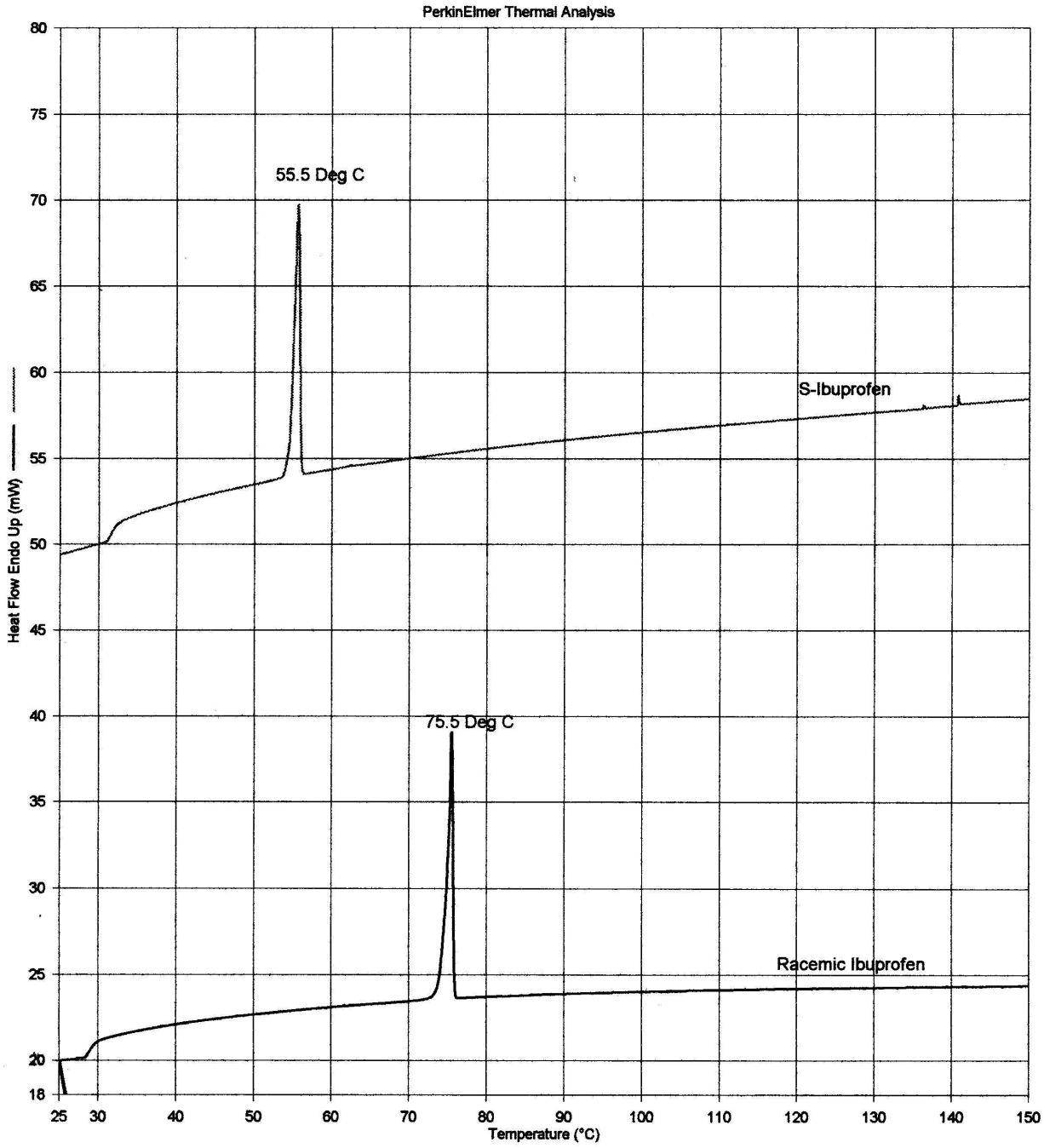
PerkinElmer Thermal Analysis
55.5 Deg C
S-Ibuprofen
75.5 Deg C
Racemic Ibuprofen
Heat Flow Endo Up (mW)
Temperature (°C)
80
75
70
65
60
55
50
45
40
35
30
25
20
18
25
30
40
50
60
70
80
90
100
110
120
130
140
150

Figure C1