PREPARATION AND EVALUATION OF TABLETED MICROSPHERES OF

IBUPROFEN ENCAPSULATED IN BEESWAX

by

SWATI P. SHAH

(Under the Direction of A.C. CAPOMACCHIA)

ABSTRACT

Ibuprofen was encapsulated with beeswax by the hydrophobic congealable disperse phase method. Incorporation of stearyl alcohol in the formulation decreased the average size of the microspheres and led to a modified drug release. The microspheres showed a log-normal particle size distribution and a high drug encapsulation efficiency of about 94%. The *in vitro* release of ibuprofen from the microspheres could be modified according to the size distribution of the microspheres. Higuchi spherical matrix dissolution kinetics was followed. The appropriate size fraction of the microspheres was blended with microcrystalline cellulose and each formulation was compressed at different pressures. The effect of the compression pressure on various tablet properties was determined. Tableted microspheres appeared deformed but intact on the scanning electron micrographs. Drug release from the tableted microspheres was slightly slower than that from uncompressed microspheres. Increasing compression pressure led to a small decrease in drug release rate from the tableted microspheres.

INDEX WORDS: Microspheres, Tablet, Compression pressure, Matrix microspheres,

Ibuprofen, Hydrophobic Congealable Disperse Phase, Beeswax,

Dissolution.

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B.Pharm., Bombay College of Pharmacy, India, 2002

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment

of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2004

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August, 2004

To Mamma, Daddy, Tina and Kunal

ACKNOWLEDGEMENTS

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INTRODUCTION

Controlled release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing the active ingredient over an extended period of time after the administration of a single dose. Most oral sustained release products have been formulated as non-disintegrating tablets or encapsulated particles (5). Encapsulated controlled release dosage forms have specific advantages over the core tablet design. Disintegrating compressed tablets containing encapsulated drug particles can combine the advantages of tablet dosing as well as controlled release particulate therapy if the controlled release particles can withstand compression into tablets and still maintain controlled release properties. The disintegrating tablets promote rapid break up of the tablet matrix into smaller subunits to allow access of the GI fluid to the controlled release particles. The sustained release offered by this mechanism offers several advantages over non-disintegrating tablet systems, such as ready distribution over a large surface area, more reproducible drug release rate, less GI tract irritation and lower chance of catastrophic failure of the drug release mechanism, that is, less chances of dose dumping. Release from multiple unit products is also less dependent on the gastric transit time.

Microencapsulation is a means of encapsulation of small particles of solids or droplets of liquids and dispersions either by applying relatively thin coatings or the formation of small spherical polymeric or waxy matrices containing drug. Several microencapsulation methods such as coacervation phase separation, emulsion solvent evaporation, congealable disperse phase and interfacial polymerization have been described in the literature. Considering the relative insolubility of ibuprofen in water and solubility in excess of 5% in most organic solvents, the hydrophobic congealable disperse phase procedure becomes the method of choice. Other

advantages of employing this method include its simplicity, economic advantage and avoiding the use of organic solvents.

Microcapsules and matrix microspheres have been tableted to control the release of the drug and to avoid gastric irritation (6). Tableted microspheres of ibuprofen have an advantage over tablets in that the small particles help the drug moieties to be widely distributed throughout the gastrointestinal tract, thus improving drug absorption. Considering the GI tract irritation of the NSAID ibuprofen, a multiple unit dosage system in the form of wax matrix microspheres would protect the gastric mucosa from the irritant effect of the drug and thus decrease the magnitude of this side effect.

OBJECTIVE

The objectives of this study were:

1. To develop and evaluate controlled release microspheres of ibuprofen in wax by the hydrophobic congealable disperse phase method.

2. To characterize the microparticulate drug delivery system using particle size analysis, entrapment efficiency, *in vitro* drug release (dissolution testing) and scanning electron microscopy (SEM).

3. To prepare tablets containing the microspheres and to study the effect of compression pressure on the physical properties of the tablet and on the drug release from the tableted microspheres.

LITERATURE REVIEW

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of the drug in the plasma (or at the site of action) and maintains it constant for the entire duration of the treatment. This is possible through the administration of a conventional dosage form in a multiple dose regimen at a particular frequency. The frequency of administration or the dosing interval of any drug depends on its half-life or mean residence time and its therapeutic index.

Conventional dosage form therapy has a number of limitations such as:

1.   For a drug with a short half-life, frequent administration is necessary. This may result in poor patient compliance with increased chances of missing a dose.

2.   A typical peak-valley plasma concentration time profile is obtained and this makes attainment of steady-state conditions difficult.

3.   The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with a small therapeutic index.

There are two ways to overcome such a situation:

1.   Development of new, better and safer drugs with long half-lives and large therapeutic indices.

2.   Effective and safer use of existing drugs through concepts and techniques of controlled and targeted delivery systems.

The second approach has the advantage of reducing the cost of discovering, testing and commercializing new drug molecules. There is also a need to design effective delivery systems as it presents an opportunity to utilize new technologies to make the drug dosing more convenient to the patient, improve the patient compliance, and to introduce an element of novelty that will extend the proprietary position of the final product.

The basic objective of dosage form design is to optimize the drug delivery so as to achieve a measure of control with respect to the spatial placement and the temporal rate in the body. The therapeutic amount of the drug must be delivered to the required site in the body to achieve promptly and to maintain the desired drug concentration (1).

The potential advantages of a controlled delivery system include:

1. Reduction or elimination of fluctuations in the drug blood level allows better disease state management.

2. Patient compliance is improved because of reduced dosing frequency

3. Less total drug is employed. This helps to minimize local or systemic side effects by decreasing drug accumulation in chronic therapy

4. Improved bioavailability for some drugs (2).

5. Reductions in health care costs through improved drug therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.

Oral Controlled Release Systems:

The oral route has been the most popular and successfully used route used for controlled delivery of drugs. The reasons for its popularity include:

1.   The administration of drugs by this route is easy and convenient.

2.   There is great flexibility in dosage form design because of the versatility of the GI anatomy and physiology

3.   Ease of production and low cost of production compared to the production of dosage forms that are formulated for injectable and topical use (3).

Microencapsulation involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size (6). When the encapsulated substance is present as a distinct single core (droplet or a crystal that is not necessarily spherical) surrounded by a solid envelope, the system is known as a reservoir microcapsule. Alternatively when the core material is dispersed as many discrete core particles or droplets, or is dissolved within the polymer, it is more accurately referred to as a matrix microsphere or matrix microparticle (7).

The process of microencapsulation has several advantages. Microspheres are a class of multiple-unit dosage forms and offer the advantage of combining various types of subunits in a single system and offer diversity in achieving dissolution profiles (8). The smallness of the particles helps the drug moieties to be widely distributed throughout the gastrointestinal tract, thus improving drug absorption. In addition, the microcapsules can spread over a wide area in the GI tract and thus minimize GI toxicity of the NSAID drug. The uniqueness of microencapsulation is

the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications (6).

There are several methods for encapsulating the drug. These can be broadly classified into two types, physical methods and chemical methods.

The chemical methods to encapsulate a drug core include:

1.   Coacervation- Phase separation- In this process, the core is dispersed into a solution of the coating polymer. The coating polymer is then converted from a solublized state to an immiscible polymer in liquid state by the careful change in temperature or by the addition of a salt or a non- solvent in the presence of insoluble core particles. The immiscible liquid polymer is then deposited on the core by adsorption. The adsorbed polymer is then converted to a rigid coating by thermal, cross-linking or desolvation techniques to form a microcapsule (6). Miller *et al.* dispersed ethyl cellulose in cyclohexane to yield a polymer concentration of 2% by weight. This mixture was heated to its boiling point to form a homogenous polymer solution. Paracetamol was used as the core material and was dispersed in the polymer solution with stirring. Allowing the mixture to cool with stirring effected the phase separation of the ethyl cellulose and the microencapsulation of paracetamol. Allowing the mixture to cool further to room temperature accomplished the solidification of the coating. The microcapsules were then collected from cyclohexane by filtration, decantation or centrifugation techniques (9).

2.   Interfacial polymerization: This technique involves the reaction of monomeric units of two reactive polymers at the interface existing between the two immiscible phases to form a film

that encapsulates the dispersed core. One of the monomers is present in the aqueous disperse phase containing a solution or dispersion of the core. The other polymer is present in the aqueous external phase (11).

The physical methods used in microencapsulation include:

1. Spray drying

2. Centrifugal extrusion

3. Spinning disk or rotational suspension separation

4. Fluidized bed coating

5. Emulsion- Solvent Evaporation

6. Congealable Disperse Phase Emulsification

1. Emulsion-Solvent Evaporation: In this process, the microcapsule coating is dissolved in a volatile solvent. The core is the dispersed into the coating polymer solution. The coating solution is added with agitation to a liquid manufacturing vehicle in which the core, the coating polymer and the volatile solvent are all immiscible. The mixture is then heated, if necessary, to evaporate the solvent. This causes the coating polymer to shrink around the core. Once all the solvent is evaporated the temperature of the liquid manufacturing phase is reduced to ambient temperature with constant agitation. Perumal *et al*. prepared modified release microcapsules of ibuprofen using this method (10).

2. Congealable disperse phase encapsulation: This is a relatively simple microencapsulation procedure. It involves dispersing or dissolving the core at an elevated temperature in a

hydrophilic or hydrophobic vehicle that solidifies when cooled to normal ambient temperature (11). The hydrophilic vehicles include gelatin, agar and starch solutions. Suitable hydrophobic phases include waxes and hydrogenated castor oil. The core must be stable at the melting temperature of the wax.

Microencapsulation by the melting solidification method (Hydrophobic Congealable disperse phase encapsulation):

MICROENCAPSULATION BY EMULSION-SOLIDIFICATION (HOT MELT)

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  ┌──────────────────┐      ┌──────────────────┐
  │ MOLTEN COATING   │      │    ACTIVE        │
  │ MATERIAL         │      │  CONSTITUENT     │
  └──────────────────┘      └──────────────────┘
              ┌──────────────────┐
              │   DISPERSION     │
              └──────────────────┘

 HOT WATER    ┌──────────────────┐
 OR OIL       │   HOT EMULSION   │
              └──────────────────┘
                    ? T
 COLD WATER   ┌──────────────────┐            ┌──────────────┐
 OR OIL       │ SOLIDIFICATION   │   WATER OR  │ MICROSPHERES │
              │ OF THE EMULSION  │   SOLVENT   └──────────────┘
              └──────────────────┘

       ┌────────────┐  ┌──────────┐  ┌──────────┐  ┌──────────┐
       │ SEPARATION │  │ WASHING  │  │ DRYING   │  │ SIFTING  │
       └────────────┘  └──────────┘  └──────────┘  └──────────┘

 RECYCLING ──── WATER OR OIL
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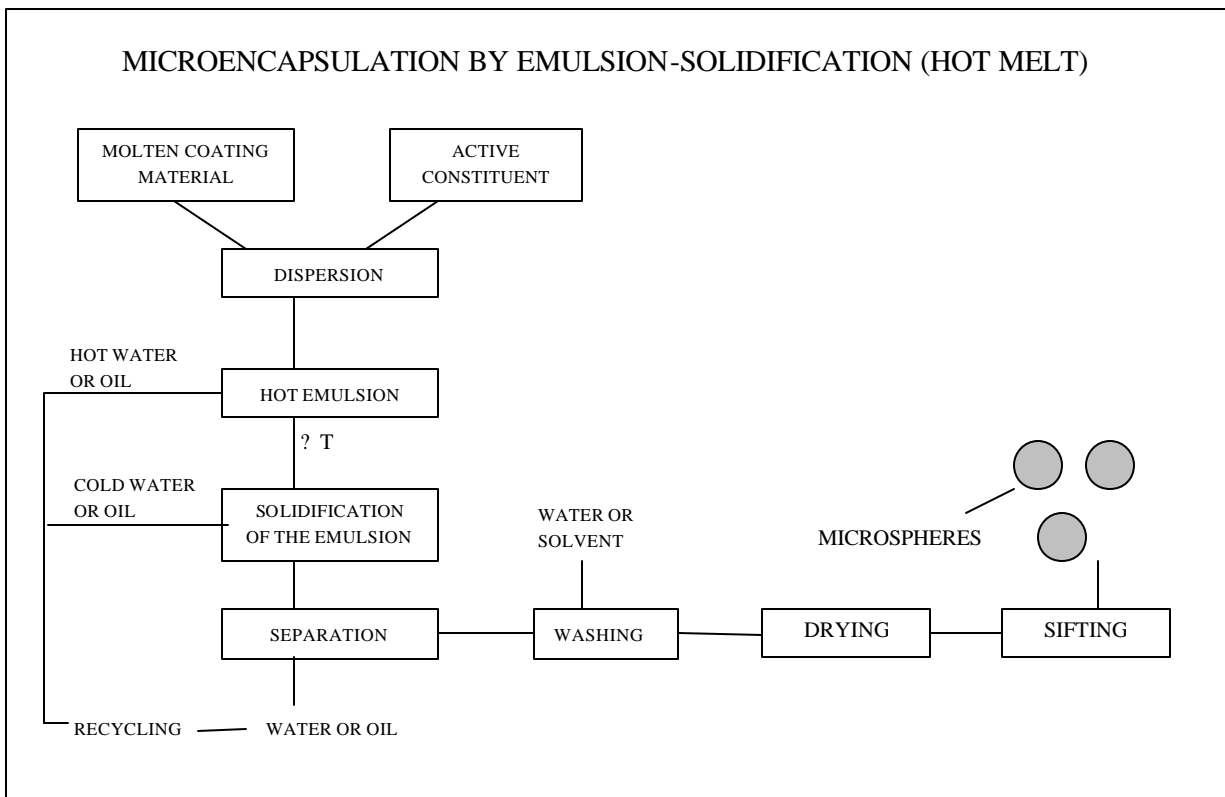
Figure 1. Hydrophobic Congealable disperse phase encapsulation

In this method, the active constituent is dissolved or dispersed in a molten substance (waxes, fats or oils with low melting points). The mixture is emulsified in a dispersing phase such as hot

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water, organic solvent, inorganic or vegetable oil, which dissolve neither the molten polymer (wax) nor the active drug. Encapsulation is carried out when the molten polymer droplets solidify coating the drug as a result of lowering the temperature. This process results in the formation of matrix type microspheres. The choice of encapsulation materials has been directed towards waxes and polymers with melting points preferably between 50° and 100°C and which give low viscosity molten phases.

When the external phase is water, this process has the advantage of using no organic solvent. The stabilization of the microdrops of molten wax can be obtained by adding a surfactant such as sodium lauryl sulfate, in the case of waxes with low hydrophilicity. As in the case of the emulsion solvent evaporation processes, water insoluble substances can be encapsulated using direct emulsion (o/w), the active drug being dissolved or dispersed in the molten wax. In the case of water-soluble substances, following emulsification of an aqueous solution of the active constituent in the molten wax, the emulsion formed is redispersed in an external phase (w/o/w). Microspheres measuring 20-500 microns are generally obtained. The process of preparing microcapsules usually involves several variables and the development of an ideal formulation procedure involves optimizing the levels of the variables involved. Experimental design models are used to identify the most suitable combination of variables to optimize the microspheres for properties such as drug loading, dissolution profiles, particle size distribution, and concentration of the excepients used. The rate of release in the aqueous phase by diffusion of the active drug depends on the particle size distribution (the size of the particles mainly being controlled by the rate of stirring), the active constituent content and the degree of hydrophilicity of the wax.

Adeyeye and Price used the congealable disperse phase method to prepare sustained release microspheres of the hydrophobic drug ibuprofen (12). The drug was dissolved in a molten

ceresin wax and a one-phase melt was obtained. A dispersant solution (5% PVP) at 5°C above the melting point of the wax phase was added to the melt with constant stirring to form an o/w emulsion. Hardening of the internal oily phase was accomplished by rapidly pouring the emulsion volume of ice- cold water to generate the microspheres.

Draper and Becker to prepare sulphaethylthiadazole by dispersion the drug in molten bleached beeswax or glycowax S-932 used this method (13). The wax-drug mixture was emulsified into hot water containing a surfactant and the o/w emulsion formed was stirred while the temperature was gradually lowered to room temperature and the drug wax particles obtained were filtered, washed with water and dried. Bodemeier used this method to prepare microspheres of the water-soluble drug pseudoephedrine hydrochloride by the multiple emulsion method (w/o/w). A heated aqueous drug solution was emulsified into a wax melt yielding a w/o emulsion. This primary emulsion was then emulsified into a heated aqueous external phase (w/o/w). On cooling and congealing the wax phase, the drug- loaded microspheres were formed (14).

Waxes:

Waxes are defined as any of a class of pliable substances, organic compounds of animal, plant, mineral, or synthetic origin, less greasy, harder, and more brittle than fats.

Waxes contain mostly compounds of high molecular weight (fatty acids, alcohols, and saturated hydrocarbons). Many melt at moderate temperatures and form hard films that can take a high polish. Animal and plant waxes are esters of fatty acids and either a sterol or a straight-chain higher alcohol (e.g., cetyl alcohol).

Animal waxes include beeswax; wool wax (lanolin), used in pharmaceuticals and cosmetics; and spermaceti (from sperm whales).

Plant waxes include carnauba wax, candelilla wax, and sugarcane wax, used in polishes.

About 90% of the waxes in commerce are recovered by dewaxing petroleum. There are three main types: paraffin, microcrystalline wax and petrolatum. Earth wax includes ozokerite, the origin of which is believed to be linked to that of petroleum. It is derived from the carbonization and concomitant distillation of animal or vegetable remains, under the heat and great pressure deep under the earth's surface, during one of the middle periods in geological history.

Synthetic waxes (CARBOWAX), derived from ethylene glycol, are commonly blended with petroleum waxes.

Microcrystalline wax and Beeswax were used in this study, and an account of these waxes is given below.

White beeswax:

USP defines white wax as the product of bleaching and purifying Yellow wax that is obtained from the honeycomb of the bee [*Apis mellifera* Linne (Fam. Apidae)]

White wax has a melting range of 61-65°C. Beeswax consists of 70-75% of a mixture of various esters of straight chain monohydric alcohols with even numbered carbon chains from C_{24} to C_{36} esterified with straight chain acids. The chief ester is glyceryl palmitate. Also present are free acids (about 14 %) and hydrocarbons (about 12%) as well as approximately 1% free wax alcohols and stearic esters of fatty acids. Beeswax is soluble in ether, chloroform, and carbon tetrachloride and it is insoluble in water. White wax is used to stabilize water in oil emulsions. It is also used as a film-coating agent in the sustained release tablets. White wax may be used in oral dosage forms to retard the absorption of an active ingredient from the stomach, allowing majority of the absorption to occur in the small intestine (15).

Microcrystalline wax: It is a petroleum wax consisting of very minute crystals (micro crystals) and is of high melting point. The melting range is 54.0-102.0 °C. The USPNF describes microcrystalline wax as a mixture of straight-chain, randomly branched chain, and cyclic hydrocarbons obtained by solvent fractionation of the still bottom fraction of petroleum by suitable means of dewaxing or de-oiling. The carbon chain lengths range from C_{41} to C_{57} and cyclic hydrocarbons are also present. Microcrystalline wax is used in oral controlled-release matrix formulations of drugs. It is soluble in benzene, chloroform and ether, slightly soluble in alcohol and practically insoluble in water (16).

The hydrophobic nature of the waxes enables their use as a coating material or a matrix carrier in a variety of controlled release dosage forms including tablets (Goodhart et al, 1974, Parab et al, 1986, Flanders et al, 1987, Kopcha and Lordi in 1988, Yu-E Zhang and Joseph B. Schwartz, 2001), or matrix or coated beads (Ghali et al. 1989, Bodemeier et al 1989) and microspheres (Adeyeye and Price, 1993, Varshosaz and Keihanfar, 2001) (17).

The advantage of using wax in the melting-solidification method over the use of a polymer in other chemical methods of microencapsulation, is the ease with which the low-viscosity melts can be processed, and the exclusion of the use of an organic solvent and toxic polymers. If an organic solvent is used, as in the coacervation method, it becomes important to ensure the absence of trace amounts of the solvents, and additional measures have to be considered for environmental and personnel safety.

Kinetics of Drug Release from Microspheres:

The drug may be distributed evenly or it may be partially dissolved through the polymer or macromolecular matrix. In case of a polymeric matrix, the drug molecules are either molecularly distributed in the polymer as a solid solution or they may be largely in the form of micronized particles or they may be in the form of particles whose size is a substantial fraction of that of the microspheres (18). The release rate of a drug from such a device is not zero order, since it decreases with time, but it may clinically be equivalent to constant release for many drugs. However the advantages of this system include the comparative ease of preparation and the ruggedness of the microspheres.

The rate of release of a drug dispersed in a solid matrix has been first described by T. Higuchi (19). Firstly it is assumed that the drug is uniformly distributed throughout the matrix with a concentration C_0 and this total amount of drug is substantially greater than the saturation solubility of the drug per unit volume in the matrix, C. This means that excess solute is present. Secondly it is assumed that the release medium is a perfect sink at all times. The third assumption is that the drug particles are much smaller than average distance of diffusion. Lastly, it is assumed that the diffusion coefficient of the drug (D) remains constant. The drug concentration is zero at the interface between the matrix and the external medium.

In the case of a planar slab model, it is assumed that the solid drug dissolves from the surface layer of the device, when this later becomes exhausted of the drug, the next layer begins to be depleted of the drug by dissolution and diffusion through the matrix into the external solution. In this way, the interface between the region that contains the dissolved drug and that containing the

dispersed drug moves into the interior as a front. The drug released from a uniform matrix in a planar slab model is given the equation, (2)

$$M = [C_s\, D_m\, (2C_0 - C_s)\, t]^{\frac{1}{2}}$$

Where,

M is the total amount of drug in the matrix

C_s is the saturation solubility of the drug

C_0 is the Concentration of the drug in the matrix at time t

Dm is the diffusion coefficient of the drug

t is time

Or simply as,

$$M = kt^{1/2}$$

Where k is a constant. So, th e plot of amount of drug released versus the square root of time should be linear if the drug released from the matrix is diffusion controlled.

In case of a spherical model too, it is assumed that a pseudo steady state exists, since $C_0 >>> C_s$. If r_0 is the radius of the whole sphere and r_u is the radius of the still unextracted portion, then the release of the drug can be given by the equation,

$$1 - 3(r_u / r_0)^2 + 2\,(r_u / r_0)^3 = B\, t$$

Where $B = 6\, D\, C_s / C_0\, r_0^2$

C_s is the saturation solubility of the drug in the matrix,

C_0 is the initial concentration of the drug in the matrix

r_0 is the radius of the whole microsphere

r_u is the radius of the still unextracted portion

And (r_u / r_0) represents the fraction of the drug remaining, as a function of time, t.

For microspheres having a homogenous matrix, the equation is (18)

$$B = 6 \, D \, C_s / C_0 \, r_0{}^2$$

For microspheres that have a granular (non-homogenous matrix), the equation is (18)

$$B = 6 \, D \, C_s \, V_{sp} / \tau \, C_0 \, r_0{}^2$$

Where V_{sp} is the specified volume of the drug and τ is the porosity of the system

The drug release from a matrix system may be more difficult to model than a reservoir membrane type of system, because of the additional number of variables to be accounted for (18). The changing surface area considerations, drug loading and drug particle size may have interacting effects on dissolution.

At a low drug loading, and where the drug release is a result of dissolution of the drug in the polymeric matrix, followed by the diffusion of the drug through the matrix into the environmental interface, a decrease in the particle size of the drug results in an increase in the rate of drug release (18). This is because the smaller drug particles can diffuse across the polymer barrier more rapidly resulting in a higher drug release rate. Also smaller are the drug particles, more is the area exposed for dissolution into the polymer.

 On the other hand, at high drug loadings, and where the solubility of the dug in the membrane is unimportant, reduction of drug particle size may decrease the rate of drug release. This is because at high drug loadings, particles come close together. As the particles dissolve they leave channels in the microcapsule matrix, thus increasing the access to the dissolution environment

and consequently increasing the release rate. However very small particles dispersed in the polymer are less likely to form continuous channels as they dissolve (18). The dissolution of smaller insoluble particles results in a tortuous path for the dissolution medium and this leads to a decrease in the release of the drug.

Ibuprofen or (±)-2-(4-isobutyl phenyl) propionic acid is a non-steroidal anti-inflammatory drug (NSAID) for the treatment of a wide range of indications, including pain, inflammation, arthritis, fever and dysmenorrhoea (20). The typical effective oral doses range from 600 to 1800 mg/day.
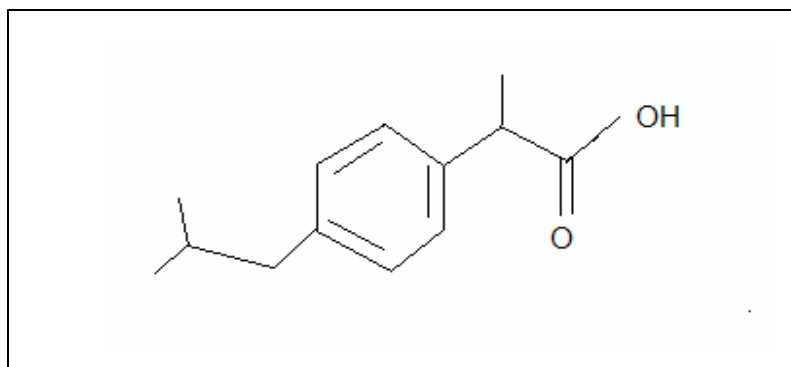
Figure 2. Ibuprofen

The mechanism of action for the anti-inflammatory actions of Ibuprofen is the inhibition of prostanoid biosynthesis via blockade of cyclo-oxygenase (COX). The COX enzyme exists as two isoforms, COX-1 and COX-2. COX-2 is the inducible form of the enzyme and is expressed in macrophages and other immnoregulatory cells after trauma. By inhibiting this enzyme, ibuprofen and other NSAIDS exhibit their anti-inflammatory activity. COX-1 is a constitutive protein present in a wide range of cells, and is important in the regulation of the prostaglandins that are involved in the protection of the lining of the GI tract from noxious agents. The inhibition of this

isoform of COX contributes to gastric ulceration, and this is one of the most common adverse effects of NSAID therapy (21).

Ibuprofen is rapidly absorbed when administered orally. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between the amount of drug administered and the integrated area under the serum drug concentration vs. time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. The administration of ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

The aim of this study is to develop a controlled release multiparticulate system, which would have a reduced dosing frequency, and reduced gastric irritancy that is a side effect of the NSAID ibuprofen. Disintegrating oral solid dosage forms that spread over the gastrointestinal tract offer statistically less variation than solid dosage forms that remain intact during transit (22). Multiple unit dosage forms have been extensively used for drug delivery due to their clinical advantages over single unit dosage forms (23). Multiple-unit disintegrating dosage forms consist of several subunits, which spread out uniformly in the gastrointestinal tract and thus reduce the risk of local irritation and dose dumping, which are often seen with single-unit dosage forms (24).

Microcapsules and matrix microspheres have been tableted to control the release of the drug and to avoid gastric irritation (25). Tableted microspheres of ibuprofen have an advantage over tablets in that the small particles help the drug moieties to be widely distributed throughout the

gastrointestinal tract, thus improving drug absorption. Considering the GI tract irritation of the NSAID ibuprofen, a multiple unit dosage system in the form of wax matrix microspheres would protect the gastric mucosa from the irritant effect of the drug and thus decrease the magnitude of this side effect. Both microcapsules as well as matrix monolithic microspheres have been tabletted in the past to control the release rate of the drug. However compression of the microcapsules may lead to damage to the capsule wall, as reported by Nixon et al in 1980. Damage to the microcapsule wall at higher compression pressures may lead to unpredictable dissolution rates of the tableted microcapsules. However, in the study carried out by Dubernet et al., in 1987, the *in vitro* release rate of nitrofurantoin from poly (e- caprolactone) microcapsules decreased after tableting probably due to the formation of a non-disintegrating matrix at higher compression pressures. Matrix monolithic microspheres are reported to be more robust and more resistant to rupture on tableting compared to the thin wall microcapsules, which are more fragile because of the relatively thin wall of encapsulating coating (26).

MATERIALS AND INSTRUMENTS

The materials are shown in Table 1 and the instruments and equipments are shown in Table 2.

Table 1: Materials

Materials	Manufacturer	Lot Number
White Wax, N.F. (Beeswax)	Amend Drug and Chemical Co. Irvington, NJ 0711	F15341A02
Ibuprofen USP 40 grade	Ablemarble Corporation Baton Rouge, LA 29801	LPL6312

Microcrystalline Wax	Frank B. Ross Co. Inc.	1135/15W
Stearyl Alcohol USP/NF	Gallipot St. Paul, MN 55122	9903112
Dodecyl Sodium Sulfate USP	Matheson Coleman & Bell East Rutherford, N.J.	DX295
Potassium Phosphate Monobasic Anhydrous	Sigma Aldrich Co. St. Louis, MO 63178	63178
Sodium Hydroxide, 50%w/w Solution	J. T. Baker NJ 08865	3727-01
Microcrystalline Cellulose Avicel® PH 101	FMC Corporation Philadelphia, PA 19103	1449
Sodium Carboxymethyl Starch	Eli Lilly and Co. Indianapolis, IN 46285	BO8369
Methylene chloride	J.T. Baker, NJ 08865	EO4621

Table 2: Instruments and Equipment

Equipment	Sources
Optical Microscope Model No.	Bausch and Lomb Inc., Rochester, NY 14602
Dissolution Apparatus	Prolabo Dissolutest Dissolution Apparatus,

	75526, Paris, France
Stainless Steel Mini Basket	Instruments Workshop University of Georgia, Athens, GA 30602
Spectronic 2000 UV Spectrophotometer	Bausch and Lomb, Rochester, NY 14625
Water Bath Shaker	Precision Reciprocal Water Bath, Model # 25, Precision Scientific, Winchester, VA.
Mechanical stirrer	Lab Stirrer LR 400C Fischer Scientific Co. Japan
Tablet Press	Fred S. Carver Inc., Summit, NJ, USA
Hardness Tester	Erweka Chemical and Pharmaceutical Co., NJ, USA
Tablet Dimensions Measure	Digital Caliper

METHODS

PREPRATION OF MICROSPHERES

The external phase was prepared as a 200 ml of a 0.25% w/v solution of sodium lauryl sulfate (SLS) in de-ionized water. This aqueous phase was heated to about 80 °C (temperature higher than the melting point of wax). It was simultaneously stirred at 1000 rpm using a three blade

mechanical lab stirrer. Two grams of white beeswax and 0.05 grams of stearyl alcohol were weighed into a porcelain crucible and melted over a water bath. 1.33 g of Ibuprofen was weighed and stirred into the molten wax phase. This one phase melt was added to the heated aqueous phase in a drop wise manner while stirring at 750 rpm for 2 minutes followed by stirring at 600 rpm for 3 minutes. The aqueous phase was maintained at all times at about 5 °C above the melting point of the one phase wax- ibuprofen melt. This is necessary because the drug wax melt must remain as individual oily liquid droplets, that are uniformly dispersed in the heated external aqueous phase. After 5 minutes, the oil-in-water emulsion was rapidly cooled by pouring into about 400 mls of ice-cold water (about 4°C) and stirring was continued as the emulsion cooled. This caused the oily droplets to rapidly congeal into solid microspheres. The hydrophobic nature of the ibuprofen causes the drug to stay dispersed in the newly solidified wax microspheres instead of partitioning into the cold aqueous phase.

Once the solution stabilized at room temperature, the microspheres were collected by vacuum filtration through Whatman #1 filter paper. The microspheres were washed with about 100 ml of phosphate buffer at pH 7.5 to remove any drug crystals that were not encapsulated. About 600 ml of water were used for washing the microspheres to remove any traces of drug or surfactant residues. Blank microspheres were prepared in a similar way for each batch without the drug. The microspheres were dried for 12 hours in an oven maintained at 35 ºC. The microspheres were freely flowing and free of aggregates, on drying, when they were prepared with a surfactant such as sodium lauryl sulfate. The recovery yield was about 92.48% ± 2.078 % of the starting material.

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┌─────────────────────────────────────────────────────────────────────┐
│                                                                       │
│              ┌──────────────────────────────────────┐                 │
│              │  Molten White Beeswax + Ibuprofen+ Stearyl │            │
│              │                                        │                 │
│              │               Alcohol                  │                 │
│              └──────────────────────────────────────┘                 │
│                             ↓                                          │
│        ┌──────────────────────────────────────────────────────┐       │
│        │ Emulsification into a 0.25% w/v solution of sodium lauryl sulfate in de-ionized water │
│        │                                                        │       │
│        │   (Stir for 2 min. at 700 rpm and 600rpm for 3min. at 80°C)  │
│        └──────────────────────────────────────────────────────┘       │
│                             ↓                                          │
│           ┌────────────────────────────────────────────┐              │
│           │ Poured into ice cold water (about 4°C) to solidify │        │
│           │                                              │              │
│           │   wax microspheres containing ibuprofen      │              │
│           └────────────────────────────────────────────┘              │
│                             ↓                                          │
│                    ┌──────────────────┐                                │
│                    │ Vacuum filtration │                               │
│                    └──────────────────┘                                │
│                             ↓                                          │
│        ┌──────────────────────────────────────────────────────┐       │
│        │ Wash with DI water to remove unbound drug and traces of surfactant │
│        └──────────────────────────────────────────────────────┘       │
│                             ↓                                          │
│                ┌────────────────────────────────┐                     │
│                │ Dry in oven at 35°C for 12 hours. │                   │
│                └────────────────────────────────┘                     │
│                             ↓                                          │
│            ┌──────────────────────────────────────┐                   │
│            │ Ibuprofen loaded beeswax microspheres  │                  │
│            └──────────────────────────────────────┘                   │
│                                                                       │
└─────────────────────────────────────────────────────────────────────┘
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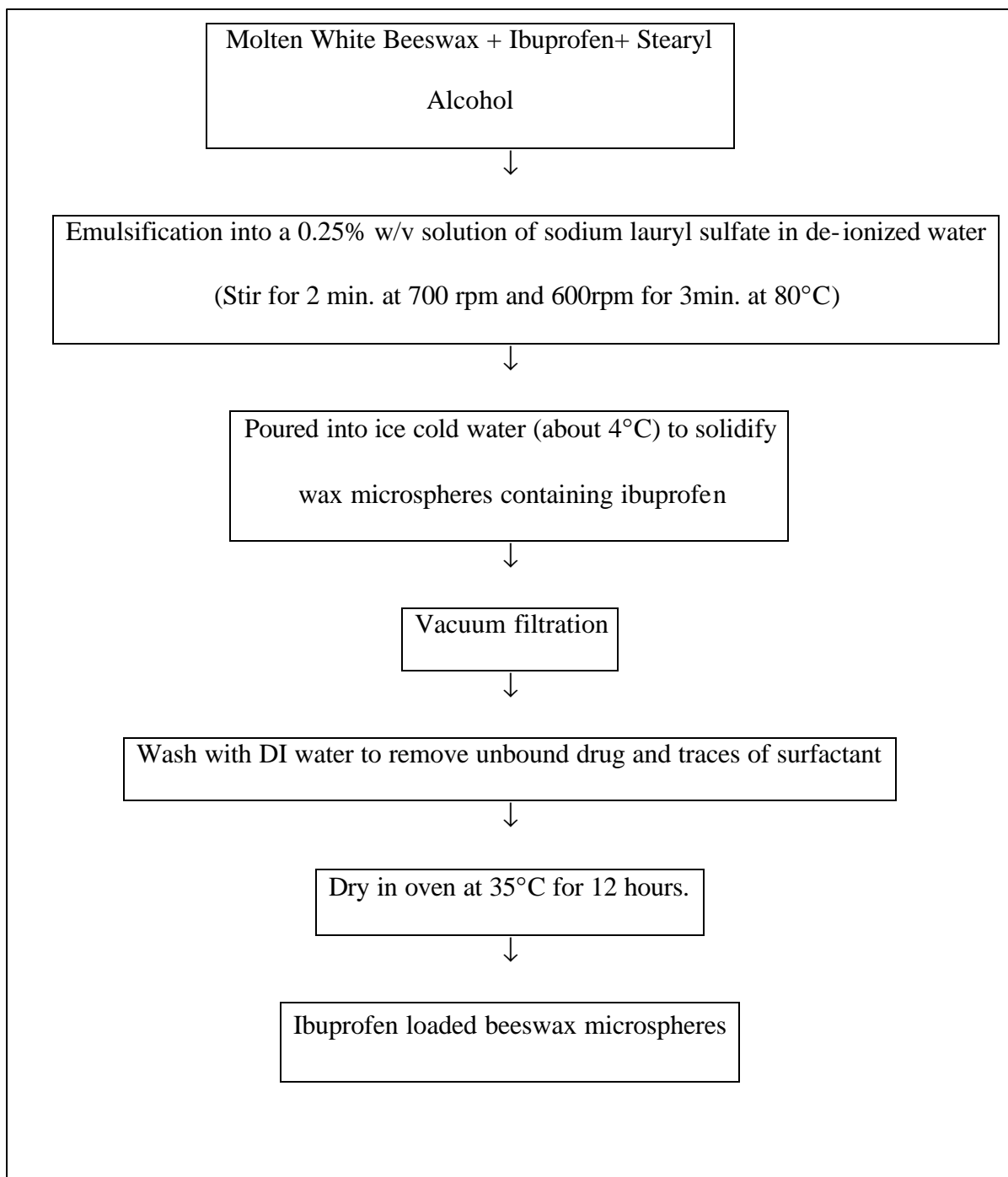
Figure 3. Preparation of Ibuprofen in White Beeswax microspheres by the Hydrophobic Congealable Disperse Phase method

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EVALUATION OF MICROSPHERES:

Particle size distribution of the microspheres:

Size analysis of the microspheres was accomplished by sieving. The batch of microspheres was placed on a nest of seven sieves in the range of 63μ to 710μ. The largest sieve (710μ) was placed on top and the sieves were arranged in descending order of aperture size from top to bottom. The sieves were manually tapped on a wooden surface from a height of about 1 inch for 5 min. The microspheres retained on each sieve were lightly pressed with a rubber spatula to separate the loosely aggregated particles. The microspheres were further shaken for 5 min and amount of the microspheres retained on each sieve was weighed. The arithmetic mean of the size of the sieve preceding and retaining sieves were assigned to the fraction of microspheres on the retaining sieve.

Batches of microspheres prepared under the same conditions were reproducible with respect to the mean size of the microsphere population.

Standard curve of Ibuprofen in methylene chloride:

A stock solution of 1 mg/ml was prepared. 100 mg of ibuprofen was weighed into a 100 ml volumetric flask. About 50 ml of methylene chloride was added to the volumetric flask and the ibuprofen was dissolved in it. The volume was made up to 100 ml in the volumetric flask. From this solution successive dilutions of 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml and so on were prepared. The absorbance of these solutions was recorded and a standard curve was prepared. Another solution of 10 mg/ml was also prepared and from this solution successive dilutions were made of

1 mg/ml, 2 mg/ml, and 3 mg/ml and so on. The absorbance of these solutions was also recorded and a standard curve was prepared that was linear from 0.1 mg/ml to 4 mg/ml.

Determination of microsphere drug content:

One hundred mg. of drug-loaded microspheres of each batch and size were randomly taken. They were observed under the microscope for consistency. The microspheres were added to a tared volumetric flask. Sufficient methylene chloride was added to the volumetric flask to dissolve the microspheres. The wax was completely dissolved releasing the entire incorporated drug. The volume was then made upto 100 mls. The solution was then filtered through a 0.45 μ filter and absorbance was determined spectrophotometrically at 261.7 nm wavelength against a blank prepared with microspheres containing no drug. The corresponding calculations were calculated from a standard curve, which was linear from 0.1mg/ml to 4 mg/ml.

Determination of saturation solubility of the ibuprofen in the dissolution medium.

The dissolution medium used in this study was modified Simulated Intestinal Fluid (SIF) USP. The SIF used in the study was prepared as recommended by the USPNF, except that no enzymes were used, 0.02% Tween 80 was added to ensure wetting of the wax microspheres by the medium and the pH of the medium was adjusted to 7.2 instead of 6.8 as recommended by the USP. In order to determine the saturation solubility of ibuprofen in this medium, excess drug (1.5 g) of Ibuprofen was added to 20 ml of dissolution media. This suspension was shaken in water bath at 37 °C for 48 hrs at 75 rpm.

At the end of 48 hrs, the solution was filtered at 37 °C. This solution was too concentrated to be analyzed as such by the spectrophotometer. So, 1 ml of the filtrate was diluted to 100 ml in a

volumetric flask with dissolution medium at 37 °C. The absorbance of this solution was recorded and the calculations were made to determine the saturation solubility of ibuprofen in the dissolution medium used in the study.

In vitro dissolution testing of microspheres:

The in vitro drug release of the drug from the microsphere formulations was determined by the *in-vitro* dissolution tests. For these studies, pooled samples of each formulation type were used. The USP Apparatus I (Paddle type) was used for dissolution testing. Since the wax microspheres had a tendency to float in the dissolution medium, the USP paddle apparatus was modified. Six 3 x 2 cm-diameter stainless steel baskets with 100 mesh screens (Figure 3, 4) were constructed at the machine shop at the University of Georgia. These mini baskets were used to hold the microsphere sample at the bottom of the vessel. The minibaskets were stationary and the only stirring elements were the paddles. The stirring speed used was 100 ± 1 rpm. The temperature was maintained at 37 °C ±0.1 °C. Nine hundred ml of Simulated Intestinal Fluid (SIF) USPNF, (no enzymes, 0.02 % w/v Tween 80, and pH 7.4) was used as the dissolution medium. (Figure 9) Aliquots were withdrawn at the specific intervals and they were filtered through a 10μ Vankel input filter. The same volume of fresh dissolution medium was replaced after withdrawing an aliquot, so that the volume of the dissolution medium remained constant. The samples were analyzed at 262.1 nm wavelength spectrophotometrically. The cumulative amount of drug released at the end of 24 hours was plotted against time to find the release profile of the microspheres. The results were reported as the mean of four dissolutions.
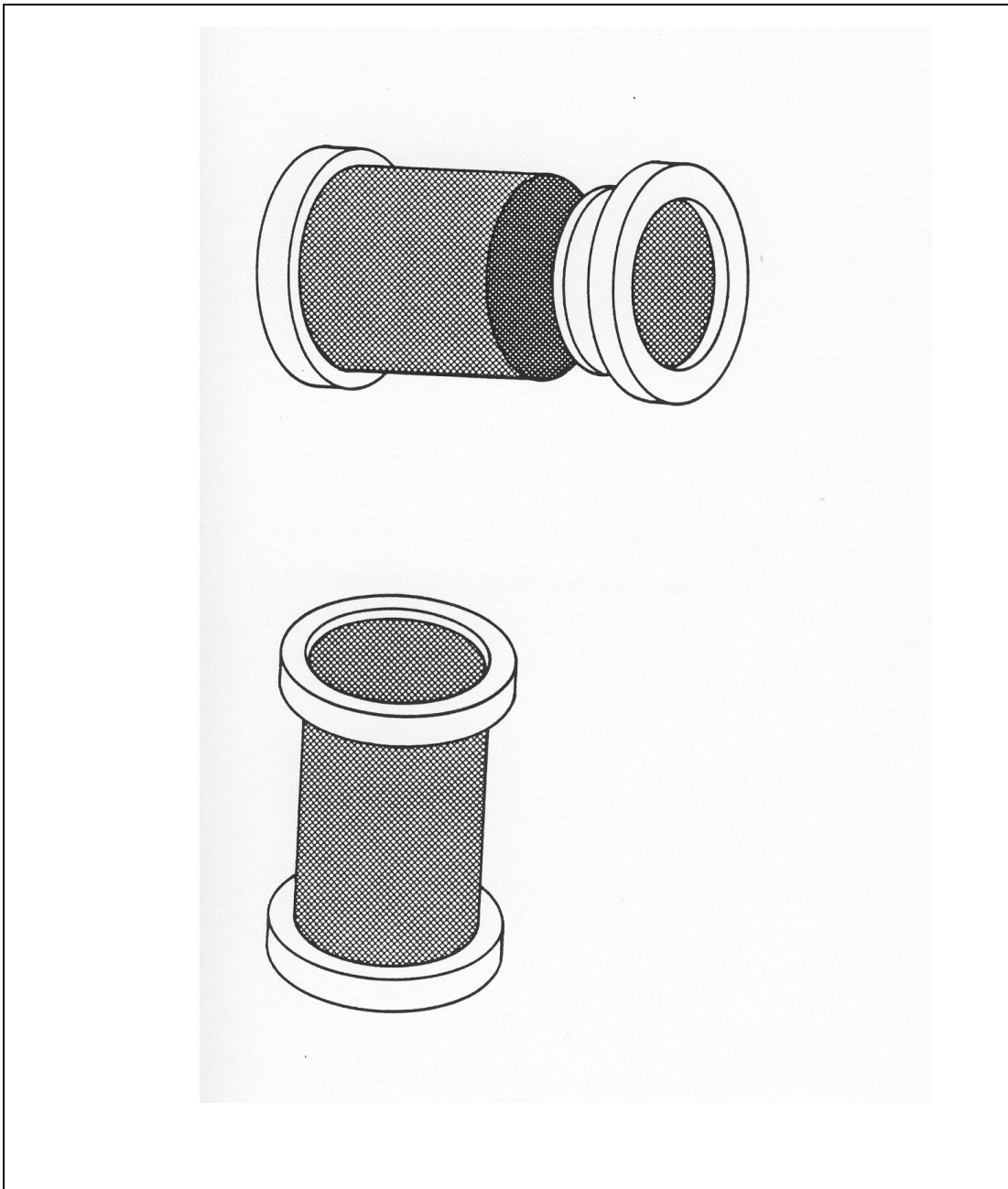
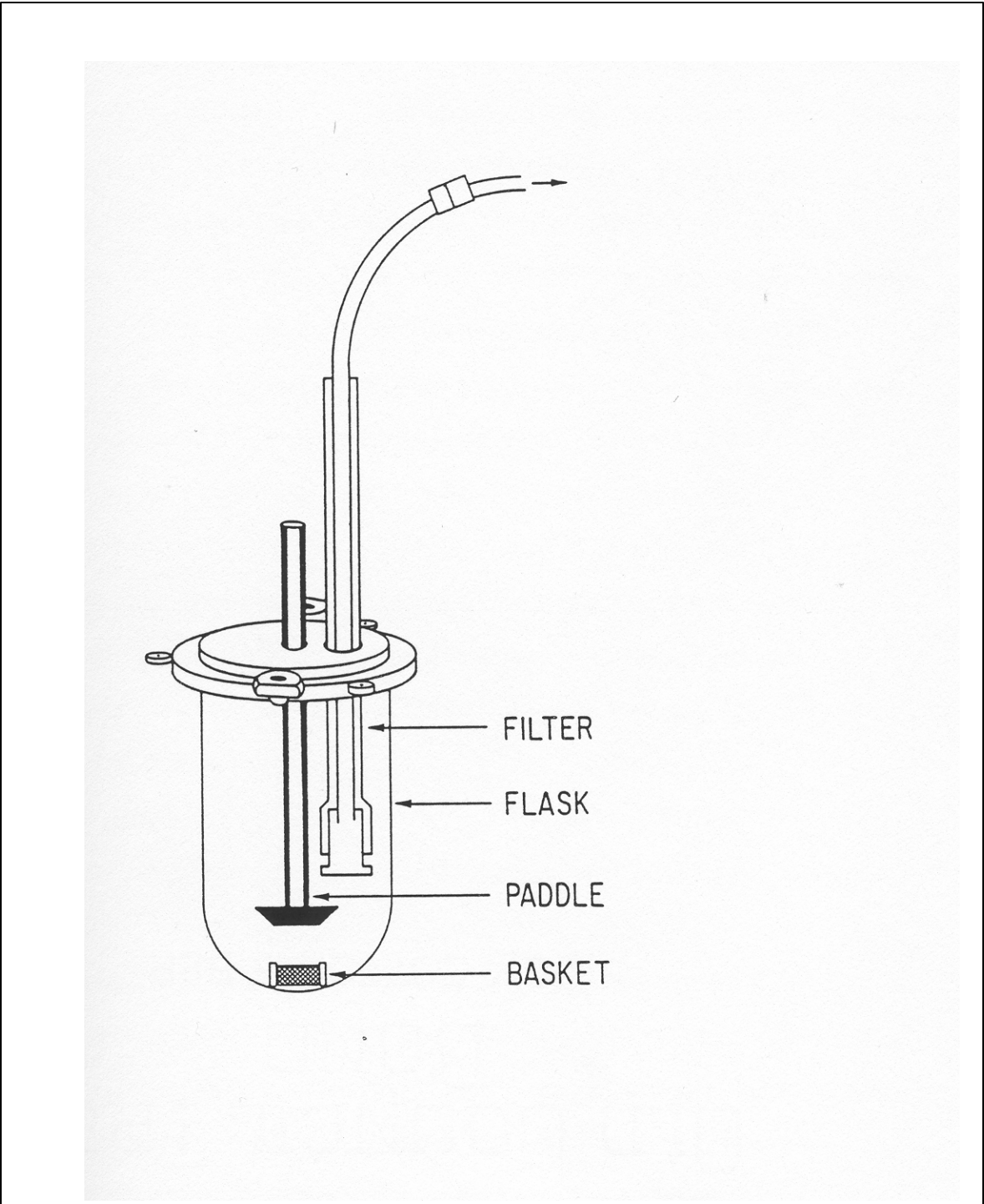Figure 4: Minibasket used for the in vitro drug release studies

Figure 5: Dissolution flask and minibasket arrangement for dissolution testing

Microscopic evaluation of the microspheres:

A scanning electron microscope (LEO 982) was used to study the surface characteristics of the microscopes before and after dissolution. Samples were attached to aluminum stubs with 12mm diameter carbon adhesive tabs. Samples were coated for 90 sec with gold palladium in a sputter coater (Structure Probe Inc) for a coating thickness of approximately 23.0 nm.

PREPARATION OF TABLETED MICROSPHERES:

Tableting process:

Appropriate amounts of microspheres (formulation 3) were blended with Avicel PH 101® and Explotab®. (Table 3) The mixture was then compressed by direct compression in a Carver hydraulic press (Fred S. Carver, Inc., NJ, USA) to a weight of 550 mg per tablet. A ½ inch (12.70mm) diameter fat-face punch and die set was used to compress microsphere-excepient mixtures into tablets at compression pressure from 600 PSI (pounds per square inch) to 4000 PSI. (3 different compression pressures were used). Each compression pressure was held at 40 s followed by a quick release. Each tablet contained 81.83 mg of ibuprofen

Table 3: Microsphere tablet formulation

Ingredients	%
Ibuprofen microspheres	42
Avicel PH 101®	55
Explotab®	3

The effect of the different compression pressures was studied by evaluating the tablets in terms of their physical properties and their drug release.

EVALUATION OF TABLETED MICROSPHERES

Determination of tablet thickness and density:

Six tablets from each batch were weighed and their mean weights were calculated. The thickness and diameter of each tablet was measured using a digital caliper and the average thicknesses as well as diameters were calculated. The tablet densities were calculated from the mean volume and the mean weight of the tablets. Variation in the size and weight of individual tablets was determined.

Determination of tablet crushing strength (hardness):

The crushing strength of the tablets was measured using a hardness tester (Erweka Chemical and Pharmaceutical Industry Co., NJ, USA). This applied compressional force diametrically to the tablets. Six tablets were measured from each batch. The force required to crush the tablets was recorded in kilograms.

In vitro dissolution studies

The *in vitro* dissolution was performed using the USP Type II apparatus (Prolabo Dissolutest Dissolution Apparatus). Four replicates of tablets were placed in the dissolution medium. The dissolution medium used in this case was 450 ml of SIF (Simulated Intestinal Fluid) pH 7.2 containing 0.02 % Tween 80. Samples of 5 ml were taken at the time intervals of 30minutes, 1h, 2h, 4h, 6h, 8h and 12h. The dissolution medium was maintained at 37 ºC ±0.5 ºC throughout the

study. The dissolution samples were filtered through 10µ inline filters. The samples were analyzed by UV spectrophotometry at 262.1 nm against a blank tablet dissolution. (Figure9)

Microscopic evaluation:

The morphology of the broken diametrical surface of tablets was observed using a scanning electron microscope (FE-SEM, LEO electron microscopy, Inc., Thornwood, NY). The broken tablet surfaces were sputter coated with gold to a thickness of 50 nm to observe the surface morphology of compressed microspheres.

RESULTS AND DISCUSSION:

PRELIMINARY STUDIES:

In the initial studies microcrystalline wax (MP: 92°C) was used as the wax to encapsulate the ibuprofen using the melt congeal method. During these experiments about 25 % Stearyl alcohol was used as the wax modifier because the wax droplets had a tendency to agglomerate on cooling. On solidification the microspheres formed chains and aggregates. The concentration of the surfactant used in the aqueous phase was 0.5% SLS. The microspheres obtained in this study had a mean particle size of 90µ (Figure 4). However, the drug content of these microspheres was only 36.43%. The drug content of these microspheres was calculated from a standard curve of ibuprofen in cyclohexane linear up to 1 mg/ml. (R^2 =0.9999) (Figure 6.)
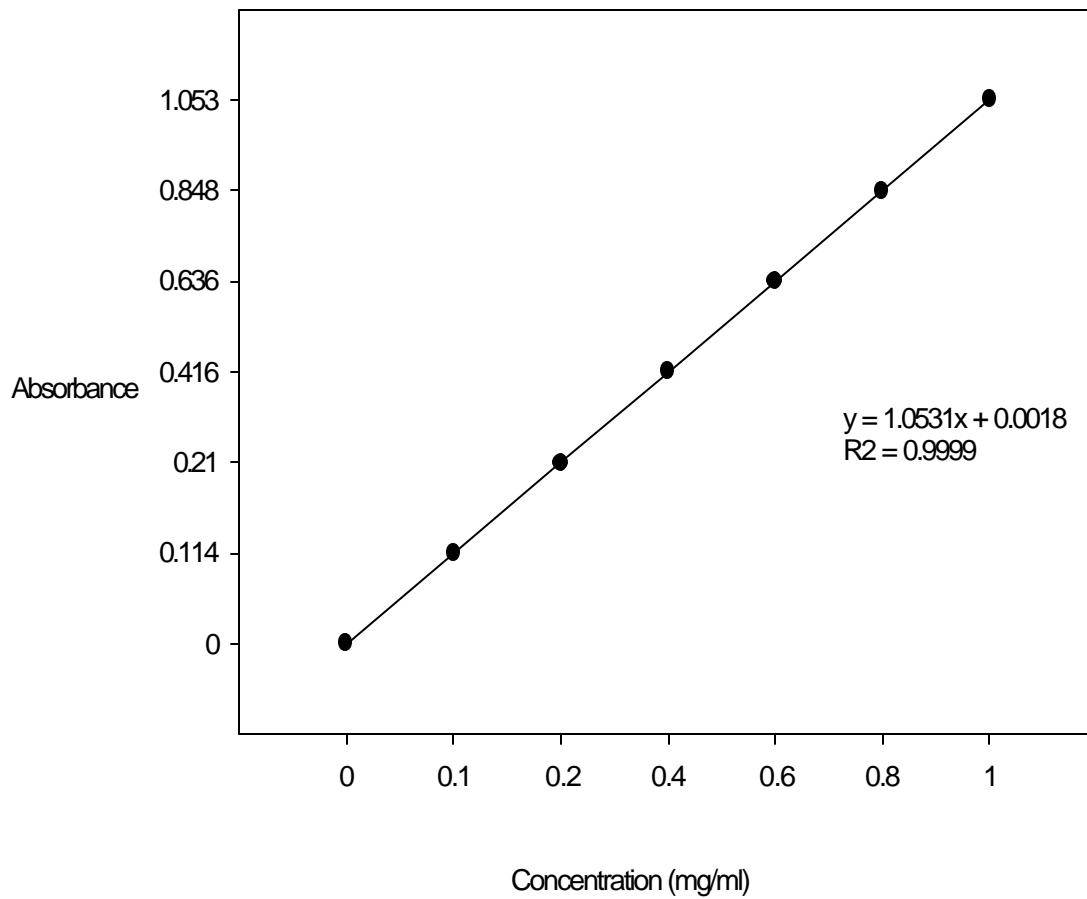
Figure 6. Standard Curve of Ibuprofen in Cyclohexane

Incorporation of ibuprofen into the microcrystalline wax microspheres required the use of a surfactant in the aqueous phase. Sodium lauryl sulfate was used to decrease the interfacial tension between the hydrophobic material and the external aqueous phase and to aid in wetting of the oily droplets of the internal phase. The optimum surfactant concentration found was 0.5 % w/v. At this concentration the microspheres produced did not aggregate. Microcrystalline wax has a high melting point of 90 °C. Emulsification was carried out at 100 °C. At this higher temperature, the particles produced were very small (mode of particle size was 91μ). (Figure 7) The emulsification speed used was 1000 rpm because at lower speeds (800 rpm), the microspheres had a tendency to agglomerate. The yield of the microspheres (solids recovery) was about 80.23%. The lower yield may be attributed to the fine particles being washed away during filtration and recovery of the microspheres from the aqueous phase. A dissolution study of these microspheres was carried out. However, the lesser drug content of the microspheres in addition to the small sample amount led to very low drug release. At these concentrations, the readings obtained were not reliable. To increase the drug content and obtain a better dissolution profile, a higher drug wax ratio was attempted with a higher percentage of stearyl alcohol (0.75 g or 25 %). The formulation contained a drug wax ratio of 1:2, and 25% stearyl alcohol. This formulation released about 56.93% of the drug in 15 min and 90% of the drug was released in 4 hr. The dissolution profile of this formulation did not have good sustained release characteristics. (Figure 8)
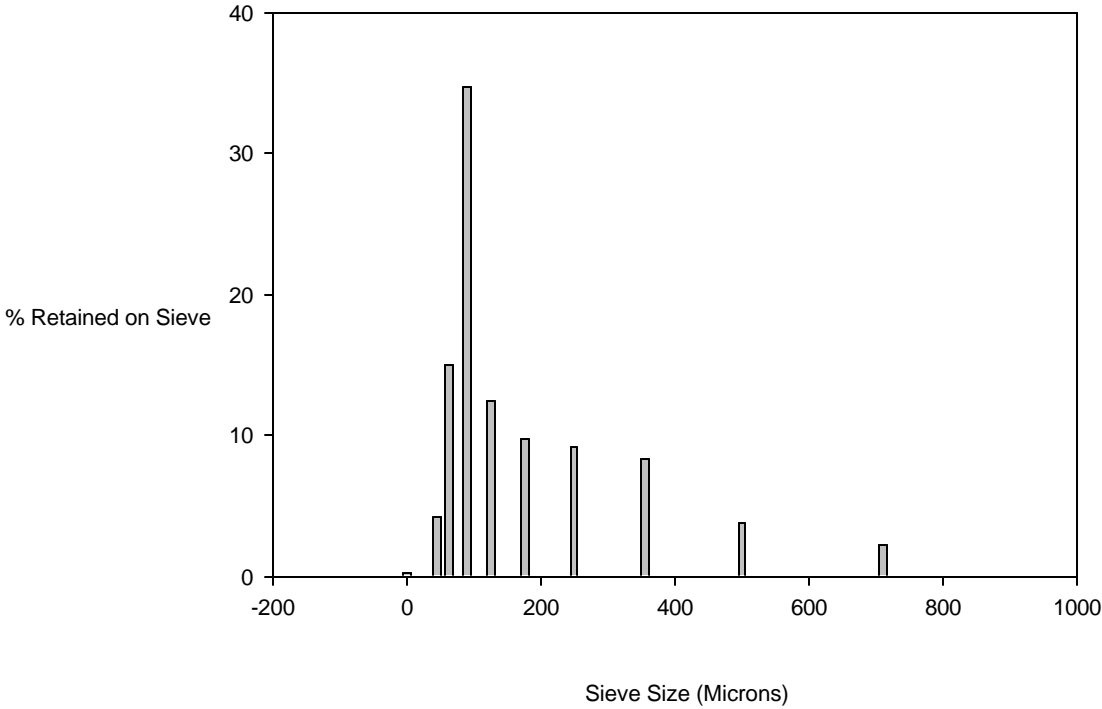
Figure 7: Average particle size distribution for microspheres prepared with microcrystalline wax and stearyl alcohol containing ibuprofen in drug wax ratio of 1:2 (Formulation A)
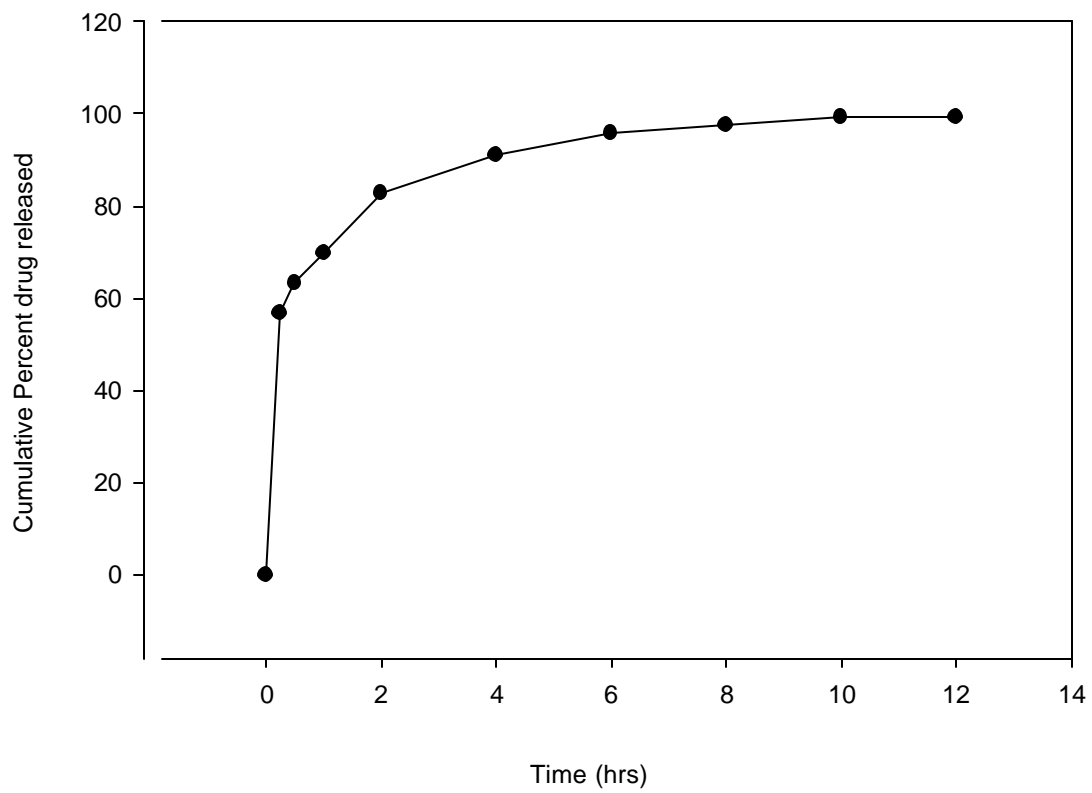
Figure 8: Dissolution profile of microspheres prepared with microcrystalline wax and stearyl alcohol containing ibuprofen in a drug wax ratio of 1:2 (Formulation A)

PREPARATION OF MICROSPHERES

In order to improve the encapsulation efficiency and the yield of microspheres, and drug release profile, beeswax was used instead of microcrystalline wax. The formulation was prepared in a similar way as the microcrystalline wax microspheres. The drug: wax ratio used was 2:1.33 and the stirring speed used was 700 rpm for 4 min. This formulation did not provide a sustained release as 50% of the drug was released in 1 hr in the dissolution studies and 80% of the drug was released in 6 hrs (for the particle size fraction of 250 micron). (Figure10)

$y = 0.7683x + 0.0056$
$R^2 = 0.9997$
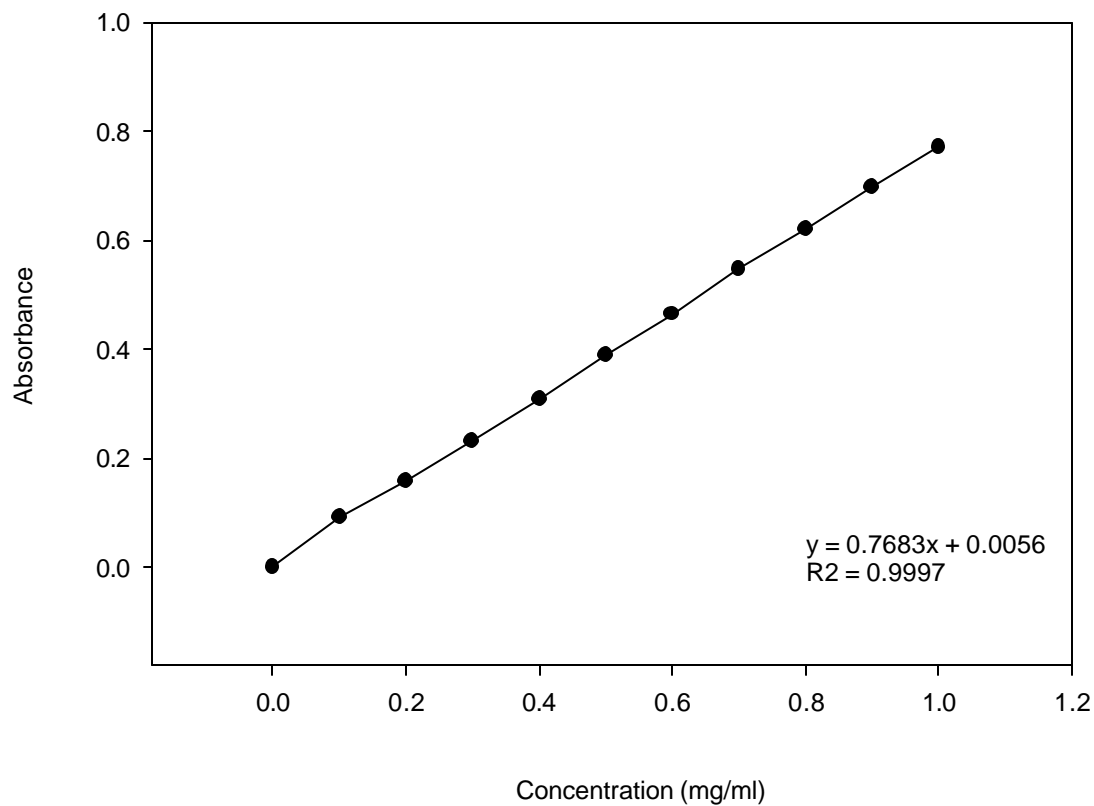
Figure 9: Standard curve of Ibuprofen in the dissolution medium, Simulated Intestinal fluid, pH 7.2, containing 0.02% Tween 80
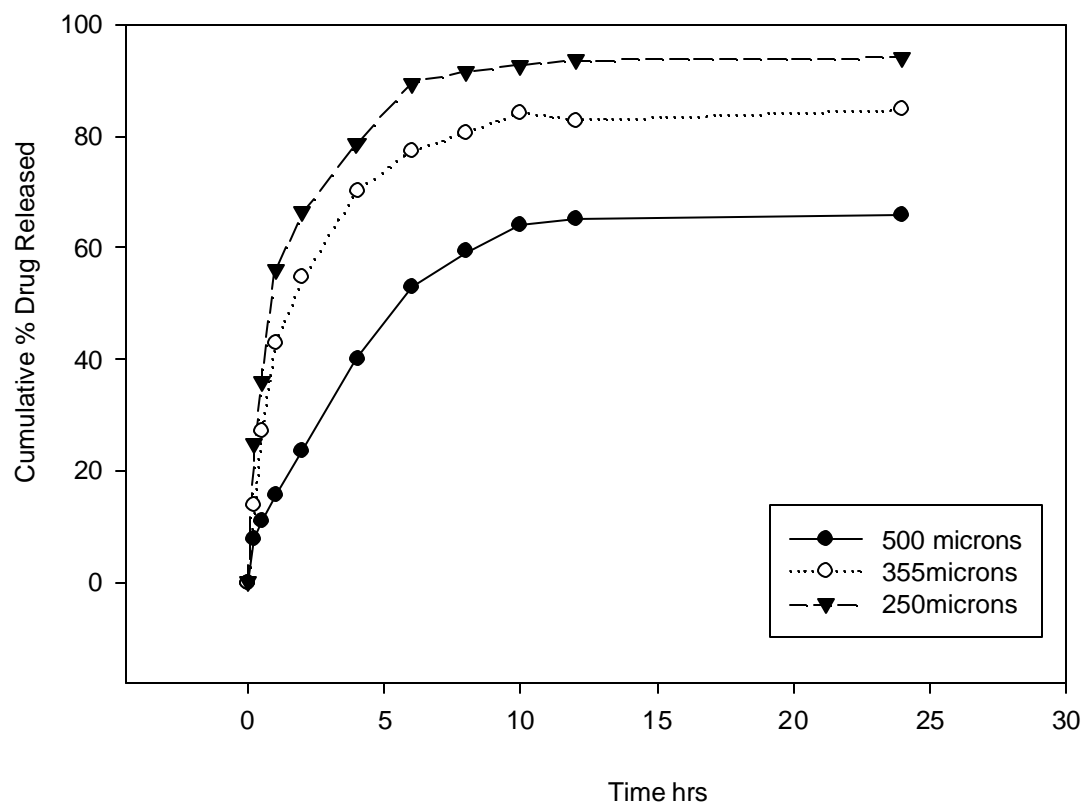
Figure 10: Dissolution profile of microspheres prepared with beeswax and ibuprofen in a ratio of 2:1.33 at a stirring speed of 700 rpm for 4 min, containing no stearyl alcohol. (Formulation B)

To improve the release pattern and to assure more completely release, stearyl alcohol was used as a wax modifier. (Figure14) Stearyl alcohol used in a concentration of 20% as well as 10% gave very fine particles, which could not be separated by vacuum filtration. Stearyl alcohol used at 2.5 % gave satisfactory results when the stirring speed was dropped to 700rpm for 2 minutes followed by 600rpm for another 3 minutes. (Formulation C)

The amount of SLS required to emulsify the one phase melt of ibuprofen and beeswax into water was found to be only 0.25 % SLS in deionized water as the surfactant. The solids recovery was found to be 92% w/w.

It has been reported by Giannola et al in 1995, that during the emulsification stage, the entrapment of the acidic drug valproic acid was pH dependent (24). As the pH of the external phase decreased, the solubility of valproic acid decreased and the encapsulated amount of the drug increased. Hence, the pH of the 0.25 % SLS solution was reduced to pH 4.5 using 0.2 N HCl and this was used as the external phase for the emulsification of beeswax and ibuprofen melt. However no significant change in the drug entrapment was found in this study although ibuprofen is an acidic drug. These results showed that the entrapment of ibuprofen was not pH dependent over this pH range, therefore pH 7 was used for emulsification for the remainder of the studies. The microspheres prepared with beeswax had some ibuprofen crystals outside the microspheres. The microspheres were washed with about 100 ml of phosphate buffer pH 7.4 to remove the unencapsulated ibuprofen crystals.

EVALUATION OF MICROSPHERES

Drug Content

A higher drug yield was observed for formulations containing stearyl alcohol as the emulsifier

The drug content of the formulation C was found to be 94.122 %. The microspheres prepared with beeswax were not completely soluble in cyclohexane, but showed good solubility in methylene chloride. (Figure 11) The assay of the microspheres was carried out in methylene chloride instead of cyclohexane.

Table 4: Percentage yield of Ibuprofen in three different particle size fractions of Formulation C (pooled 3 samples)

Pooled Batch	Theoretical drug content %			Assayed Drug Content %		
	350μ	250μ	125μ	350μ	250μ	125μ
I	100	100	100	95.3	96.1	93.7
II	100	100	100	92.8	90.1	95.3
III	100	100	100	94.7	95.9	93.2

y = 0.7683x + 0.0056
R2 = 0.9997
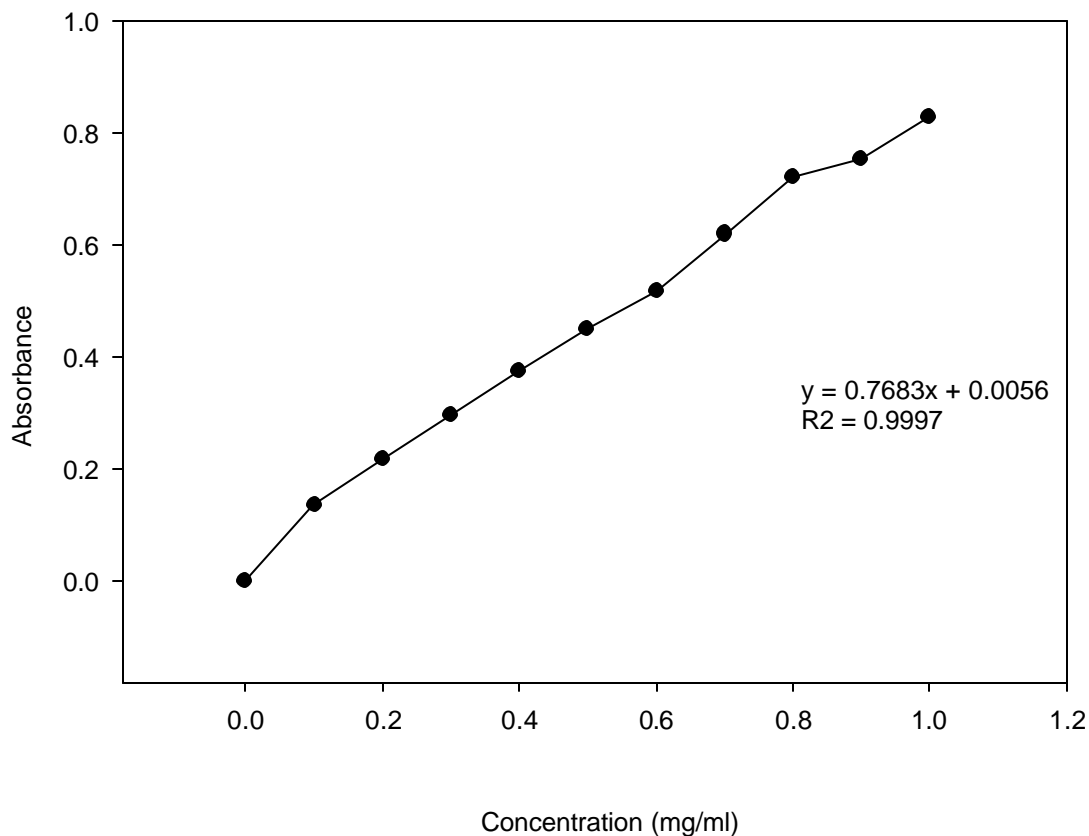
Figure 11: Standard curve of ibuprofen in methylene chloride

Particle size:

The microspheres prepared by formulation C showed a log normal distribution. (Figure12). The average particle size was smaller for the microspheres prepared by the formulation C compared to Formulation B that was prepared without any stearyl alcohol. The stearyl alcohol acts as a supplementary emulsifier and helps to form a better primary emulsion during the emulsification of the beeswax ibuprofen melt in the sodium lauryl sulfate solution. The resulting smaller droplets formed with stearyl alcohol explain the formation of smaller particles with formulation C. However the particles were much larger than the microspheres formed with the use of

microcrystalline wax. This can be explained by the lower temperature required for the emulsification of beeswax (M.P. 64ºC) versus microcrystalline wax (M. P. 93ºC). It has been reported that finer particles are produced at higher temperatures (28).
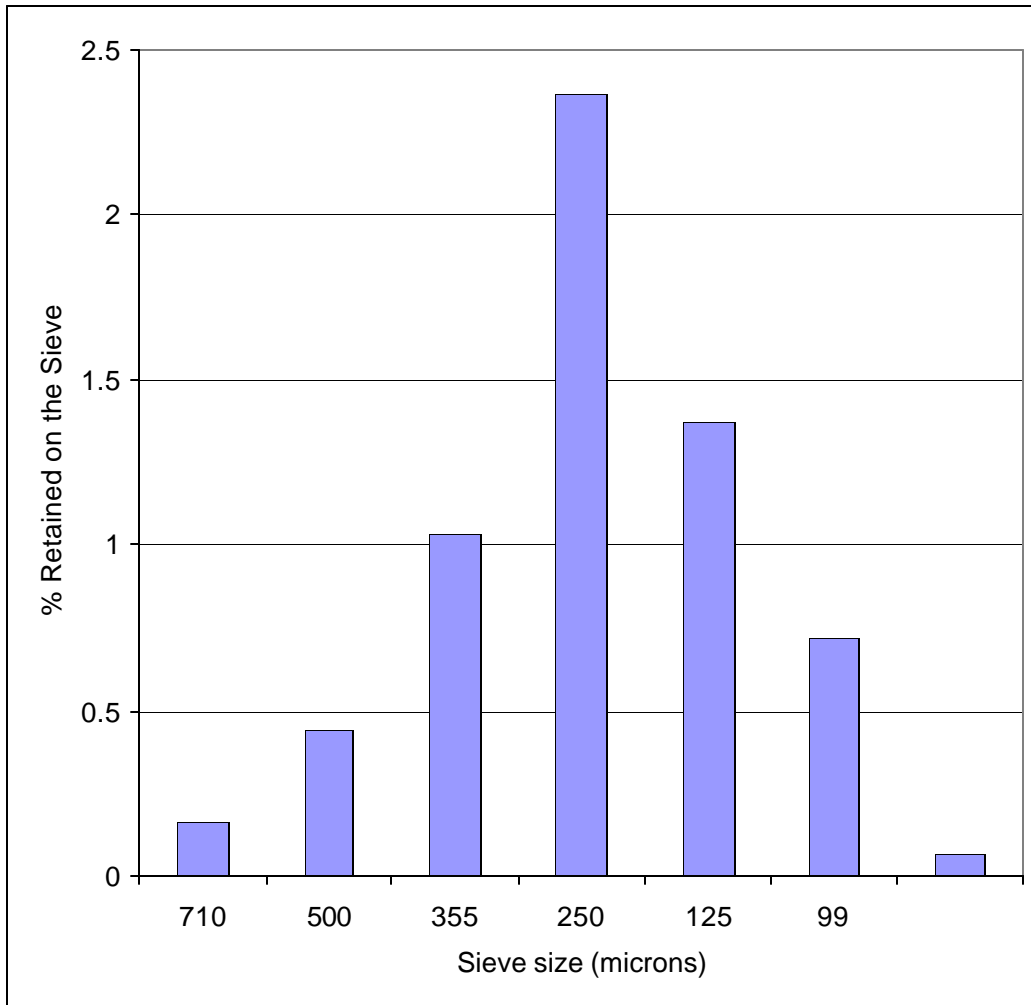
Figure 12: Average particle size distribution for microspheres prepared with beeswax and stearyl alcohol containing ibuprofen in drug wax ratio of 2:1.33, prepared at a stirring speed of 700 rpm for 2 min followed by 600 rpm for 3 min. (Formulation C)

IN VITRO DISSOLUTION TESTING OF MICROSPHERES:

For the *in vitro* drug release studies, in order to maintain sink conditions, amount of drug corresponding to 5% of the saturation solubility is recommended. The saturation solubility of ibuprofen in the dissolution medium used in this test was found. The saturation solubility of ibuprofen in enzyme less SIF at pH 7.2 containing 0.02% Tween 80 was found to be 27 mg/ml. Five percent of this concentration is 1.35mg/ml. Considering the use of 900 mls of dissolution medium, the maximum drug that can be used in sink conditions is 1215 mgs of ibuprofen.

In the dissolution studies with beeswax, 1000 mgs of microspheres were used. Each dissolution vessel containing 900 mls of simulated intestinal fluid (SIF) as dissolution medium contained about 389.66 mg of ibuprofen. This quantity of ibuprofen is much below the concentration of drug required to achieve the sink conditions. (Figure 6)

The dissolution studies were carried out on three different particle size fractions of Formulation C to study the effect of particle size on the drug release from the formulation. The pooled samples from 4 different batches of microspheres retained on the 350μ, 250μ and 125μ sieves were used for this study.

Effect of Microsphere size on the Dissolution from Beeswax containing 2.5% Stearyl Alcohol:

An increase in the particle size decreased the dissolution rate. (Figure 13) The T50 values for the different sizes were 2 hr, 4.35 hr and 7.2 hr for the microspheres of sizes 125μ, 250μ and 355μ respectively. As the particle size increases the dissolution T50 increases due to decreased surface area and increased diffusion path length.
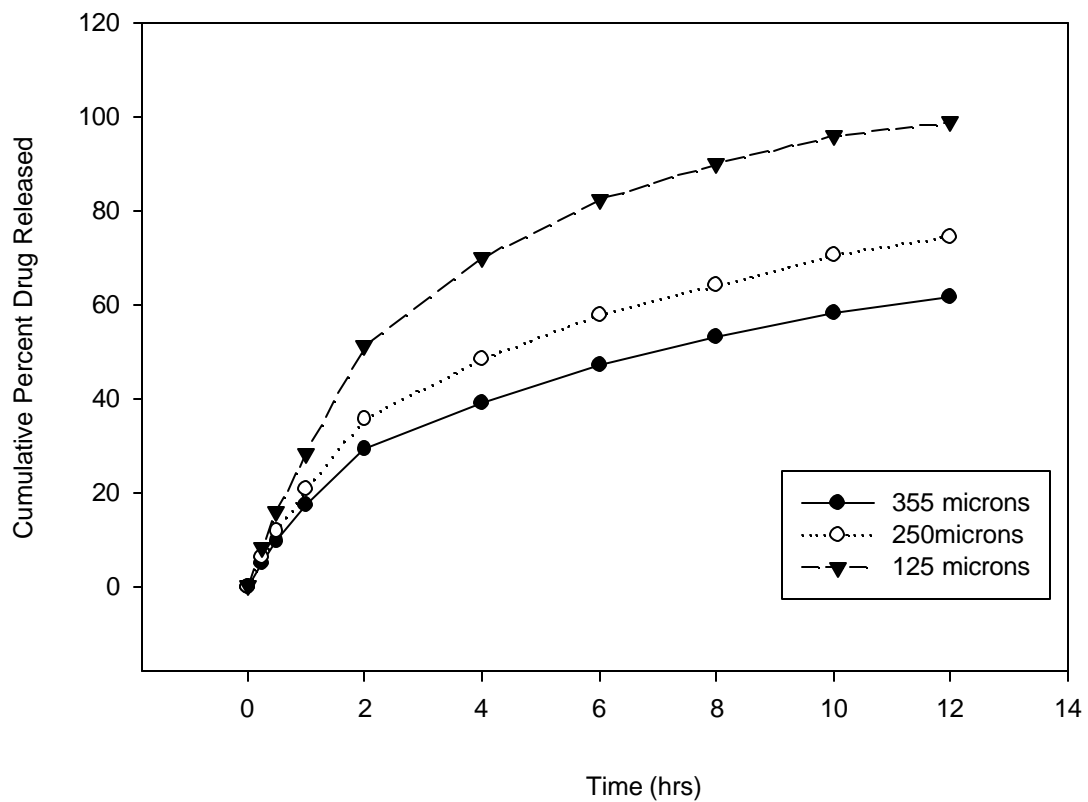
Figure 13: Dissolution Profile for ibuprofen from three different particle size fractions of formulation C microspheres containing 0.25% stearyl alcohol in simulated intestinal fluid, pH 7.2.
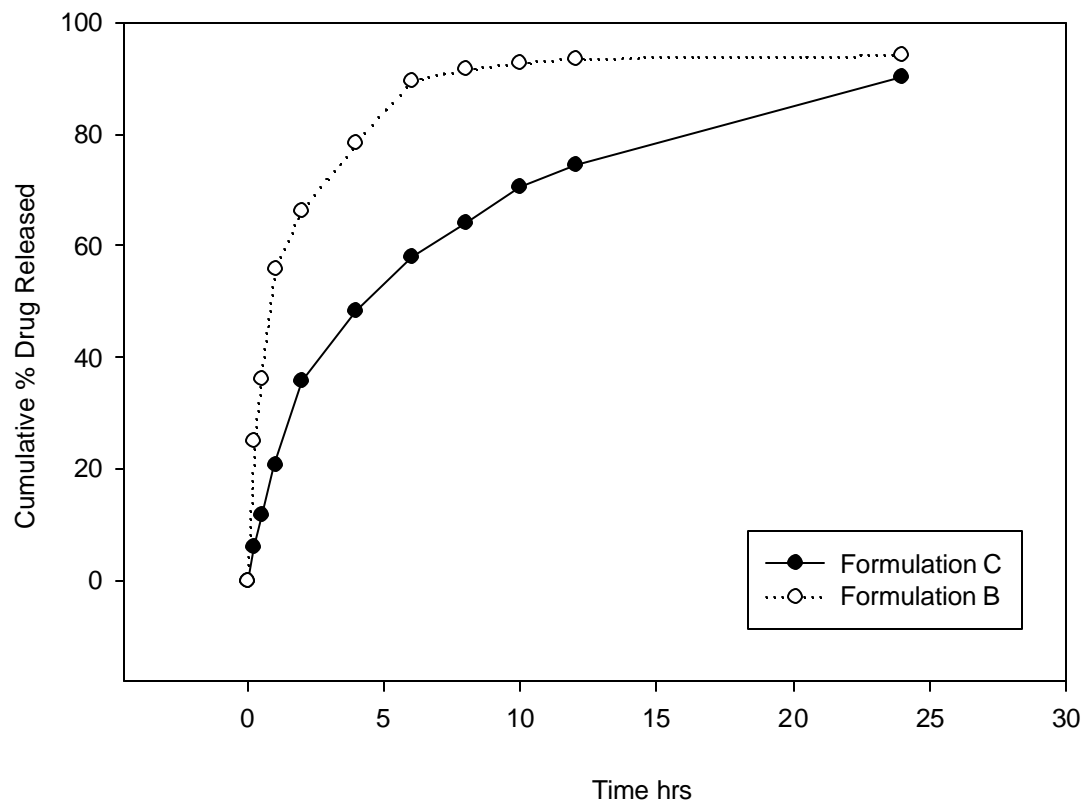
Figure 14: Effect of wax modifier (stearyl alcohol) on the drug release from microspheres.

Formulation B is prepared without stearyl alcohol

Formulation C contains 2.5 % stearyl alcohol as wax modifier.

Kinetic Evaluation of Dissolution Data of the three different Microsphere Sizes:

The correlation of the dissolution data from the different microsphere sizes indicated a linear relationship between the dimensionless value ($1+2\,F\text{-}3\,F^{2/3}$) and time T. of the Higuchi model (19). (Figure 15) The data had a correlation coefficient of greater than 0.99, (Table 5) for the 125μ, 250μ and 355μ particle sizes. The slope increased as the particle size decreased. These results indicate that the Higuchi spherical matrix model can be readily applied to the drug release data.

Table 5: Calculated Correlation Coefficients, Slopes and Intercepts for the Higuchi Model for dissolution data for different sizes of microspheres (Formulation C)

Higuchi Spherical Matrix Model $1+2\,F\text{-}3\,F^{2/3} = KT$			
Values	355μ	250μ	125μ
Correlation Coefficient	0.9912	0.9954	0.998
Intercept	0.0131	0.0033	0.0266
Slope	0.0122	0.0239	0.0738

F = Fraction of Drug Remaining

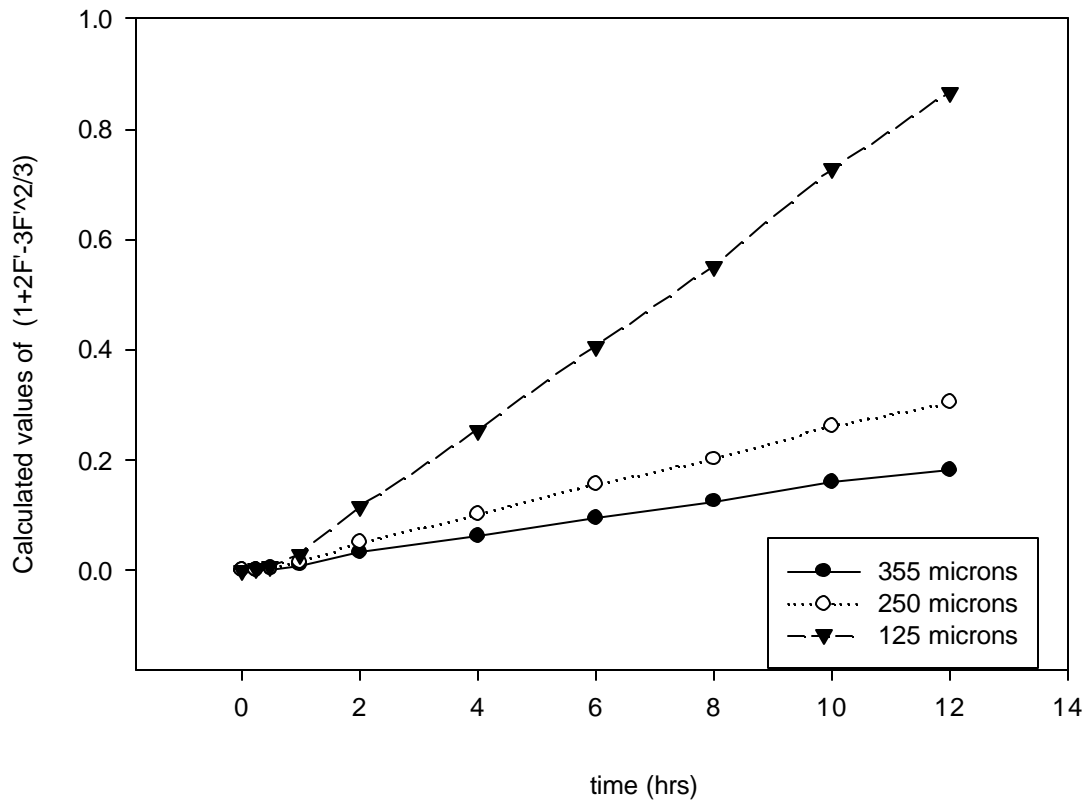K is a combined constant

T = Time

Figure 15: Higuchi spherical matrix plots for dissolution data of different microspheres sizes (formulation C) $[1+2\,F-3\,F^{2/3} = KT]$
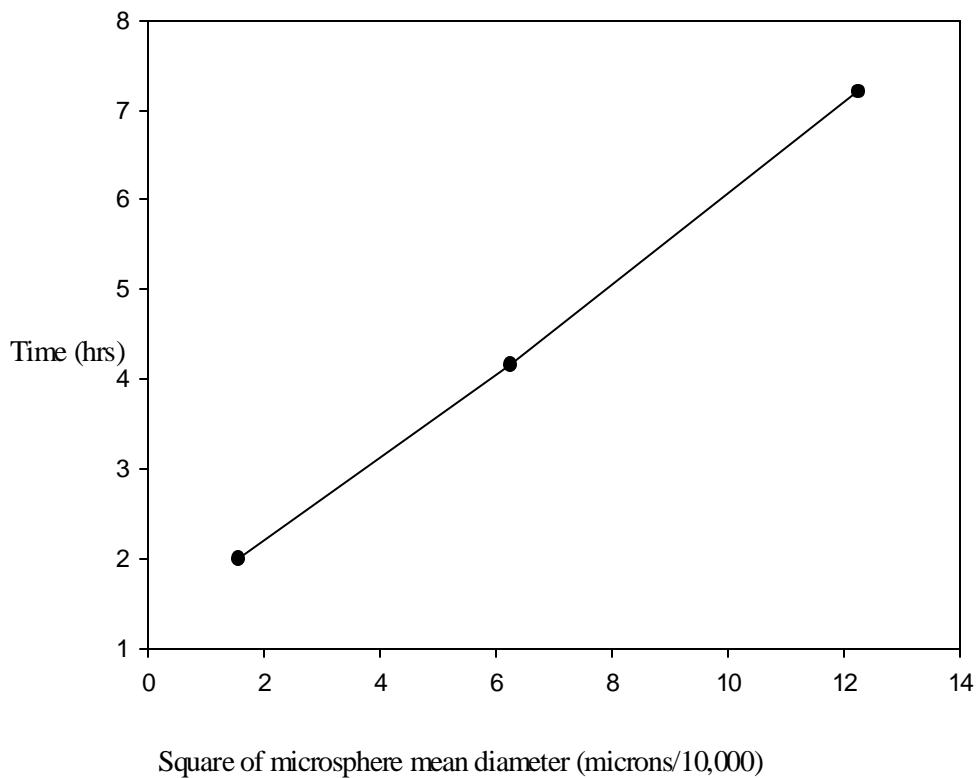
Figure 16: Relationship of Dissolution T50 to (Square of Microsphere Size/10,000)

MICROSCOPIC EVALUATION OF MICROSPHERES:

Scanning electron micrographs of the Formulation C microspheres are shown. The microspheres appear spherical with no external formation of drug crystals. (Figure 17)
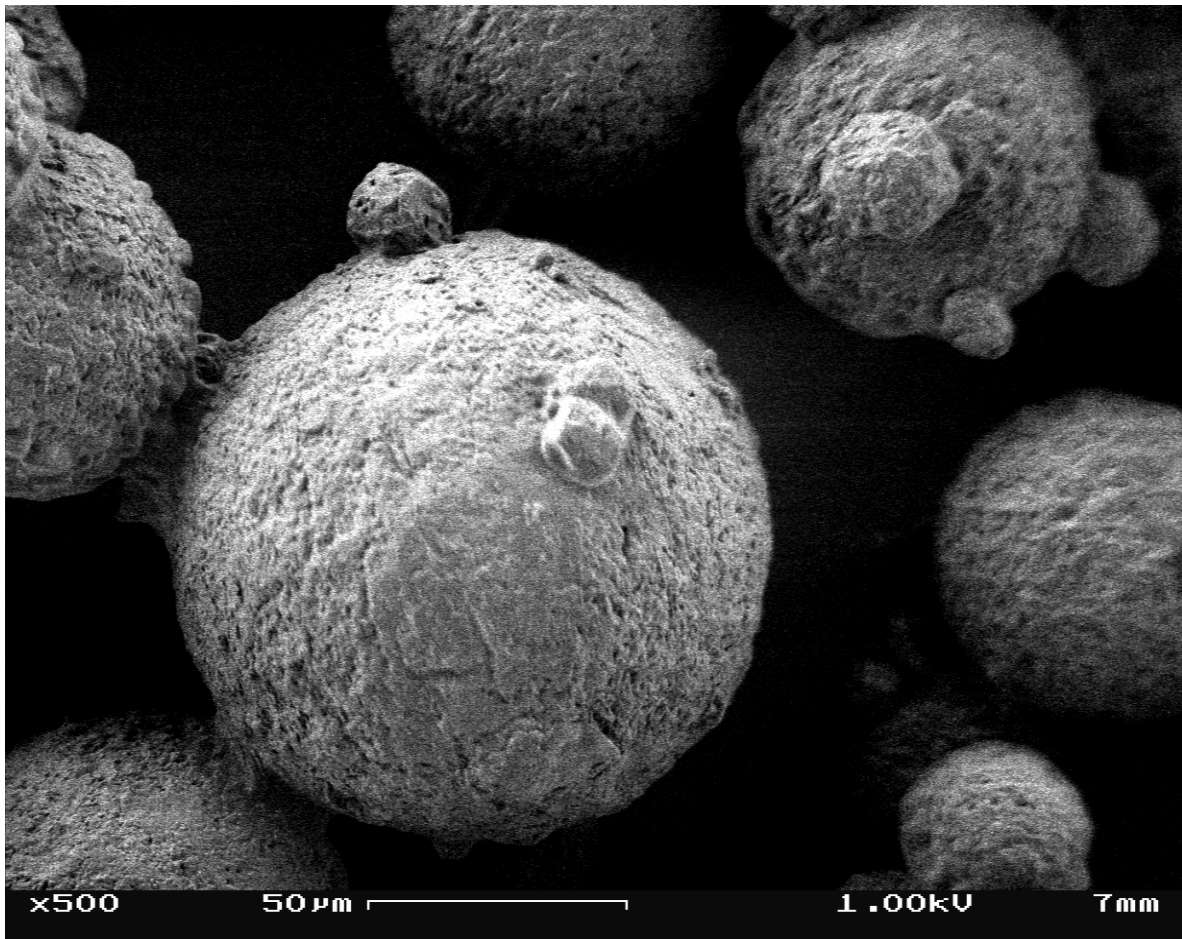
Figure17: SEM of microspheres prepared as Formulation C

After 12 hour dissolution study the microspheres maintained their spherical appearance with no drug crystals on their outer surface. (Figure 18)

The microspheres appear to have a matrix framework of wax from which diffusion of the drug occurs.
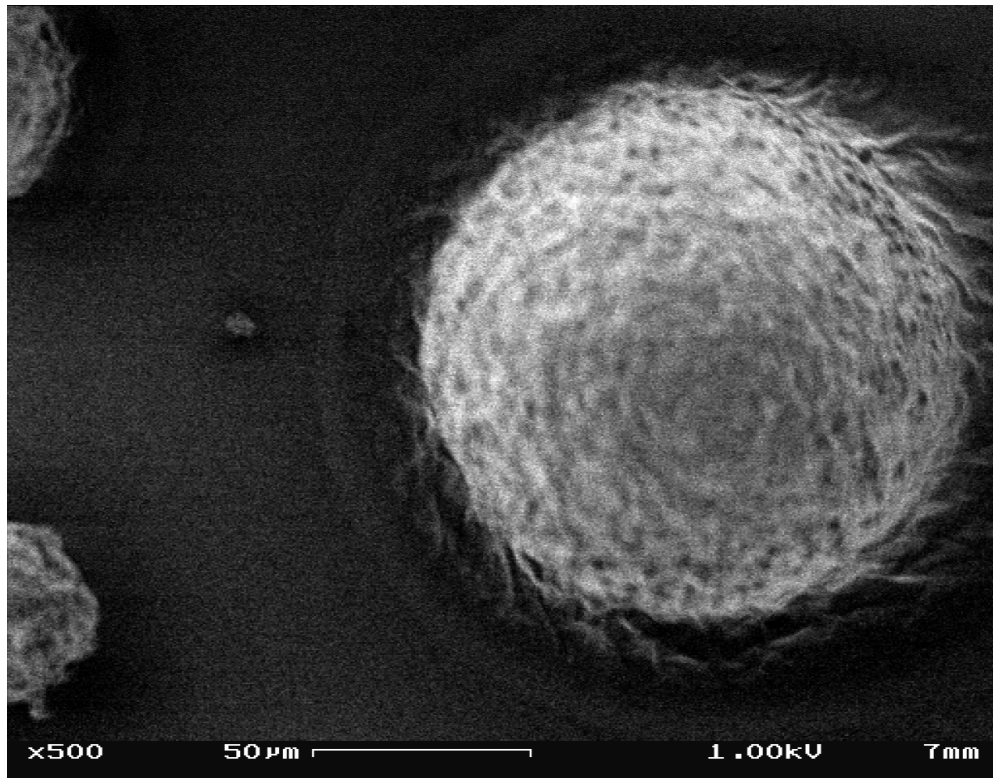

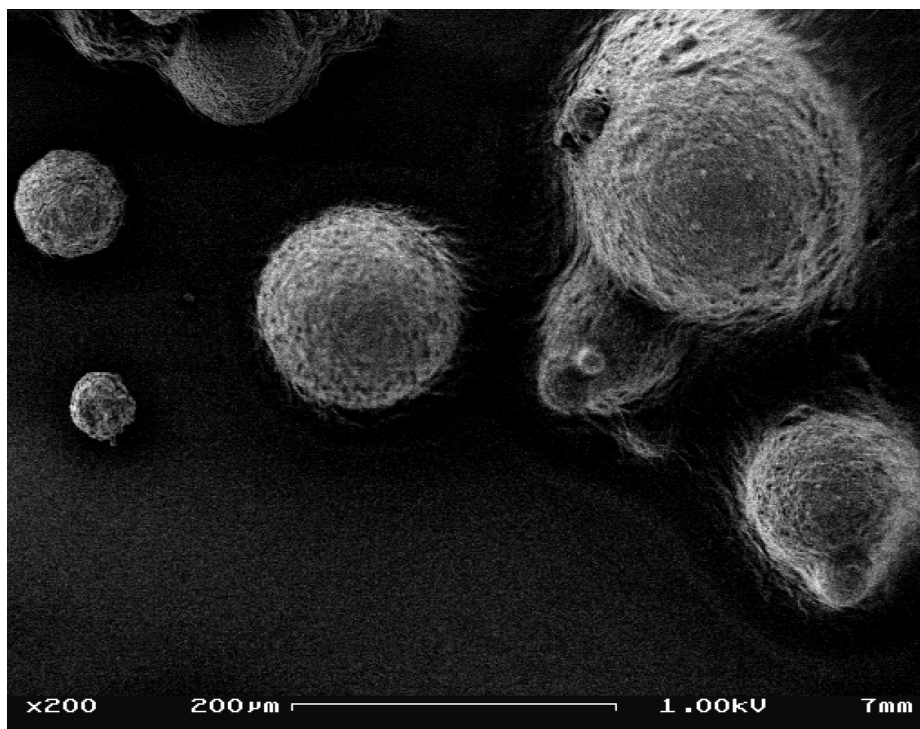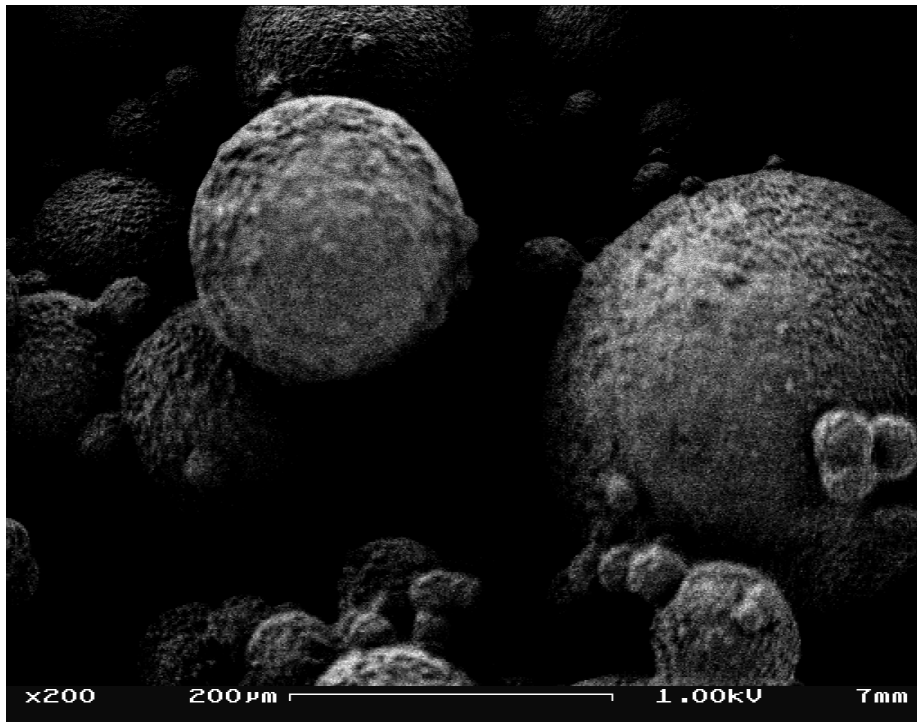Figure18 (a): SEM of microsphere after 12 hour Dissolution study

Figure18 (b) and (c): SEM of Formulation C microspheres after 12 hour Dissolution study.

PREPARATION OF TABLETED MICROSPHERES

The Formulation C microspheres were prepared with beeswax and ibuprofen in a ratio of 2:1.33 as previously described. The fraction of microspheres with a modal particle size of 250μ was compressed with Avicel® PH 101 and Explotab®. The tablet formulation used was shown in Table 3. Microcrystalline cellulose has been used as a diluent to assist in the compaction of the microspheres and to prevent the rupture and damage of the microspheres. It has been reported in literature that tablets containing Avicel® PH show fast disintegration (29), lower friability and higher hardness compared to other excepients such as lactose and Encompress (5, 30).

Explotab® (sodium starch glycolate) is a modified starch and has been described as a disintegrant whose disintegrating properties are independent of compression force (31). The concentration of the diluent and the disintegrant was kept constant throughout the study.

EVALUATION OF TABLETED MICROSPHERES

Effect of Compression Pressure on Tablet Properties:

Tablet formulations containing 42% microspheres, 55% Avicel PH101®, 3% Explotab® were compressed at pressures of 1000, 2000, and 4000 PSI (Pounds per Square Inch). The compression pressure was maintained for 40 seconds and then rapidly released.

(a)   Hardness: Tablet hardness has been defined as the force required to break the tablet in a diametric compression test. To perform this test the tablet was placed between the two anvils of the tester and the crushing force required to just break the tablet recorded. In the Erweka tester the tablet is placed on its edge on the lower anvil and the anvil adjusted till the tablet just touches

the upper test anvil. A suspended weight, motor driven, moves along a rail that slowly transmits pressure to the tablet. A pointer moving along a scale provides the breaking strength in Kilograms. The hardness of a tablet is a function of the die fill and the compression pressure. At a constant die fll, as the compression pressure increases, the hardness of the tablet usually increases. This relationship holds up to a certain maximum value for hardness and a minimum value for the thickness. With some formulations, further increases in the pressure cause the tablet to laminate or cap, thus destroying the integrity of the tablet. At constant compression force, the tablet hardness increases with increasing die fills because the testing force is applied over a larger area of the tableted material.

In this study, the compression pressure was varied and the die fills remained constant. The crushing force for the tablet increased as the compression pressure increased. Six tablets prepared at a particular compression pressure were tested and their average was reported. No capping or lamination was observed at the compression pressures used in this study.

Table 7: Effect of compression pressure on tablet hardness

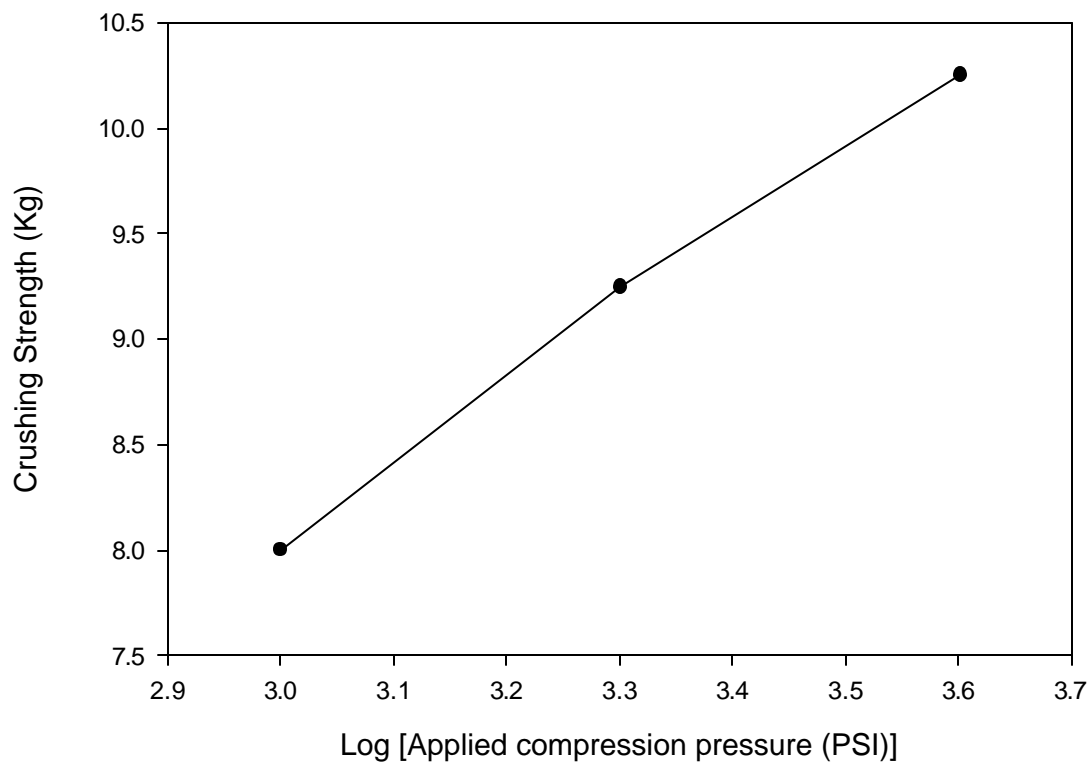| Compression Pressure [Pounds per Square Inch (PSI)]	Hardness [Kilograms]
1000	8.0 ($\pm$ 0.2)
2000	9.25 ($\pm$ 0.5)
4000	10.25 ($\pm$ 0.4)

Figure 19: Effect of compression pressure on tablet crushing strength.

In this study the hardness was directly proportional to the logarithm of the tablet compression pressure.

(b)   Tablet Thickness:

A compressed tablet's shape and dimensions are determined by the tooling used during the compression process. The thickness of a tablet is the only dimensional variable related to the process. Tablet thickness, like hardness is a function of the die fill and the compression pressure applied. Tablet thickness is consistent batch to batch or within a batch only if the tablet granulation or the powder blends is adequately consistent in its particle size and size distribution.

Six tablets from each batch were evaluated for their physical dimensions. The thicknesses of the tablets were inversely proportional to the compression pressure. As the compression pressure increased, the thickness of the tablets decreased.

The apparent density of the tablet is the quotient of the weight and the geometric volume. The apparent density of a tablet is exponentially related to the applied pressure, until the limiting density of the material is approached (32). Thus as the compression pressure increases, the void volume of the powder mix and the porosity decrease, whereas the apparent density of the material (calculated using the weights and the volumes of the finished tablets) increases.

Table8: Effect of Compression pressure on Tablet Thickness and Tablet Density

Compression pressure	Average Tablet Weight	Average tablet thickness	Average measured Radius of the tablet	Geometric Volume of the tablet (calculated)	Density of the tablet
Pounds per Square Inch (PSI)	(g)	mm	mm	(cm^3)	(g/ cm^3)
1000	0.503	3.58	6.34	0.4518	1.1132
2000	0.502	3.47	6.34	0.4380	1.1462
4000	0.503	3.29	6.35	0.4165	1.2075

The applied compression pressure was plotted against the apparent density of the tablets to give a linear curve. (Figure 20) This relationship indicates that consolidation of the particles results in plastic deformation but crushing and rearrangement of the microspheres is negligible.
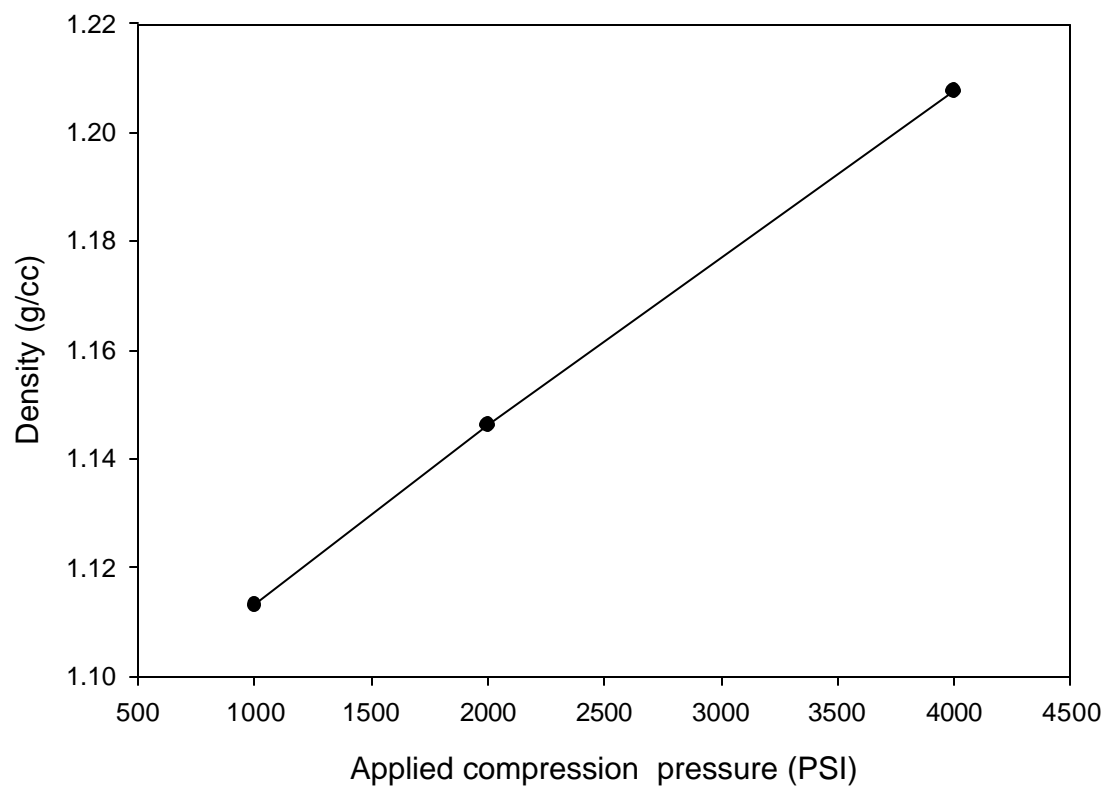
Figure 20: Effect of compression pressure on the apparent density of the tablets

This may be attributed to the good compressional characteristics of Avicel PH 101® and also to some extent to the pliable nature of the beeswax microspheres. Apparently on compression, plastic deformation of the particles occurs but fracture of particles is limited.

IN VITRO DISSOLUTION TESTING OF TABLETED MICROSPHERES:

Compression pressure was increased from 1000 PSI to 4000 PSI and tablets were prepared using the microspheres of particle size fraction with modal size 125μ. It has been reported that the compression of larger microspheres cause a notable increase in the drug release compared to the tablets prepared from smaller microspheres (5). The tablets were tested for drug release in SIF. It was found in this study that the increase in the compression pressure from 1000 PSI to 4000 PSI showed slightly slower release. The release from the tablets was slightly slower than the release from the untableted microspheres. (Figure 21)

This may be explained by the fact, that the formulations contained high amounts (55% of tablet formulation) of Avicel, which did not cause any rupture or fracture of the microspheres on tableting. The microspheres retained their sustained release properties, but showed a slight decrease in the drug release compared to the microspheres. This may be due to the formation of a hydrophobic tortuous matrix during compression of the microspheres. The increase in the T50 of tablets compared to microspheres is very small. This may be due to the good compressibility characteristics of Avicel, which did not cause significant fracture of the microspheres.
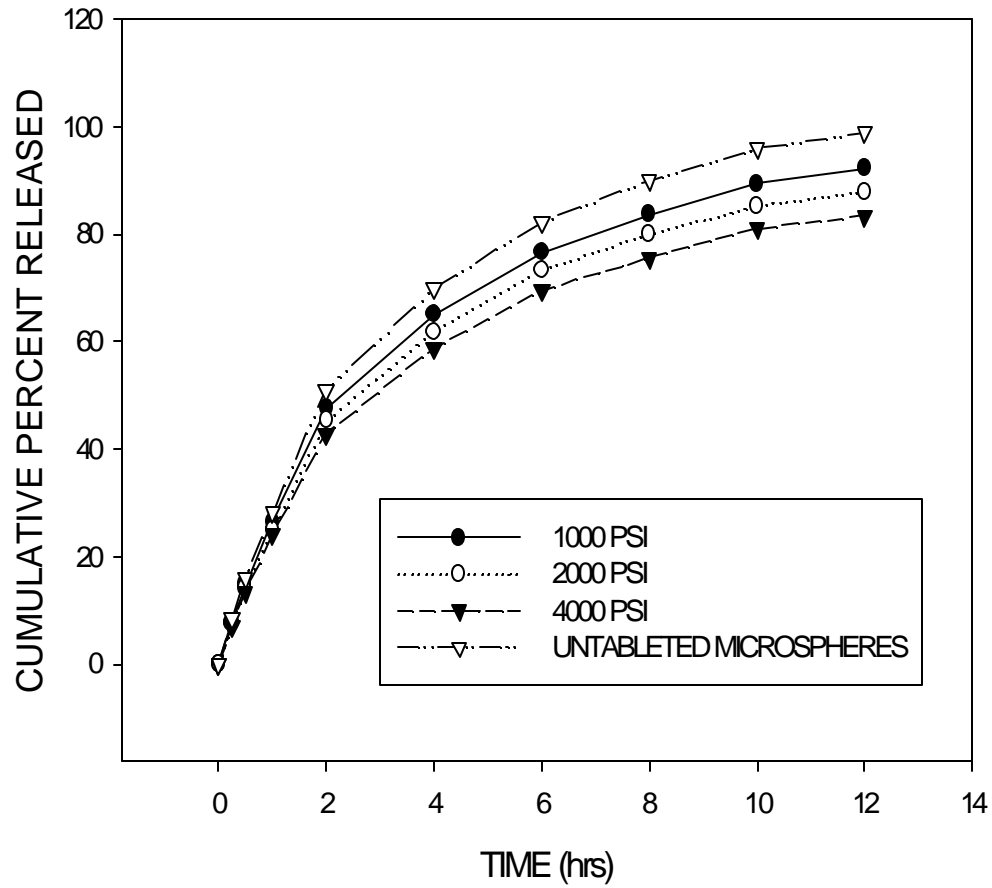
Figure 21: Effect of compression pressure on the drug release from the tableted microspheres and comparison of drug release from the tablets to the untableted microspheres (125μ).

Each tablet contains 42% microspheres (125μ, formulation C), 55% Avicel PH 101®, and 3% Explotab®.
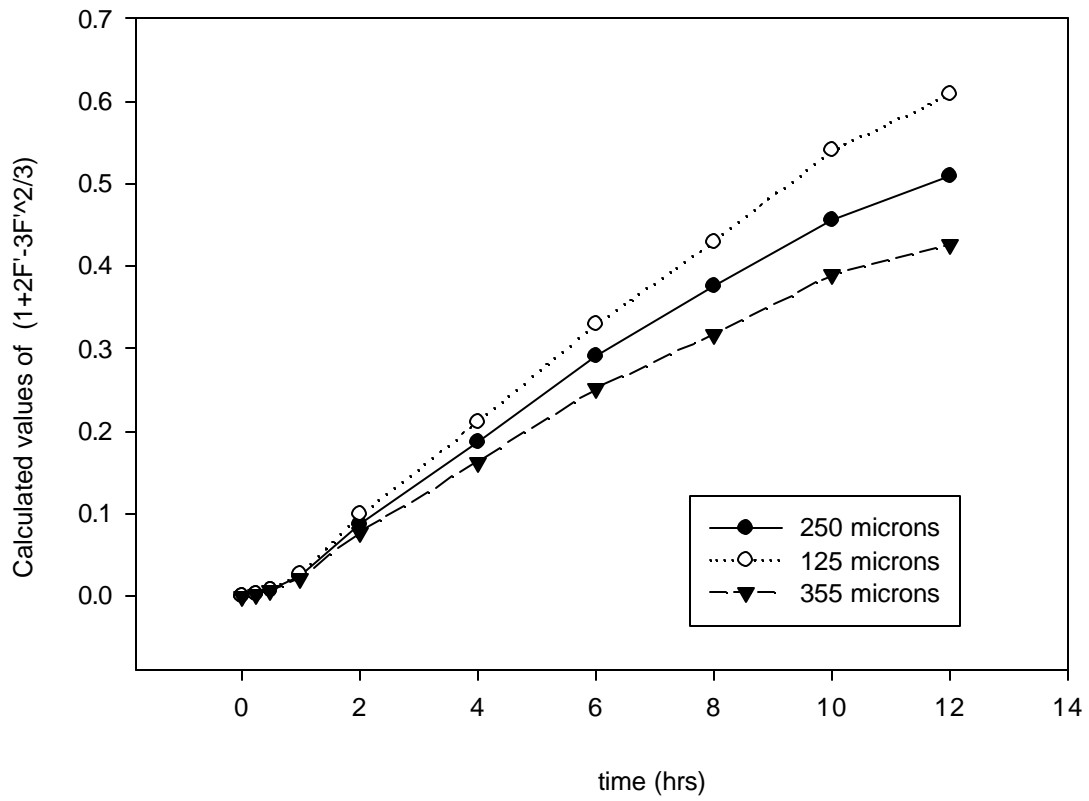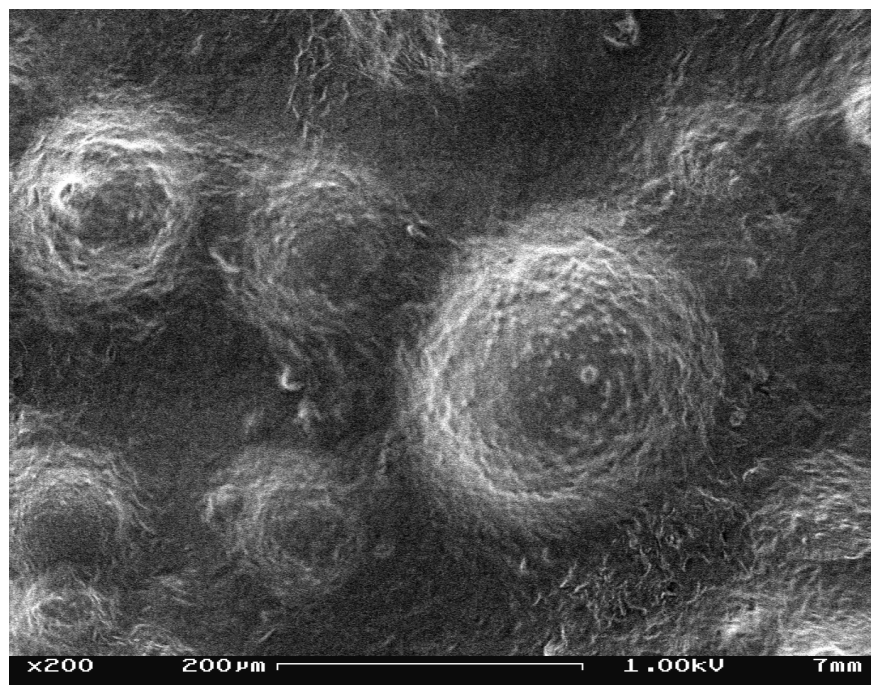
Figure 22: Higuchi spherical matrix plot for dissolution data from disintegrating tablets of

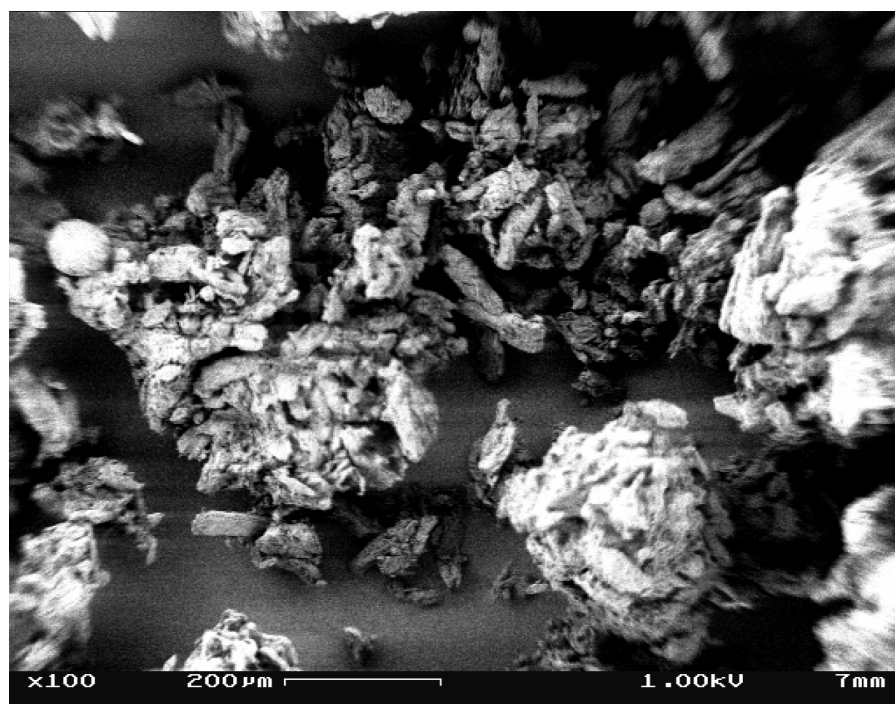microspheres compressed at different pressures.

(a)

(b)

Figure 23: SEM of tableted microspheres post dissolution study (a) 2hrs and (b) 12 hrs

MICROSCOPIC EVALUATION OF TABLETED MICROSPHERES:

Scanning Electron Micrographs of tablet surface and broken tablet surfaces are shown in Figures 17 and 18. The microspheres appeared deformed but intact. This would explain the similar in vitro dissolution profiles for both the tablets and the microspheres.
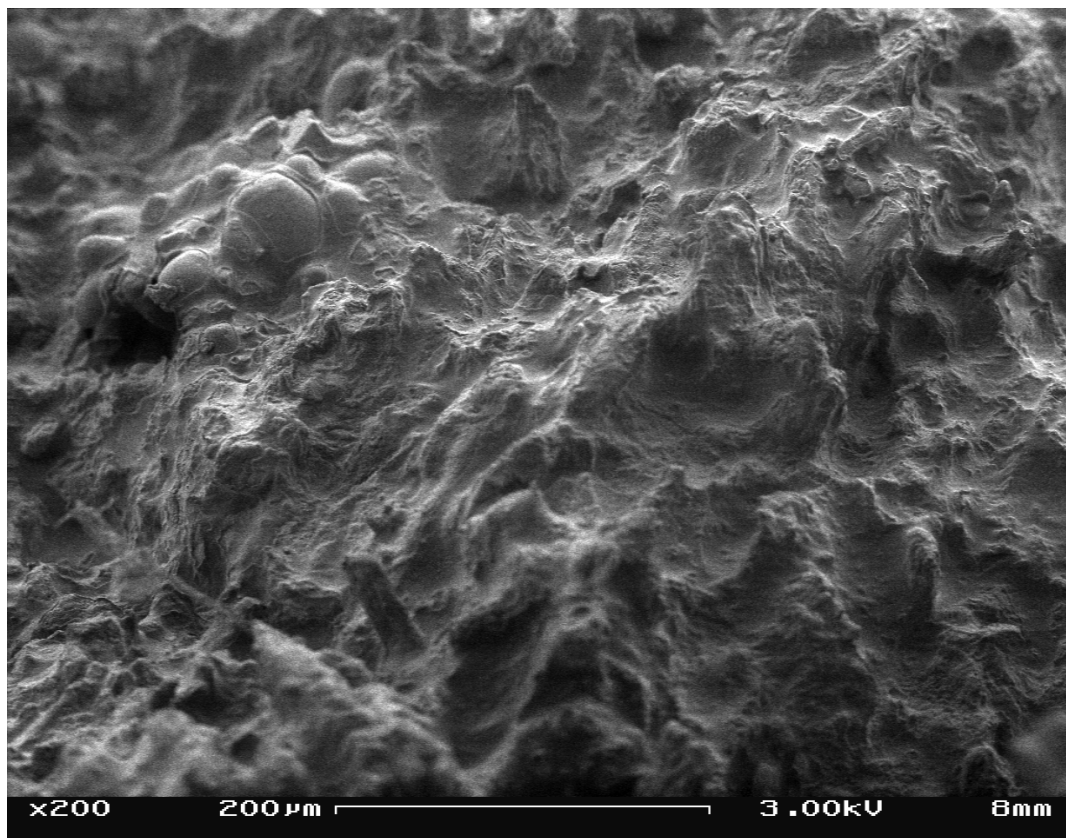

Figure 24: Scanning electron micrograph of tableted microspheres compressed at 2000 PSI

CONCLUSION:

Controlled release microspheres containing ibuprofen were prepared for ibuprofen using the hydrophobic congealable disperse phase microencapsulation method. Microspheres prepared with beeswax showed better encapsulation efficiency than with microcrsytalline wax. Microspheres prepared without stearyl alcohol to modify release did not show acceptable controlled release characteristics. The drug release from the microspheres was by diffusion of the drug and the drug release profile was described by Higuchi spherical matrix model over a substantial portion of the release. As particle size of the microspheres decreased, greater surface area became available for diffusion and diffusion path was shorter, hence they showed faster drug release. The optimized microsphere formulation was tableted at different compression pressures. The smaller microspheres are least likely to rupture and cause changes in drug release characteristics after compression. In this study it was found that as the compression pressure increased, the drug release rate from the microspheres decreased. At greater compression pressures, a small portion of the microspheres may be compressed together and did not disintegrate as the tablet disintegrates. This would reduce the surface area of the microspheres exposed to the dissolution medium. It was found that the compression at different pressures did not affect the drug release to a great extent. This may be due to the cushioning effect of the directly compressible diluent Avicel®. Due to the rapid disintegration of the microsphere tablet into smaller particles, it behaves as a multiple unit dosage form. This dosage form has a clinical advantage over the matrix controlled release or the conventional single dose tablets. The disintegrating multiple unit tablet prepared in this study provides a controlled release of the drug and could potentially have a more predictable gastric emptying and decrease the GI irritation caused by the non-steroidal anti-inflammatory drug, ibuprofen.

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