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Pharmaceutical approaches towards design and development of microsponges containing etodolac

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Abstract---The goal of the present study was to develop and evaluate microsp sponge-based gelatin Capsule for oral delivery system of Etodolac for controlled release and enhanced bioavailability and solubility of insoluble drug. Microsponges containing Etodolac were prepared by a Quasi-emulsion solvent diffusion method. The effect of formulation and process variables such as, polymer ratio and stirring speed on the physical characteristics of microsponges were examined on optimized drug/polymer ratio. The optimized microsponges were incorporated into a gelatin capsule shell. *In vitro* drug release studies were carried out. Capsules containing microsponges showed desired physical properties. The effects of drug to polymer ratios on physical characteristics of the microsponges were investigated. Thermal behavior, surface morphology, particle size and pore structure of the microsponges were examined. *In-vitro* drug release rate from the microsponges was also investigated. *In-vitro* dissolution study showed that the release rate of the drug has been modified. This study presents a new approach based on microsponges for colon specific drug delivery. The sizes of microsponges were found to be uniform and in the shape. The Infrared (IR) spectral analysis suggested that there was no interaction between the drug and formulation polymer. Microsponges containing Etodolac was prepared by quasi emulsion diffusion method and the best fit model was Higuchi with n value < 0.5 suggesting that the drug was released by fickian mechanism i.e., the drug was released diffusion-controlled mechanism. The release was found to be steady after 2 h and extended up to 8 h with sustained action and as the concentration of the polymer increases the drug release was decreased.

Keywords---microsponges, microsp sponge delivery system, eudragit (RS100), etodolac, controlled drug delivery system.

Introduction

Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. Although the microsp sponge size may vary, a typical 25 μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g (Kawashima et al., 1989). This results in a large reservoir within each microsp sponge, which can be loaded with up to its own weight of active agent. The microsp sponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to

these microsp sponge materials. various companies are utilizing its patented Microsp sponge system in the development of oral drug delivery system for improved bioavailability. There are many drugs that have a very low rate of solubility and whose efficacy could substantially be improved if their rate of solubilisation and hence bioavailability could be increased. Such systems are still in early research and developmental stage, but successfully done *in vitro* studies and preliminary *in-vivo* studies indicate that a microsp sponge drug delivery enhance the rate of dissolution of poorly water-soluble drugs by entrapping such drugs in microsp sponge pores. These pores are very small and the drug is in effect reduced to microscopic particles and thus significantly increases surface area by increasing the rate of solubilization (Wester et al., 1991).

Etodolac is a non-steroidal anti-inflammatory drug (NSAID) acting by a preferential inhibition of cyclo-oxygenase-2 (COX-2) enzyme. It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, osteoarthritis, and for the treatment of acute pain. It has an elimination half-life of 7 h, and the recommended oral dose, 200 to 400 mg, is given every 6 to 8 h to a maximum of 1.2 g daily (Indian pharmacopoeia, 2007, Raymond, 2006). To provide the desired drug concentration at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency, controlled-release preparations for once-daily use are desirable. In present study, microsp sponge based drug delivery system of Etodolac was planned to develop and characterize for reducing dosing frequency and thus to enhance patient compliance.

Materials and Methods

Materials

Etodolac was kindly provided by Windlas Biotech, Dehradun, Uttrakhand. Eudragit RS-100 provided by Evonik India, Mumbai, Maharashtra. Ethyl Cellulose and Triethyl citrate were purchased from Spectrochem. Pvt. Ltd., Mumbai. Ethyl Alcohol (Ethanol), Polyvinyl Alcohol, Acetone, Sodium Hydroxide (NaOH) and Di Sodium Hydrogen Phosphate were from Qualigens fine chemicals, Mumbai. Other chemicals (analytical grade) were used as received.

Methods

Preparation of microsp sponge by Quasi emulsion solvent diffusion method

The loading of drug in microsponges depends on physico-chemical properties of drug to be entrapped. If the drug is inert and non-polar type, then there is need to create the porous structure which is called porogen. All the microsponges were prepared using quasi-emulsion solvent diffusion method. All the ingredients were weighed as per the formula given in Table 1. Etodolac was accurately weighed and is dissolved in ethyl alcohol, to this Eudragit-RS 100 is added for the formulations FE1-FE6 and Ethyl Cellulose for FEC1-FEC6 at 60°C results in the formation of internal phase. To the internal phase, triethyl citrate was added to facilitate plasticity. Poly vinyl alcohol which is dissolved in water acts as external phase. Then internal phase is added to the external phase at room temperature and is stirred for 2 h. The mixture was filtered to separate microsponges and dried at

40°C for 2- 24h. For the evaluation of effect of drug: polymer ratios on the physical characteristics of microsponges, different ratios were employed (Perumal, 2001).

Selection of internal and external phase

For the selection of the internal and the external phases, various investigations were carried out using different combinations of internal and external phases with constant drug to polymer ratio of 2:1 and the stirring speed of 2000 rpm for a period of 8 hrs. Initial selections of both the phases were based on the solubility of the Etodolac and Eudragit and ethyl cellulose polymers (Mandal et al., 2001). Various combinations of internal and external phases were investigated and the results are shown in Table 1.

Effect of surfactant concentration

In order to know the optimum concentration of surfactant required for the formation of microsponges different concentration of polyvinyl alcohol ranging from 0.1%, 0.3 %, 0.5%, 0.75, 1.0%, 2% and 3% w/v of the external phase was used. Drug to polymer ratio of 2:1 and stirring speed of 2000 rpm for a period of 8hr was kept constant and the formed microsponges were observed for their physical characteristics (Tansel et al., 2002).

Effect of volume of external phase

In order to evaluate the effect of volume of external phase different volumes of external phase i.e. distilled water were evaluated using 30ml, 60ml, 90ml, 120ml, 150ml, 180ml, 210ml, 240ml, 270ml, and 300ml of the external phase but the drug to polymer ratio was kept constant at 2:1 in 20ml of ethanol as internal phase, stirring speed of 2000 rpm for a period of 8hr with surfactant concentration of 0.05% w/v of the external phase. The formed particles were evaluated for their physical characteristics, particle size and free drug content (Beruto et al., 2002).

Effect of volume of internal phase

In order to evaluate the effect of volume of internal phase different volumes of external phase i.e. ethanol were evaluated using 5ml, 10ml, 15ml, 20ml, 25ml, 30ml, 40ml and 50ml of the internal phase but the drug to polymer ratio was kept constant at 2:1 in 90ml of distilled water as external phase, stirring speed of 2000 rpm for a period of 8hr with surfactant concentration of 0.05% w/v of the external phase (Tansel et al., 2003). The formed particles were evaluated for their physical characteristics, particle size and free drug content and the results are tabulated in Table 1.

Effect of Stirring Speed on the formation of Microsponges

In order to evaluate the effect of stirring speed on the formation of microparticles, micro articles were prepared with different rpm of 500, 800, 1200, 1500, 2000, 2500 and 3000 keeping all the other variables constant and the formed

microsponges were evaluated for their free drug content and particle size as represented in Table 1 (Kilicarslan et al., 2003).

Effect of Stirring Time on the formation of Microsponges

In order to evaluate the effect of stirring time (duration of stirring) on the formation of microsponges, microsponges were prepared at different time intervals of 2hr, 4hr, 6hr, 8hr and 10hr keeping all the other variables constant and the formed microsponges were evaluated for their free drug content and particle size as represented in Table 1 (Tansel et al., 2003).

Effect of Drug: Polymer Ratio

In order to evaluate the effect of drug on the microsponges and its release characteristics, different Eudragit polymers to etodolac ratios (1:2, 1:4, 1:6, 1:8, 1:10, 1:12, and 1:14) were used to prepare microsponges. The concentration of Eudragit polymer was maintained at 10% and the internal phase volume was maintained at 20 ml. The formed microsponges were evaluated for their drug content, free drug, entrapped drug, loading efficiency and particle size. Results are reported in Table 1 (Kilicarslan et al., 2003).

Characterization of microsponges

Determination of percentage yield and percentage entrapment efficiency

Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of microsponges (Sato et al., 2004). Percentage yield can be calculated by using the formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} * 100$$

Accurately weighed Etodolac microsponges were taken in a stoppered test tube and extracted with 5× 10 ml quantities of phosphate buffer pH 7.4. The extracts were filtered and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer pH 7.4. The solutions were subsequently diluted suitably with phosphate buffer pH 7.4 and Spectrophotometric absorbance was taken at 223 nm to calculate percentage drug entrapment and the percentage entrapment efficiency (PEE) is calculated (Hazenedar et al., 2004) by the formula is given below.

$$\text{Percentage entrapment efficiency} = \frac{\text{Drug loading in microsp sponge}}{\text{Theoretical drug loading}} * 100$$

Surface Morphology of Microsp onge

The surface morphology of the prepared microsponges was observed by scanning electron microscope (SEM) using HITACHI S 3400 N, Japan in Birbal Sahni Institute of Paleobotany. Pictures of the prepared microsponges were taken at different accelerating voltages at 30 and 36 µm working distance (Rojnik et al., 2005).

Particle size Determination

Particle size and size distribution of microsp sponge particles was done by using optical microscopy. The values were given for the formulations in the form of mean particle size range. This is done by stage micrometer and eye-piece micrometer (Chen et al., 2005).

Fourier-transform infrared (FT-IR) Spectrophotometric Study

To identify the presence of organic functional groups, FT-IR spectrum of Etodolac was recorded in potassium bromide (anhydrous grade) pellets, on FTIR spectrophotometer (Perkin Elmer Model 1700) (Chen et al., 2005).

Differential Scanning Colorimetry (DSC)

DSC was performed using Differential scanning calorimeter (Mettler Toledo, Model 821 e DSC at National Institute of Pharmaceutical Education and Research (NIPER) Mohali, Punjab) at a scanning rate of 10°C / min over a temperature range of 0 to 300°C, under an inert nitrogen atmosphere at a flow rate of 20ml/min. The samples were accurately weighed in to aluminium pan and hermetically sealed with aluminium lid. The thermograms of drug, Polymer and microsp sponge formulation were recorded (Orlu et al., 2006).

X-Ray Diffraction

The X-ray diffraction patterns were determined for the drug, polymer and microsp sponge formulation. Samples were exposed to a monochromatic nickel-filtered copper radiation (45 kV, 40 mA) in a wide-angle X-ray diffractometer (Seiffert.in, USA from ACMS lab at Indian Institute of Technology, (IIT), Kanpur) with 2 θ angle (Chen et al., 2005).

Preparation of capsules with optimized microsponges

The preparation of microsp sponge capsule was done manually accurately weigh the microsp sponge powder which contains the equivalent amount of 200 mg of Etodolac and fill in the gelatin capsule shell (Chadavar et al., 2007).

***In Vitro* dissolution studies of microsp sponge capsule**

The dissolution rate of Etodolac microsponges Capsule were studied using USP dissolution test apparatus employing Basket method. Accurate number of capsules was taken which samples of microsponges were calculated to contain 200 mg Etodolac. They were in basket and then placed in 900 ml of phosphate buffer pH 7.4 with a basket speed of 50 rpm and temperature of 37°C \pm 0.5°C was employed. Aliquots (5ml) were withdrawn at 1, 2, 4, 6, 8 hr and assayed spectrophotometrically at 223 nm. The percentage of drug released at various time intervals was calculated and plotted against time (Yan et al., 2006).

Kinetic Modeling of Dissolution Profiles

In phosphate buffer (pH 7.4), the dissolution profiles of the medication from all formulas were fitted to zero-order, first-order, and Higuchi models. The best-fitting model was determined by having the greatest correlation coefficient.

Result & Discussion

Selection of parameters

Etodolac is insoluble in water. Hence, water was selected as external Phase with PVA as surfactant to facilitate the formation of emulsion. Both the drug and the polymer are found insoluble in water and get solidified when poured into water. Ethanol was selected as internal phase as it showed the highest drug entrapment of about 63.04% for RS 100 and 60.22% for ethyl cellulose. The rate of diffusion of this solvent was high when compared to other solvents, thus decreasing the time required for preparation. The drug and polymer were found to be freely soluble in Ethanol the solvent providing better entrapment of the drug and imparting good microsponges characteristics. The minimum concentration of retardant material required in the internal phase was found to be 7% w/v in case of Eudragit RS 100 and 8% w/v in case of Ethyl Cellulose (Bhatia et al., 2018). At these concentrations, microsphere formation was initiated and below this concentration the microspheres were formed. 10% w/v was chosen as optimum because at this concentration, the microspheres showed good physical characteristic like proper shape, size, porosity, particle size distribution and did not collapse even after removal from the solvent and subsequent drying. The type and concentration of surfactant (emulsifier) has a key role to play in the preparation of microspheres. Microspheres did not form in absence of surfactant. By varying the concentration of surfactant from 0.1% to 3.0% w/v of the external phase, the particle size also varied from 436 μ m to 668 μ m for Eudragit RS-100 and from 498 μ m to 639 μ m for Ethyl cellulose (Atmaram et al., 2015). The minimum concentration of surfactant required to bring about the formation of uniform microspheres was found to be 0.05% w/v of external phase which resulted in the particle size of 275 μ m for Eudragit RS 100 and 283 μ m for Ethyl Cellulose. Though it was found that the particle size increased with the increase in the surfactant concentration, high amounts of surfactant resulted in foaming. This resulted in formation of irregular particles and at increased concentration the encapsulation efficiency was also reduced (Mahant et al., 2015). This may be due to less amount of polymer available for encapsulating the smaller droplets of Etodolac particles. An increase in mean particle size of microspheres with increasing emulsifier concentrations and this can be attributed to an increase in the viscosity at increased emulsifier concentrations Such increased viscosity would result in larger emulsion droplets and finally in greater microspheres size. When the concentration of emulsifier was decreased, the production yield, and drug content increased, whereas, the mean particle size of microspheres decreased. The volume of external phase plays a crucial role in the formation of microspheres with reduction in free drug concentration and particle size (Perumal, 2001). The results of the study show that the particle size ranged from 237 μ m to 614 μ m for Eudragit RS-100 and 214 μ m to 596 μ m for Ethyl cellulose. The free drug concentration varied from 6.4% to 19.92% for Eudragit RS- 100 and 7.16%

to 24.7% for Ethyl cellulose, when the volume of external phase varied from 30 ml to 300 ml. It was found that 90 ml was the optimum volume necessary and resulted in the mean particle size of 325 μ m for Eudragit RS-100 and 298 μ m for Ethyl cellulose with free drug concentration of 3.56% for Eudragit RS-100 and 3.40% for Ethyl cellulose. It was found that by decreasing the solvent volume (ethanol) the particle size of microsponges increases. When the viscosities of the internal phase of these formulations were investigated, it was found that particle sizes of microsponges were directly proportional to the viscosity of dispersed phase. When the dispersed phase with higher viscosity was poured into the continuous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion could not be divided into smaller particles and bigger droplets were formed and mean particle sizes increased (Mandal et al., 2001). The results showed that the particle size was dependent on the solvent volume and the drug: polymer ratio, when the solvent diffusion method was utilized for preparing microsponges. Table 2 also shows that when the amount of ethanol was increased from 5.0 to 50.0ml the % entrapment and drug content of microsponges decreased. This was probably due to the lower concentration of the drug in the higher volume of ethanol (Sato et al., 2004). The effect of stirring rate on the physical characteristics of the formulated microsponges was examined for 2:1 drug: polymer ratio microsponges. The results of stirring rate on the mean particle size, of microsponges, drug content and % entrapment is shown in Table 2. The results showed that, increasing the stirring speed from 500 to 4000 rpm decreased the % Entrapment from 93.43% to 85.59% for Eudragit RS-100 and from 90.18% to 81.74% for Ethyl cellulose. It was also observed that at the higher stirring rates employed, due to the turbulence created within the external phase. Table 2 also shows that the stirring rate employed had a marked effect on particle diameter (Rojnik et al., 2005). It was found that the stirring rate of the emulsion at the time of manufacture influences the particle size and, in some cases, the size distribution of the prepared microsponges. Hence, a suitable stirring rate to optimize particle size, size distribution and subsequent drug release from microsponges was needed (Atmaram et al., 2015). The study showed that an increase in the stirring rate resulted in reduction of mean particle size. Any increase in mean particle size at lower stirring rates could be attributed to the increased tendency of globules to coalescence and aggregate. On the other hand, at higher stirring rates, a vigorous, uniform, increased mechanical shear is imposed and this results in a rapid dispersion of the formed droplets which may have less chance of coalescing into bigger droplets. This suggested that the size of the droplets formed during the encapsulation process might therefore be closely related to the size of the final microsponges produced. The effect of time of stirring on the microsponges was examined on the formulation with 2: 1 drug polymer ratio at stirring speed of 2000 RPM and at various duration of stirring (Bhatia et al., 2018). It was found that stirring time also played a crucial role in the formation of microsponges with reduced free drug content and particle size. The results of the study showed that the particle size ranged from 402 μ m to 436 μ m for Eudragit RS-100 and 386 μ m to 408 μ m for Ethyl Cellulose with free drug content ranging from 7.75% to 35.99% for Eudragit RS-100 and 11.62% to 34.26% for Ethyl cellulose. Stirring for 8 hours at 2000 RPM speed resulted in better microsponges. It was found that drug to polymer ratio in the internal phase had some effect on the particle size. The results of the effect of drug: polymer ratio on production yield, drug loading

efficiency and mean particle size are shown in Table 2. The mean particle size ranged from 419 μ m to 119 μ m and 404 μ m to 103 μ m for Eudragit RS-100 and Ethyl cellulose respectively when the drug to polymer ratio was increased from 2:1 to 14:1 (Orlu et al., 2006). The encapsulation efficiency gradually increased with increase in the Drug: Polymer ratio till 12:1 ratio but no further increase in the encapsulation efficiency was found with increasing Drug: Polymer ratio. Hence, the preparation of microsponges was stopped at the ratio 14: 1. The production yield increased with increase in the drug: polymer ratio. But the mean particle size decreased, and the particle size distribution became narrower. This may be due to higher viscosity and faster diffusion of the internal phase from the emulsion system. Two polymers like Eudragit RS-100 and Ethyl Cellulose were used to form microsponges. The effect of these polymers on particle size, size distribution, percentage yield and encapsulation efficiency were studied. The results showed that there was a significant difference between the polymers Table 2. In all the parameters Eudragit RS-100 was leading over Ethyl Cellulose. The particle size for Eudragit RS-100 was lower than Ethyl Cellulose but it was found that the encapsulation efficiency was better in case of Eudragit RS-100 (Hazenedar et al., 2004).

Particle Size Analysis

The particle sizes of different formulations are shown in Table 2. The hydrodynamic radius of the particles was measured by micrometer microscope. Particle size is often used to characterize microparticle, because it facilitates the understanding of the dispersion and aggregation. Samples for micrometer measurement must consist of a well-dispersed phase in a suspending medium. When the samples look milky, the concentration is too high, and the best procedure is to dilute the sample. Samples were diluted with double-distilled water and subjected to size and charge analysis. The importance of the emulsifier on the size of microsp sponge Particle has also been demonstrated on microparticle based microsp sponge dispersions. Because of larger surface area and attractive force between the particles, the chance of possible aggregation is high in small-sized particles. To overcome such aggregations, an addition of a TEC (Triethyl-Citrate) in the preparation was necessary. The TEC increase the Plasticity of particles by forming a steric barrier on the particle surface, thereby protecting the particles from coagulation. In the present work the same concentration of TEC is used.

Drug loading and Entrapment efficiency

The percentage drug loading and entrapment efficiency in different formulations are shown in Table 2. Loading capacity refers to the percentage of drug incorporated into the Polymer microsponges relative to the total weight of the phase (i.e., Polymer + drug). The drug loading depends on the solubility of the drug in the solid Polymer. The entrapment efficiency is the function of the characteristics of Polymer, drug and solvent. The entrapment efficiency depends on the affinity of drug and Polymer in the same organic or aqueous phase. Polymer crystalline structure has been correlated to drug loading and release behaviour. In each case, researchers reported that amorphous structure provides superior drug loading and retention than more crystalline structure. In the

microsponges structure, the lipid forming crystalline state with a perfect lattice would lead to drug expulsion. The drug can locate between polymer molecule chains, between polymer layers, and in polymer crystal imperfections. The chemical properties of the polymer affect the crystallinity of solid particle. It has been suggested that polymer that form more perfect crystalline solids, such as Eudragit and Ethyl Cellulose having a crystal structure, expel solubilised drugs and that these polymers that form less-perfect crystalline structures, possess higher loading capacities. So, the Polymers, a Eudragit RS-100 and Ethyl Cellulose, may act as the most suitable carrier for the loading of Etodolac. The formulations FE2 (Eudragit RS-100) and FEC5 (Ethyl Cellulose) produced high drug loading and entrapment efficiency than and FE1 (Eudragit RS-100) (Sato et al., 2004, Kilicarslan et al., 2003).

Analytical behavior of microsponges

DSC thermogram of Etodolac, Eudragit RS-100 and Ethyl Cellulose is shown in Figure 1. It is a tool that gives an insight into the melting and recrystallisation behaviour of crystalline materials like solid microsponges. The basis for DSC is the fact that different modifications possess different melting points and melting enthalpies. Measurements of crystalline and other modifications are necessary because these parameters are strongly correlated with drug incorporation and release rates. The thermogram of the drug showed a sharp melting peak at 176.6°C. The melting peak of Eudragit RS-100 appeared at 191.83°C whereas in Ethyl Cellulose the melting peak was found to 196.83°C. The melting point of the Microsponge decreased from 196.83°C to 191.83°C by the incorporation of the drug. This could be due to reduction in particle size (Kelvin effect), which leads to increase in surface area there by leading to a decrease in melting enthalpy as compared with heat flow through larger crystals, requiring more time and probably due to the presence of the Polymers. The endothermic peak of Etodolac in Polymers was depressed, broadened and shifted to lower temperature at 142.40°C, which may be due to the micrometric size of the particles that had a huge surface area besides a certain effect of Polymers. These results could indicate that the drug does not exist in the crystalline state in the solid Microsponges either because drug crystals completely dissolve inside the Polymer matrix during the scanning of temperatures up to the melting value or because the drug remained dispersed at molecular level inside the solid dispersion after the formation of Microsponges (Beruto et al., 2002).

X-ray diffraction has been used for the study of molecular structure and polymorphism of microsponges (Figure 2). The sharp peaks in the XRD pattern of Etodolac were indicating the crystalline nature of drug. The characteristic peaks for Etodolac were absent in the microsponges formulation. The crystalline peaks of Etodolac overlapped with the noise of coated Polymers. From this, it is evident that an XRD signal of encapsulated drug is very difficult to detect, which shows that the drug is dispersed at a molecular level in the Polymer matrix and hence no crystals were found separately in the drug-loaded matrix (Wester et al., 1991).

FT-IR peaks of pure drug Etodolac obtained at 1760 cm^{-1} is due to the aliphatic C-H group. This value is low and this may be due to strong intermolecular

hydrogen bonding. Other characteristic peaks of drug were obtained at 1611 cm^{-1} (secondary NH- stretching), 1034 cm^{-1} (C=O stretching), 1578 cm^{-1} and 1499 cm^{-1} (aromatic bending). Similarly, the characteristic peaks for the Eudragit Polymer were obtained at 1720 cm^{-1} . In the spectrum of microsphere formulation, significant peaks were obtained at 1740 cm^{-1} (secondary-NH-stretching), 1034 cm^{-1} , 1409 cm^{-1} (aliphatic CH stretching) (Figure 3). The peaks corresponding to the Etodolac and Eudragit were obtained at the same wave numbers in the microsphere formulation. This indicates that there is no interaction between the Etodolac and polymers (Kawashima et al., 1989).

SEM was used to examine the morphology and surface topography of prepared microspheres. Microspheres produced were extremely porous, primarily spherical, and there were few whole Etodolac visible in SEM photomicrographs (Figure 4). Pores were created by allowing solvent to diffuse from the surface of microspheres. Furthermore, the unique interior structure was revealed to be a spherical hollow containing a rigid shell made of drug and polymer (Wester et al., 1991).

In Vitro Drug Release

The release profile of Etodolac from microspheres in phosphate buffer pH 7.4 is shown in Figure 5. The principal reason is that the solid microspheres are solid at room temperature, and the mobility of the drug is low, which makes microspheres a potential carrier for prolonged release. The release of a drug from the microspheres can be influenced by the nature of the Polymer matrix, Solvent concentration, solubility of the drug in Buffer solution and production parameters (Atmaram et al., 2015). Super-cooled particles undermine the benefits of the solid, namely, the physical stability and increased resistance to drug release. The initial burst release followed by the Controlled release was observed in all the formulations (Figure 5). Burst release was observed in all the formulations at the initial 2 h and it released nearly 20% of the drug from the microspheres, after which a prolonged release was obtained. The initial burst release may be probably caused by the drug adsorbed on the surface of microspheres or precipitation of drug from the microspheres. The complex factor that contributes to a fast/burst release is the short diffusion distance for the drug which is possible when the drug is enriched in the outer surface region of the microspheres and such enrichment might occur during the solidification of the microsphere during the cooling period. Additional reason for the burst release of drug from microsphere might be the surface area available for drug release and the accelerating effect produced by the surfactants. All the formulations exhibited a prolonged release with less than 75% of drug released up to 8 h (Mahant et al., 2020). The interactions between drug-polymer molecules, between solvent polymer molecules, and solubility of the drug in the solid polymer play a major role in achieving the controlled drug release. The sustained release was obtained due to slow diffusion of the lipophilic drug from the polymer matrix as the surrounding polymer shell hinders the release of drug (Chadavar et al., 2007).

In Vitro Release Kinetics

In order to determine the release model which best describes the pattern of drug release, the *in vitro* release data after the burst release period (i.e., after 2 h) were substituted in zero order and Higuchi equations. The first-order rate, which describes the drug release rate is independent of its concentration. Higuchi model describes the release of drugs from an insoluble matrix as the square root of a time dependent process, based on Fickian diffusion. After the comparative evaluation of r^2 values, the kinetics of drug release from the microsponges was found to follow first order as the plots of log cumulative percentage drug release versus time were linear (r^2 value ranged from 0.951 to 0.984) and the mechanism of drug release from the solid microsphere was found to be diffusion controlled because plots of percent cumulative drug release versus square root of time were found to be linear with the regression coefficient (r^2) values ranging from 0.958 to 0.988.

The results were in agreement to the one obtained with Etodolac microsphere in which the drug release from microsphere has been reported to follow Higuchi model. This may be due to the formation of a core enriched with active compound leading to a membrane release governed by Fick's law of diffusion. Due to erosion of polymer material and diffusion of drug through the polymers, a constant release rate was observed. It was further confirmed by n values. The results indicated that increasing the proportion of Eudragit RS-100 and ethyl cellulose decreased the release rate of drug, which may be due to the slow rate of penetration of dissolution medium into the microsphere (Beruto et al., 2002).

Conclusion

Ethyl cellulose and Eudragit RS 100 were used to create a microsphere drug delivery system that entrapped etodolac. Entrapment may induce a change in the drug's release rate, resulting in a reduction in the severity of adverse effects.

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Table 1: Formulation design using deferent concentration of Ingredients

Formulation Code	Etodolac (gm)	Eudragit Rs-100 (gm)	Ethyl Cellulose (gm)	Polyvinyl Alcohol (PVA) (gm)	Tri- Ethyl Citrate (TEC) (mL)	Ethyl Alcohol	Water
FE1	1	1	-	0.05	1.92	20	150
FE2	1	1.5	-	0.05	1.92	20	150
FE3	1	2	-	0.05	1.92	20	150
FE4	1.5	1	-	0.05	1.92	20	150

FE5	2	1	-	0.05	1.92	20	150
FE6	2.5	1	-	0.05	1.92	20	150
FEC1	1	-	1	0.05	1.92	20	150
FEC2	1	-	1.5	0.05	1.92	20	150
FEC3	1	-	2	0.05	1.92	20	150
FEC4	1.5	-	1	0.05	1.92	20	150
FEC5	2	-	1	0.05	1.92	20	150
FEC6	2.5	-	1	0.05	1.92	20	150

Table 2: Table showing the percentage yield, percentage entrapment efficiency and mean particle size of microsponges

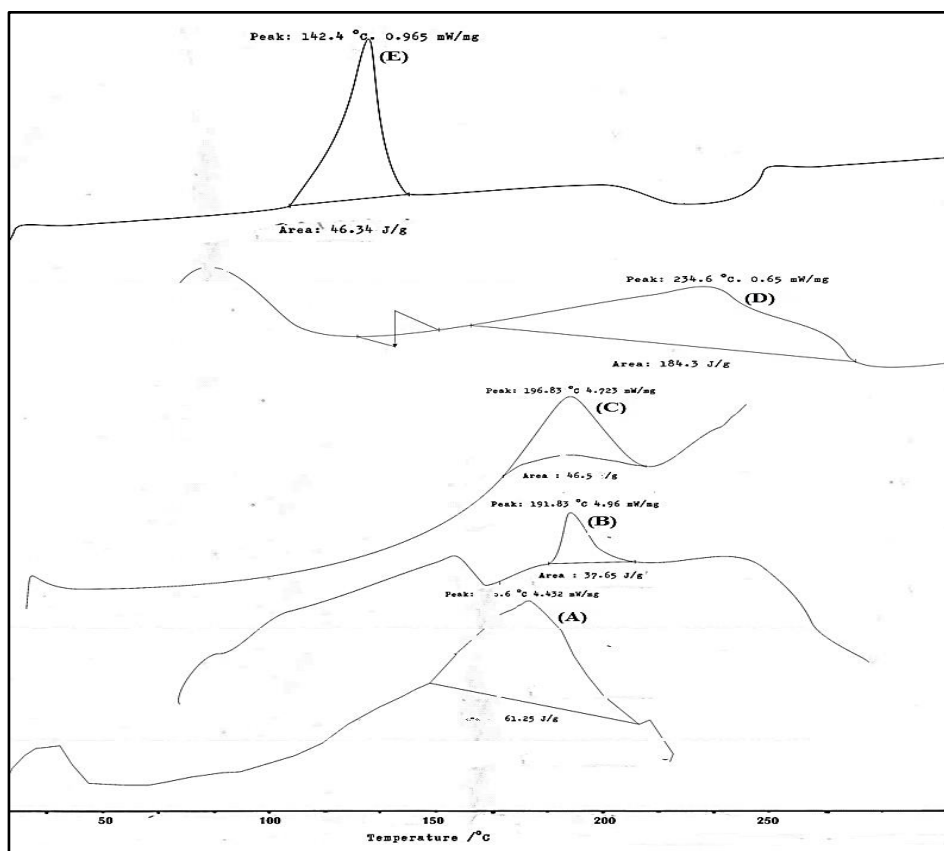


Figure 1: DSC Thermogram of (A): Pure Etodolac Drug; (B): Eudragit RS-100 Polymer; (C): Ethyl Cellulose Polymer; (D): FE1 (Etodolac: Drug 1:1); (E): FE2 (Etodolac: Drug 1:1.5)

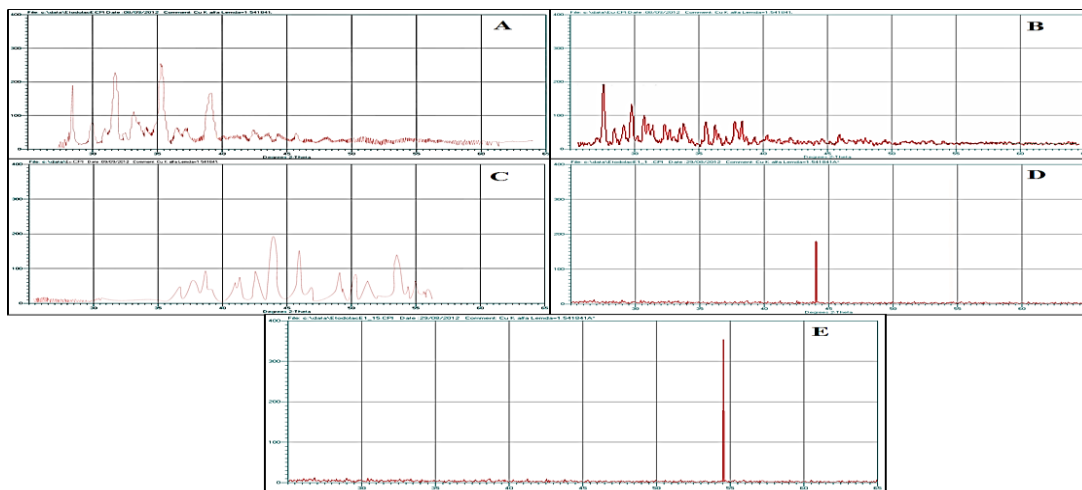


Figure 2: XRD of (A): Pure Etodolac Drug; (B): Eudragit RS-100 Polymer; (C): Ethyl Cellulose Polymer; (D): FE1 (Etodolac: Drug 1:1); (E): FE2 (Etodolac: Drug 1:1.5)

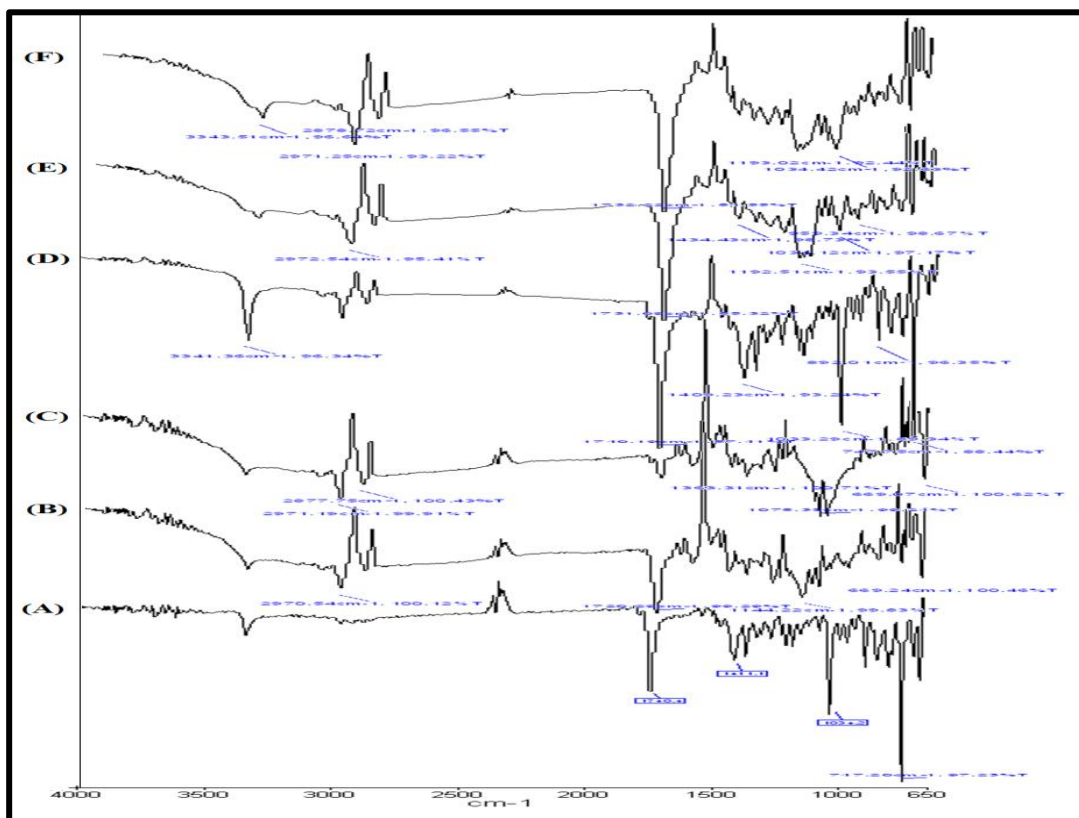


Figure 3: XRD of (A): Pure Etodolac Drug; (B): Eudragit RS-100 Polymer; (C): Ethyl Cellulose Polymer; (D): FE1 (Etodolac: Drug 1:1); (E): FE2 (Etodolac: Drug 1:1.5); (F): FEC1 (Etodolac: Ethyl Cellulose 1:1)

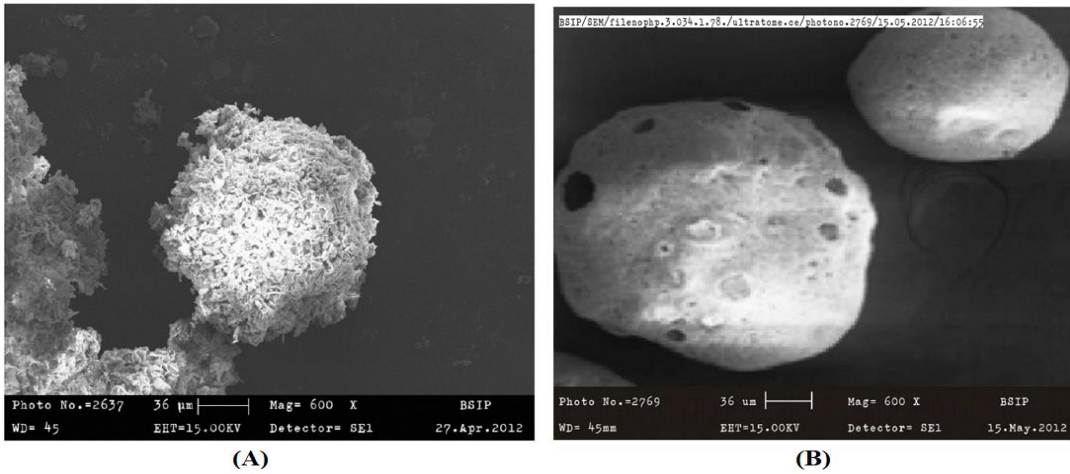


Figure 4: SEM images of Etodolac Loaded Microsponges

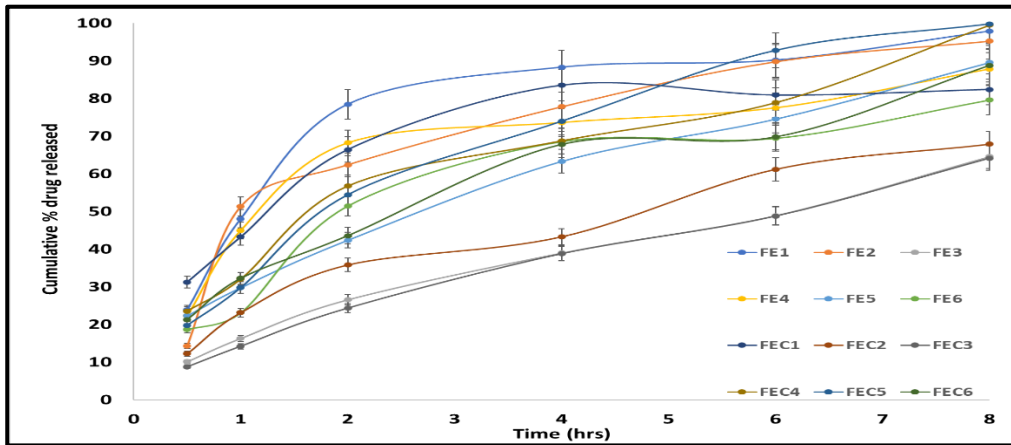


Figure 5: Cumulative % release profile of Etodolac from microsponges