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Development and characterization of sustained release microspheres by quasi emulsion solvent diffusion method

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Abstract: Ketoprofen microspheres were prepared by a solvent diffusion technique using Aerosil as an inert dispersing carrier to improve the dissolution rate of ketoprofen, and Eudragit RS as a retarding agent to control the release rate. The microspheres were found to be spherical. The average diameters were about 104-108μm and the drug contents in the microspheres were 62-96%. The concentration of Eudragit affects the release rate of ketoprofen and as concentration of eudragit increased the release rate of ketoprofen decreased. Dissolution profile showed that the release followed Higuchi matrix model kinetics. The results of X-ray diffraction and thermal analysis reveal the conversion of crystalline drug to amorphous. These results indicated that ketoprofen microspheres could be prepared providing a sustained release property.
Key words Ketoprofen; Eudragit; Aerosil; Microsphere; Solvent diffusion; Release rate.

1. Introduction

Ketoprofen is a NSAID readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5–2 h after a dose, but it causes a certain irritation in the gastrointestinal mucous membrane. The half-life of ketoprofen in plasma is about 2–3 h (Martindale, 1996). The short half-life and the low single administration dose make ketoprofen a very good candidate for the formulation of sustained release dosage forms and considerable efforts have been performed in this direction (Habib and Mesue, 1995; Khan et al., 1996; Parejo et al., 1998). At the same time, great attention has been devoted on the possibility to prepare ketoprofen microspheres or microcapsules in order to formulate oral sustained release systems, to protect the gastric mucous membrane from drug irritation (Kawashima et al., 1993; Giunchedi et al., 1994; Orienti et al., 1995).

On the other hand, Eudragit (methacrylate copolymers) have recently received increased attention for preparing modified dosage forms because of their inertness, solubility in relatively non-toxic solvents and availability of resins with different properties (Pongpaibul et al.,1984; Benita et al.,1985). Furthermore, the solvent diffusion technique of Cui et al. (2003), which was used in this study, is a simple process that is also inexpensive enough for scaling up to a commercial level.

The quasi-emulsion solvent diffusion method of spherical crystallization technique has been accepted as a useful technique for particle design for pharmaceuticals (Cui et al., 1996). It could provide remarkable advantages over conventional microsphere preparation methods.

The purpose of the present study was to prepare ketoprofen microspheres by using a quasi emulsion solvent diffusion method of spherical crystallization technique, to investigate the possibility of tailoring the drug dissolution from this form by the use of Eudragit and to study the effect of drug-polymer and drug-dispersing agent ratios on microsphere properties and drug release. The release mechanism of ketoprofen from microspheres was also discussed.

In this solvent diffusion method, the preparation of the microspheres and the solvent deposition system were combined into one step. Aerosil, an inert solid dispersing carrier, was introduced in this formulation to improve the dissolution rate of poorly water-soluble drug and the sustained-release polymer Eudragit RS 100 was employed to bind the inert solid dispersing carrier into microsphere and control the drug-release rate. This method could simplify the traditional manufacturing processes for sustained-release preparation of poorly water-soluble drugs, which usually have poor flowabilty and compressibility, and required further particle designs such as being crushed, sieved, granulated, and compacted into tablet or filled into capsules.

Experimental

Materials

Ketoprofen was obtained as gift sample from PPI Ltd (India); the acrylic resins Eudragit

RS 100 (Eu RS) from Colorcon Pvt. Ltd. (India); and light anhydrous silicic acid (Aerosil, hydrophilic) from Merck Chemical Laboratory (India). All other chemicals,

such as sodium dodecyl sulfate (SDS), dichloromethane, acetone, etc. were of analytical grade.

Method

Preparation of sustained-release microspheres

The microspheres were prepared using the quasi-emulsion solvent diffusion method of the spherical crystallization technique. Ketoprofen and Eu RS were dissolved completely in the acetone–dichloromethane mixture. Then Aerosil was suspended uniformly in the drug–polymer solution under vigorous agitation. The resultant drug–polymer–Aerosil suspension was poured into the distilled water (150 ml) containing 0.08% of SDS (i.e. poor solvent) under a moderate agitation (450–750 rpm) and thermally controlled at 0–38°C. The suspension was finely dispersed into quasi-emulsion droplets immediately under agitation, and the drug and polymers coprecipitated in the emulsion droplets. After agitating the system for 20 min, 150 ml of poor solvent was added slowly to promote the diffusion of the good solvent from emulsion droplets into poor solvent resulting in enhancement of the solidification of quasi-emulsion droplets. Agitation was extended for another 40 min until the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water, and the resultant products were dried in an oven at 50°C for 6 h.

In this study, in order to investigate the effect of the increasing amount of the polymer and dispersing agent on the microsphere formation, the drug-polymer and drug- dispersing agent ratio was altered while the amount of solvent and stirring rate were kept constant (Table 1).

Characterization of microspheres

Determination of drug loading and incorporation efficiency of microspheres

The weighed amount of microspheres powder was dissolved in acetone and the drug content was measured spectrophotometrically at 256 nm using UV-visible spectrophotometer (Shimadzu1601, Japan) for ketoprofen. The drug loading and incorporation efficiency was calculated using Eqs. (1)- (2) respectively.

$$\text{Drug loading (\%)} = \left[\frac{M_{actual}}{\text{Weighed quantity of powder of microspheres}} \times 100 \right] \quad (1)$$

$$\text{Incorporation efficiency (\%)} = \left[\frac{M_{actual}}{M_{theoretical}} \times 100 \right] \quad (2)$$

Where M_{actual} is the actual ketoprofen content in weighed quantity of powder of microspheres and $M_{theoretical}$ is the theoretical amount of ketoprofen in microspheres calculated from the quantity added in the fabrication process.

Particle size analysis

A microscopical image analysis technique for determination of particle size was applied. The morphology and particle sizes were determined in a Motic DMW2-223 Digital microscope (Motic Instruments Inc, Canada) equipped with a 1/3"CCD camera imaging accessory and computer controlled image analysis software (Motic images 2000,1.3 version). The microspheres were dispersed on a microscope slide. A microscopical field was scanned by video camera. The images of the scanned field are analyzed by the software.

Scanning electron microscopy

The morphology of microspheres was examined by scanning election microscopy. A small amount of powder was spread on an aluminum stub, which was placed latter gold sputtering in san SEM chamber (JSM 6390® India). Photographs were taken at an acceleration voltages of 20 KV electron beam.

Micromeritic properties

Flow properties of the microspheres were evaluated by determining the angle of repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing cone method of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (1 cm), H, above graph paper placed on a flat horizontal surface. The microspheres were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, the R being the radius of the base of the microspheres conical pile:

$$\tan \theta = H/R \text{ or} \quad (3)$$
$$\theta = \tan^{-1} (H/R)$$

where θ = the angle of repose.

Compressibility index (I) values of the microspheres were determined by measuring the initial volume (V_0) and the final volume (V) after subjecting to 100 tappings in a graduated measuring cylinder using the equation (4)

$$I = [1- (V/V_0)] \times 100 \quad (4)$$

X- ray diffraction studies

The crystallanities of ketoprofen and ketoprofen loaded microspheres were evaluated by X-ray diffraction measurement recorded for ketoprofen and ketoprofen loaded microspheres using an x-ray diffractometer (Brucker Axs, 08 Advance).

Thermal analysis

Differential scanning calorimetry (DSC) was performed on ketoprofen and ketoprofen loaded microspheres. DSC measurement were done on a Mettler Toledo DSC 822c

The thermograms were obtained at a scanning rate of 10^0 C/ min over a temperature range of 30 to 3000^0 C under an inert atmosphere flushed with nitrogen at a rate of 20 ml/min

Drug release studies of microspheres

The drug- release studies of the microspheres were carried out for 12 h at 100 rpm by the paddle method. The temperature of the dissolution medium was controlled at 37 ± 0.1°C. A quantity of microspheres equivalent to 150mg of drug were weighed. The dissolution medium was 900 ml of simulated intestinal fluid (pH 7.2±0.1) containing 1.0% (w/v) of SDS to keep the sink condition for the drug. Five milliliters of the dissolution fluid was withdrawn at regular time interval and was replaced with fresh quantity of dissolution fluid. The samples were filtered, and the filtrate was assayed spectrophotometrically at 256nm to determine the dissolved drug concentration using a spectrophotometer (Model 1601 Shimadzu, Japan).

Results and discussion

Preparation of the ketoprofen microspheres

When the drug–polymer–Aerosil suspension was poured into poor solvent with stirring, the finely dispersed gel-like emulsion droplets were formed immediately. As the polymer have good affinity to the organic solvent, good solvent (acetone) and bridging liquid (dichloromethane) in the droplets could not be diffused into poor solvent at once. But as stirring going on good solvent, which is discretionarily miscible with poor solvent, was diffused out from the quasi-emulsion droplets under the agitation, drug and polymer in the droplets were supersaturated, precipitated, and deposited on the Aerosil gradually. As a result, the droplets were consolidated into microspheres by the linkage action of bridging liquid. The diffusion of good solvent into poor solvent can make a part of the bridging liquid in droplets diffuse into poor solvent to achieve diphase equilibrium between the droplets and poor solvent. After the process for 20 min, 150 ml of poor solvent was added into the system to promote the diffusion speed of good solvent and part of bridging liquid. Further solidification of the droplets led to production of the microspheres. The solidified microspheres was filtrated, washed, and dried to eliminate the residual organic solvent. The Aerosil was introduced in this microspheres formulation as an inert solid dispersing carrier to improve the dissolution rate of ketoprofen. Due to its large surface area, high porosity, and unique adsorption properties, Aerosil has been successfully used as a dispersing agent to increase the dissolution rate of sparingly soluble drugs (Sheth and Jarowski, 1990). At the same time, Aerosil was an effective antiadhesion agent, and it could accelerate the solidification of droplets and be packed in the microspheres well. These suggested that the higher recovery of microspheres could be obtained comparing with other conventional methods of microspheres. In this formulation, Eu RS was used as a bond and retarding agent in order to bind the Aerosil into microspheres and control the release rate.

Characterization of microspheres

Drug loading and incorporation efficiency of microspheres

The high content of ketoprofen in microspheres was believed to be due to the poor solubility of drug in poor solvent. These suggested that the present method was suitable for the preparation of microspheres of a poorly water-soluble drug, such as ketoprofen.

Particle size analysis

The mean particle size of microspheres was shown in figure 2. According to Arshady (1990) various manufacturing parameters (apparatus design, type of stirrer, stirring speed, and viscosity of emulsion phases) affect particle size. In this study only the effect of polymer concentration, thus the inner phase viscosity, on particle formation and particle size, while keeping the other parameters constant, was investigated. Increasing the Polymer: Drug ratio caused the mean microspheres size to shift towards a higher particle size (as shown in figure 2). Higher concentration of polymer produced a more viscous dispersion which formed larger droplets and consequently larger microspheres.

Scanning electron microscopy

It can be clearly observed from the photographs of the microspheres, prepared by solvent diffusion technique, that the microspheres are smaller and have clumped shape.

Micromeritic properties

The values of angles of repose were in the range of 23.90 ± 0.55 degrees to 32.33 ± 0.90 and the values of compressibility indices were in the range of 12.67 ± 1.2 % to 24.66 ± 1.1 % for Eu RS microspheres which indicate an overall good free flowing nature of microspheres of all batches. Values of angle of repose ≤ 30° usually indicate a free flowing material, while values of compressibility index below 25 % give rise to good flow characteristics.

X- ray diffraction studies

The X-ray diffraction of the microspheres was performed and the result shows that the prepared microspheres have less crystallanity as compared to plain drug ketoprofen.

DSC study

DSC study of ketoprofen, Eu RS microspheres were performed. The result shows that there was slight decrease in the melting temperature of the ketoprofen in the microspheres which may be due to change in the crystallanity.

Drug release studies and mechanism of drug release of microspheres

The ultimate aim of this present work was to develop sustained release drug delivery system of ketoprofen. It is observed from the dissolution study that concentration of Eu RS offers sustained effect of the drug up to 12 hr. The drug release from batches F1-F5 indicates that as the polymer to drug ratio is increased the release rate is decreased. The difference was significant for 12 h with Eu RS microspheres. Ketoprofen release rate from Eu RS

microspheres was very slow and incomplete for all formulations. The release rate of ketoprofen from the microspheres could be modulated with adjusting the ratio of eudragit to Aerosil in the formulation as shown in following figures (7, 8). When the ratio of amount of drug to Aerosil was fixed at 1:2, increasing the amount of Eu RS resulted in marked decrease in drug release. It was evident that Eu RS was an efficient retarding agent to control the drug release rate.

When the ratio of amount of drug to Eu RS in the formulation was fixed at 1:4, the release rate of ketoprofen from microspheres was increased with increasing the amount of Aerosil in formulation. The release rate of microspheres of ketoprofen: Eu RS: Aerosil = 1:4:6 was much faster than that of ketoprofen: Eu RS: Aerosil = 1:4:4.

To investigate the drug release mechanism, the release data were fitted to models representation Zero order and Highuchis square root of time.

From the regression coefficient values obtained by inserting the dissolution profiles of the optimized batches in the curve fitting data of zero, Higuchi equation it was cleared that release of the drug followed a Higuchi release mechanism.

Conclusion

The purpose of present work was to develop sustained release microspheres of water insoluble drug, ketoprofen, using combination of Aerosil, an inert dispersing agent, and Eu RS, a release retardant by quasi-emulsion solvent diffusion method. From the results of characterization and drug release studies of microspheres it is concluded that this method could simplify the traditional manufacturing processes for sustained-release microspheres. On the basis of release studies it was indicated that Aerosil enhances the solubility and eudragit sustained the release of ketoprofen from microspheres, hence the present method is suitable for preparing the sustained-release microspheres for poorly water-soluble drug.

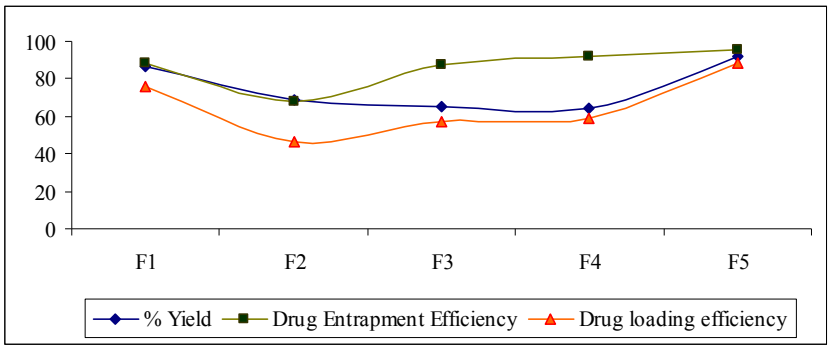

Figure 1. Drug loading and incorporation efficiency of microspheres

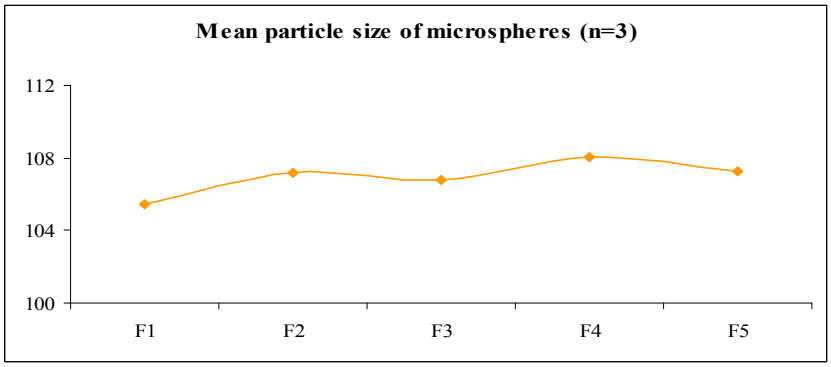

Figure 2. Mean particle size of microspheres

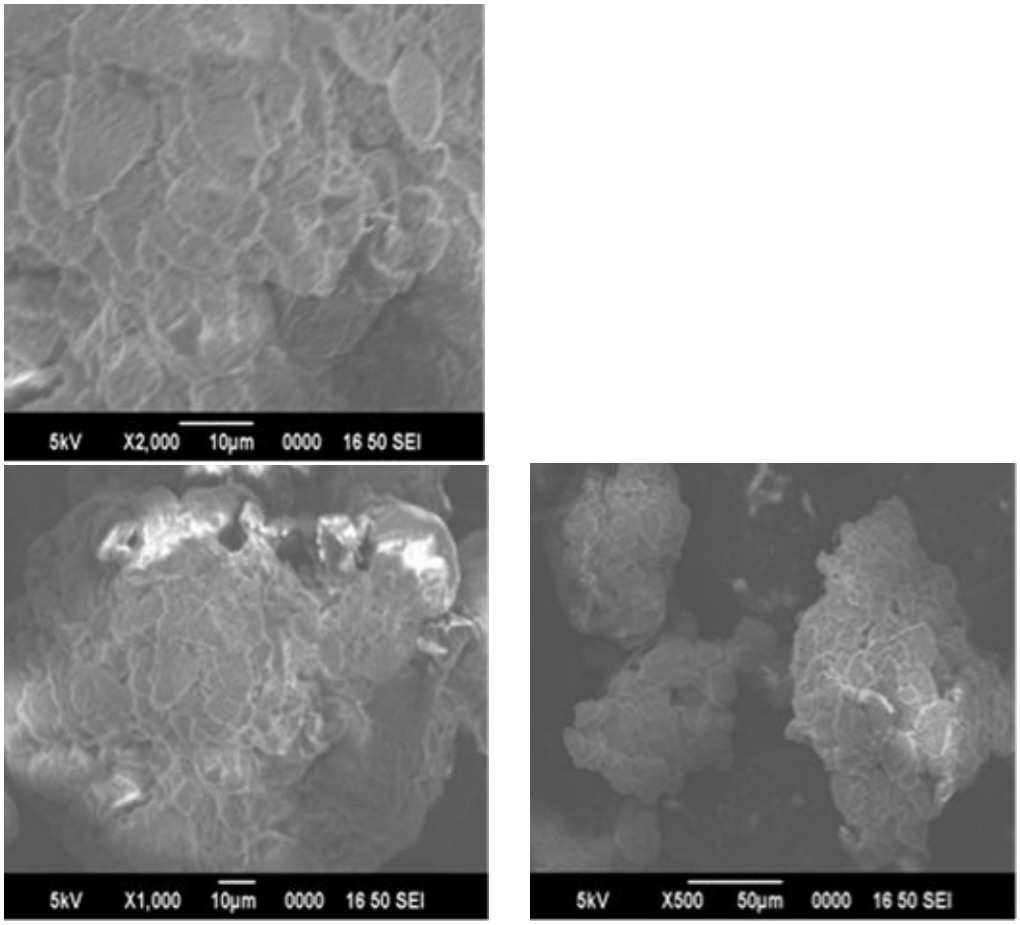

Figure 3. SEM photographs of microspheres of Eu RS

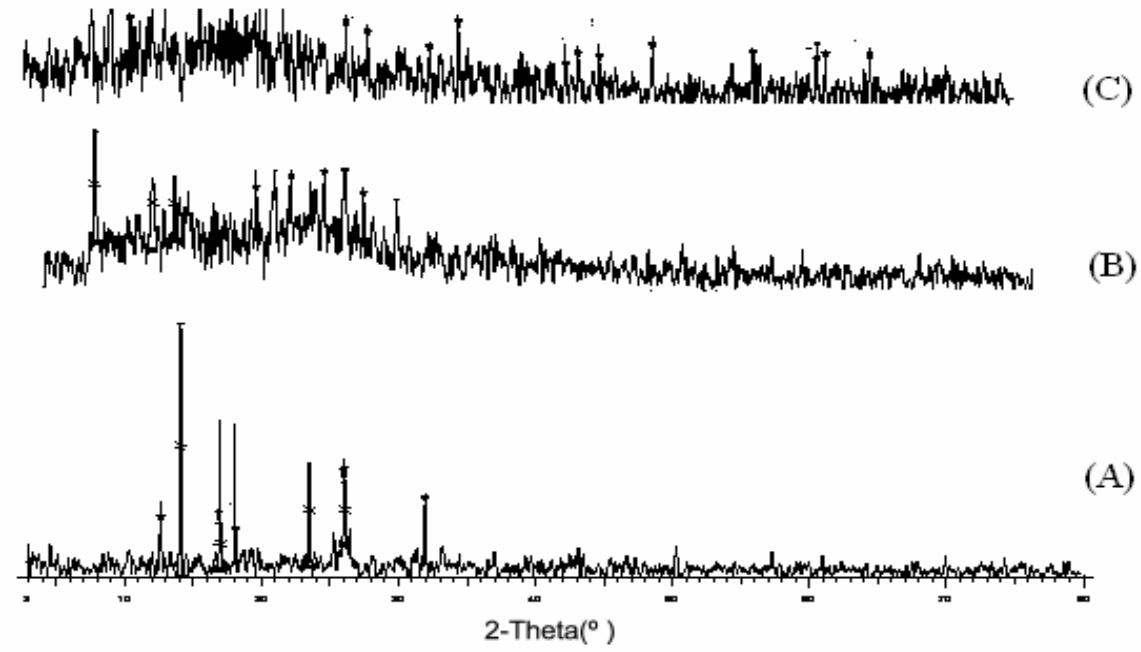

Figure 4. X-ray diffraction patterns of pure ketoprofen (A), physical mixtures of ketoprofen, Eu RS and Aerosil (B) and Microspheres.

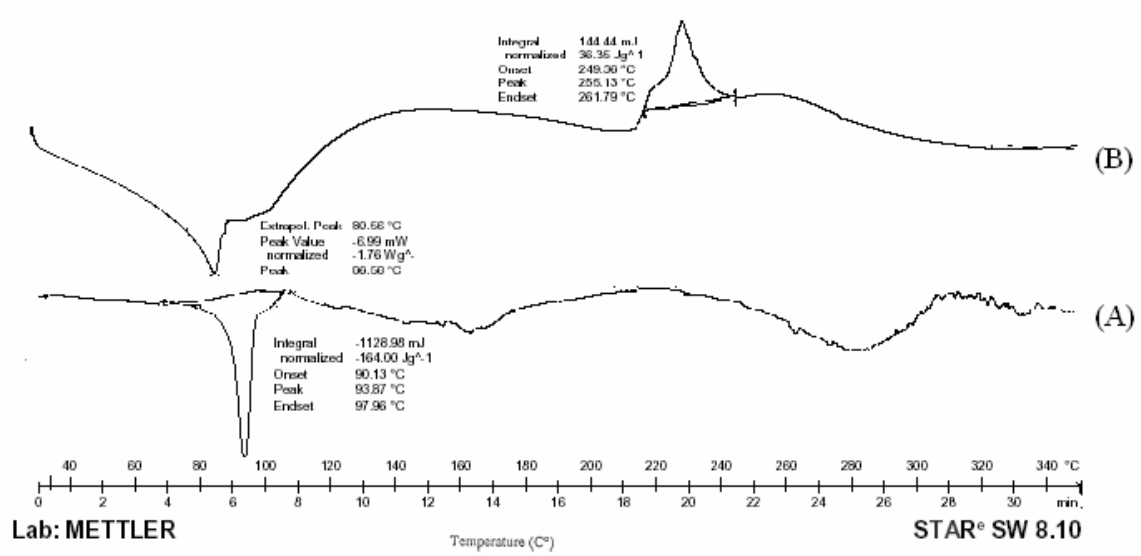

Figure 5. Comparison among DSC thermograms of pure ketoprofen and microspheres

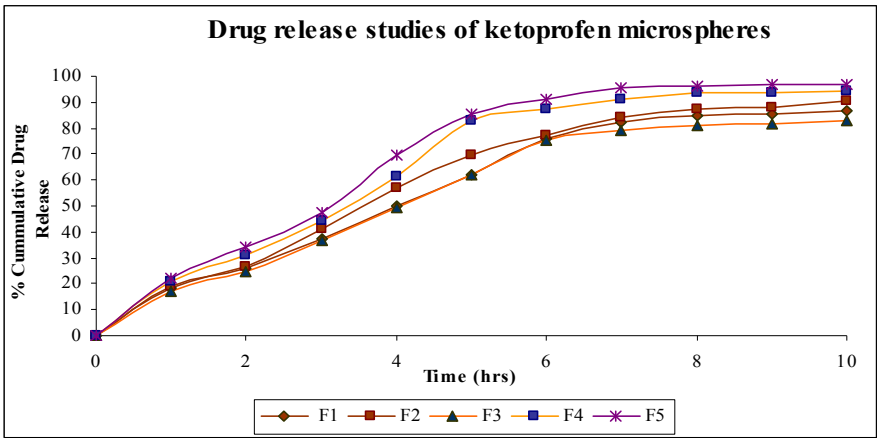

Figure 6. Drug release studies of ketoprofen microspheres

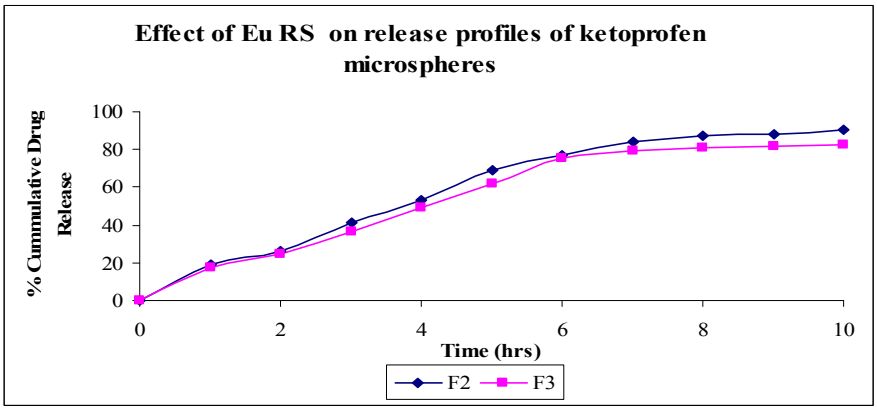

Figure 7. Effect of Eu RS on release profile of ketoprofen microspheres

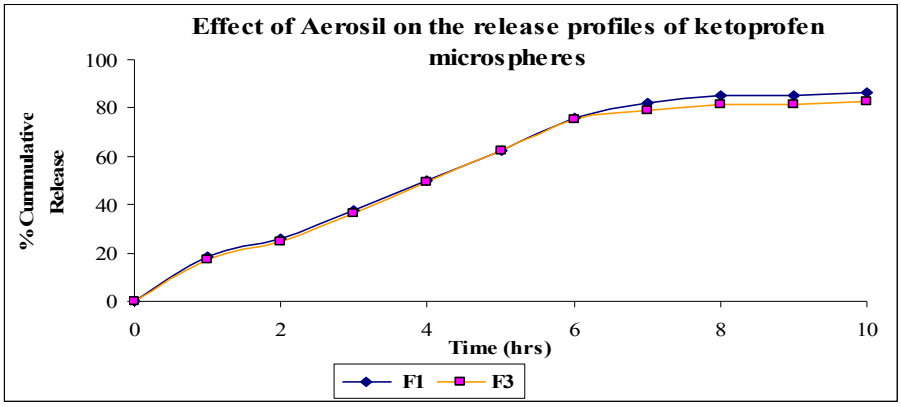

Figure 8. Effect of Aerosil on release profile of ketoprofen microspheres

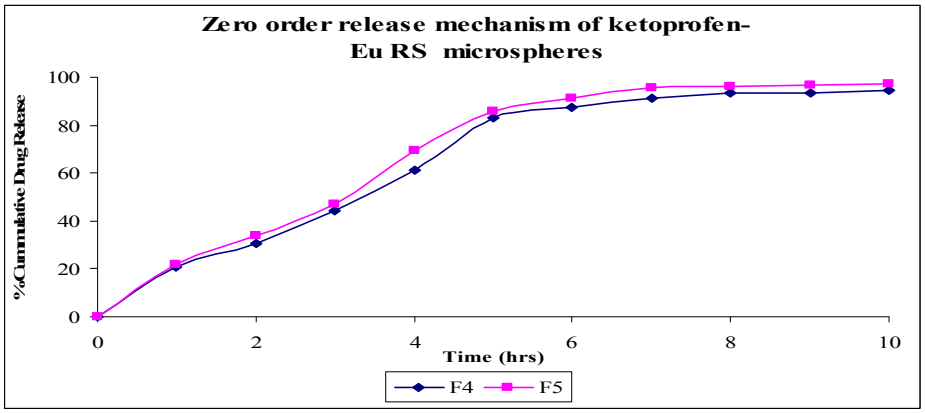

Figure 9. Zero order release mechanism of ketoprofen- Eu RS microspheres

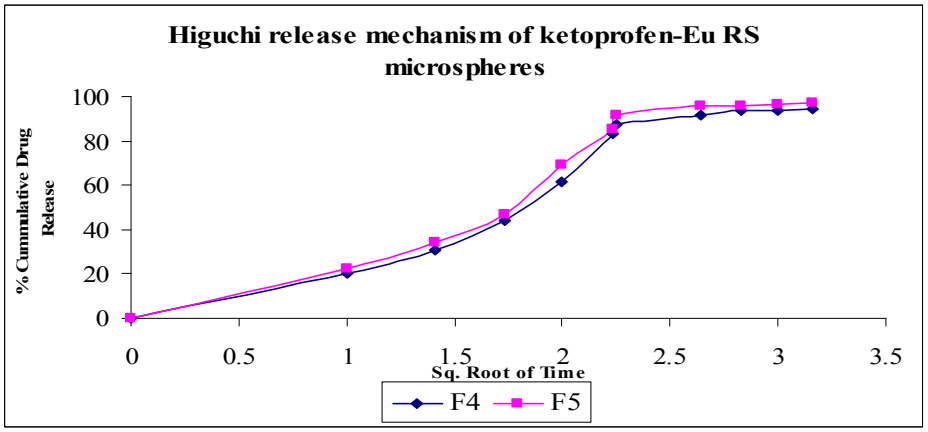

Figure 10. Higuchi release mechanism of ketoprofen-Eu RS microspheres.

Table 1 Composition of ketoprofen microspheres formulations

Ingredients	Formulation				
	F1	F2	F3	F4	F5
Ketoprofen (g)	0.1	0.2	0.1	0.1	0.2
Eudragit RS 100 (g)	0.4	0.4	0.4	1.2	1.2
Aerosil (g)	0.4	0.4	0.2	0.2	0.2
Acetone (ml)	5	5	5	5	5
Dichloromethane (ml)	4	4	4	4	4
SDS (%)	0.08	0.08	0.08	0.08	0.08
Drug/ Polymer	1:4	1:2	1:4	0.5:6	1:6
Drug/Dispersing agent	1:4	1:2	1:2	1:2	1:1

Table 2 Characteristic properties of microspheres

Batch	Particle Size (μm ± S.D.)	Drug Loading Efficiency	Drug Entrapment Efficiency
F1	105.42 ± 2.80	76.30 %	88.04 %
F2	107.21± 8.66	46.40 %	62.10 %
F3	106.77 ±10.40	57.40 %	87.79 %
F4	108.06 ± 5.90	59.05 %	91.64 %
F5	107.27 ±12.13	88.18 %	95.84 %

Table 3 Micromeritic properties of microspheres

Batch	Angle of repose $(\theta)^0$	Percentage Compressibility Index (I)
F1	24.85 ± 0.50	24.66 ± 1.1
F2	30.91 ± 0.75	12.67 ± 1.2
F3	32.33 ± 0.90	14.66 ± 1.1
F4	29.45 ± 0.80	16.66 ± 1.2
F5	23.90 ± 0.55	17.33 ± 1.2

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