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FORMULATION AND *IN-VITRO* EVALUATION OF ETODOLAC ENTRAPPED IN MICROSPONGE BASED DRUG DELIVERY SYSTEM

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ABSTRACT

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of inter connecting voids within non-collapsible structures with a large porous surface. Microsponges containing Ethyl cellulose and Eudragit RS 100 were prepared by Quasi-emulsion solvent diffusion method using Etodolac as a model drug. The effects of different 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 dug has been modified. This study presents a new approach based on microsponges for colon specific drug delivery.

Key words: Microsponges, Etodolac, Quasi-emulsion solvent diffusion, Ethyl cellulose, Eudragit RS 100 and Colon specific.

INTRODUCTION

Drug delivery systems (DDS) can control the release rate of drug and targets drug moiety to a specific site in the body and has huge impact on the human health care system. Microsponge drug delivery system is an exclusive technology that has been used for the controlled release of topically active agents. It is a highly cross-linked, porous, polymeric system usually 10-25 microns in diameter which can entrap wide range of active substances and releases them over a period of time and in response to trigger. When it is applied, microsponges releases the active substance based on its time mode and in response to other stimuli like temperature and pH. It has been used in prescription products, over the counter skin care products, cosmetics and sunscreens. It offers entrapment of ingredients and increased stability, elegance, flexibility in formulation and reduced side effects. These are stable in the pH of 1 to 11 and temperature up to 130^0C. They are self sterilizing in nature [1]. Etodolac is a non-steroidal anti inflammatory drug. It has several GI side effects like ulceration [9], bleeding, small intestine which are very severe, up on administration of 400 mg [8,11] dose twice a day and it undergoes extensive first pass metabolism. Its half-life [7] is less than 6hrs. To avoid these problems, there is a need to formulate into suitable extended release formulation that releases the drug slowly.

MATERIALS AND METHODS

Materials

Etodolac was supplied by Dr. Reddy's laboratories, Hyderabad, Eudragit RS 100 was from Ozone international, Mumbai, Ethyl cellulose and Polyvinyl alcohol are obtained from Loba chemie Pvt. Ltd, Mumbai, Triethyl citrate was from Himedia laboratories Pvt. Ltd, Potassium dihydrogen ortho phosphate, Sodium hydroxide and Benzene were

supplied by SD Fine chemicals, Mumbai and Ethanol was from Changshu Yangyuan chemicals, China.

Preparation of Etodolac microsponges:
The loading of drug in microsponges depends on physic-chemical properties of drug to be entrapped. It can be done by either one step method or two step method. 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 Ethyl cellulose is added for the formulations EC1-EC7 and Eudragit RS 100 for E1-E7 at 60^{o}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^{o}C for 2 h[2,4]. For the evaluation of effect of drug: polymer ratios on the physical characteristics of microsponges, different ratios were employed.

Infrared spectral analysis
The IR spectrum is used to determine the interaction of drug with excipients. The infrared spectra of samples were obtained using a FT-IR JASCO 410 spectrophotometer by KBr pellet method.[3,10].

Differential Scanning Calorimetry
It measures the heat flow in and out of both sample and reference during a controlled temperature program. The crystalline nature of the pure drug and its thermal behavior was studied by Differential Scanning Calorimetry (DSC). It provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and other excipients.

Surface morphology of microsponges
The surface morphology of the prepared microsponges was observed by scanning electron microscope (SEM). Pictures of the prepared microsponges were taken at different accelerating voltages at 100 and 500 µm working distance.

Determination of percentage yield and percentage entrapment efficiency [1,5,6]
Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of microsponges. Percentage yield can be calculated by using the formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

Accurately weighed Etodolac microsponges were taken in a stoppered test tube and extracted with 5× 10 ml quantities of phosphate buffer pH 6.8. The extracts were filtered and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer pH 6.8. The solutions were subsequently diluted suitably with phosphate buffer Ph 6.8 and spectrophotometric absorbance was taken at 274 nm to calculate percentage drug entrapment and the percentage entrapment efficiency (PEE) is calculated by the formula is given below.

$$\text{PEE} = \frac{\text{Drug loading in microsponges}}{\text{Theoritical drug loading}} \times 100$$

Particle size analysis [12]
Particle size and size distribution of microsponge 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.

***In-vitro* drug release studies**
The dissolution rate of Etodolac microsponges were studied using USP dissolution test apparatus employing paddle method. Accurately weighed samples of microsponges were used which were calculated to contain 300 mg Etodolac. They were placed in 900 ml of phosphate buffer pH 6.8 with a paddle speed of 100 rpm and temperature of 37^{0}C ±0.5^{0}C was employed. Aliquots (5ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, 120th min and then hourly intervals up to 8 h and assayed spectrophotometrically at 274 nm [1]. The percentage of drug released at various time intervals was calculated and plotted against time.

Drug release kinetics [4]
The dissolution profile of each formulation have been subjected to various models such as Zero order kinetics (percentage drug release against time), First order kinetics (log percentage drug unreleased against time), Higuchi (percentage drug released against square root of time) and Korsemeyer-Peppas (log percent drug released against log of time) were applied to assess the kinetics of drug release from prepared Etodolac microsponges.

RESULTS AND DISCUSSION

The flow property of pure drug was very poor and it was identified that all formulations have good flow property. Particle size of the Microsponges was also much affected by the drug: polymer ratio (Table 2). It was observed that the produced microsponges were spherical in shape and contains numerous pores (Figure 6 and7). FTIR studies reveal that there is no appearance of new peaks and disappearance of existing peaks, which indicated that there is no interaction between the drug and polymer used. The characteristic ketone (C=O) stretching vibration at 1743 cm^{-1}, C-H bending at 1411 cm^{-1}, C-O stretching at 1265.072^0 cm^{-1}, C-N vibration at 1313.29 cm^{-1} and aromatic C-H stretching at 744.38 cm^{-1} were identified in all the spectrums (Figure 1,2 and 3).

In DSC studies, etodolac dispersed in ethyl cellulose showed the same thermal behavior as pure compound. In the thermogram the endothermic peak was observed at 146^{0}C which corresponds to the melting point of the pure drug (Figure 4). Thermal behavior of Etodolac has been changed after formulating into microsponges using Eudragit RS 100. In the thermogram of Etodolac combined with Eudragit RS 100 the peak was observed at 246 ^{0}C (Figure 5). This report also indicates that the physical properties Etodolac were not altered during formulation of microsponges using Ethyl cellulose.

The result of percentage entrapment efficiency indicates maximum entrapment has been achieved when entrapped using Ethyl cellulose. It was found that percentage yield was in the range of 62.2-95% (Table 2).

Maximum drug release among the formulations containing etodolac and ethyl cellulose was found to be 99.3% within 8 h for EC7, and the minimum release was identified for EC4 which was 74.1% (Figure 8). Among the formulations containing etodolac and eudragit RS 100 maximum release was for E5 that was 87.6% and minimum was for E4 which was 75% (Figure 9). Among all the formulations prepared, formulation EC7 showed 99.3% drug release. Most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism. In table 3, the kinetic parameters for Etodolac microsponges were presented. As clearly indicated in table 3, the *in-vitro* release profile of drug from all the formulation could be best expressed by Higuchi matrix diffusion type.

CONCLUSION

Etodolac was entrapped in the microsponge drug delivery system formed by using ethyl cellulose and eudragit RS 100. Alteration in the release rate of the drug may be due to the entrapment which modifies the release of drug that causes reduction in the severity of the side effects.

ACKNOWLEDGEMENT

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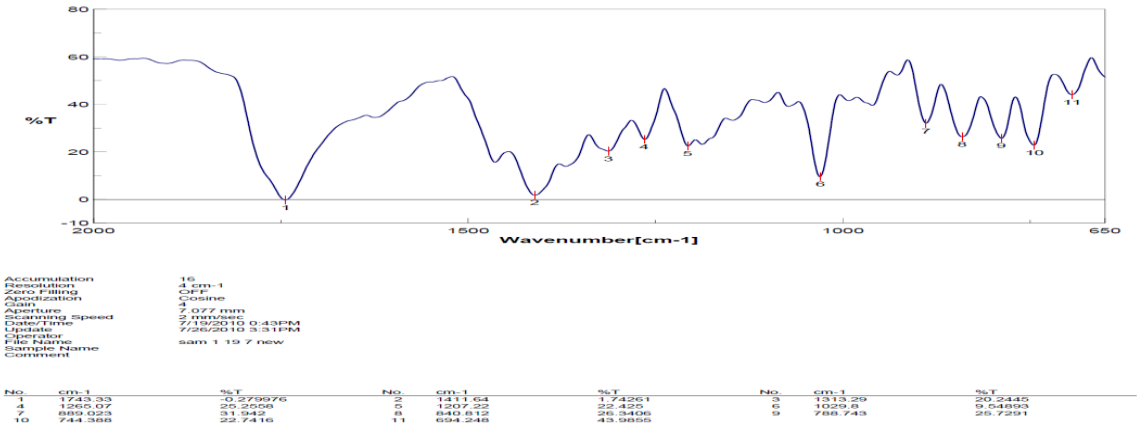
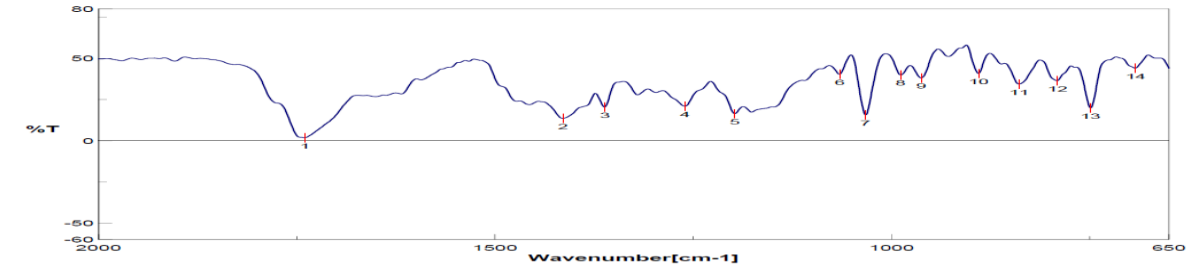


Figure 1: IR Spectrum of Etodolac pure drug



Accumulation	16
Resolution	4 cm-1
Zero Filling	ON
Apodization	Cosine
Gain	16
Scanning Speed	2 mm/sec
Date/Time	8/17/2010 2:58PM
Update	8/17/2010 3:14PM
Operator	
File Name	drug and polymer
Sample Name	
Comment	

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	1739.48	1.83509	2	1414.53	13.5879	3	1361.5	20.4557
4	1260.25	20.9226	5	1197.58	16.357	6	1065.48	40.3561
7	1032.69	15.6015	8	988.339	39.5478	9	962.305	38.0923
10	889.987	40.8036	11	838.883	34.3346	12	790.671	36.4235
13	749.209	19.9331	14	692.32	44.0497			

Figure 2: IR Spectrum of sample containing Etodolac and Eudragit RS 100

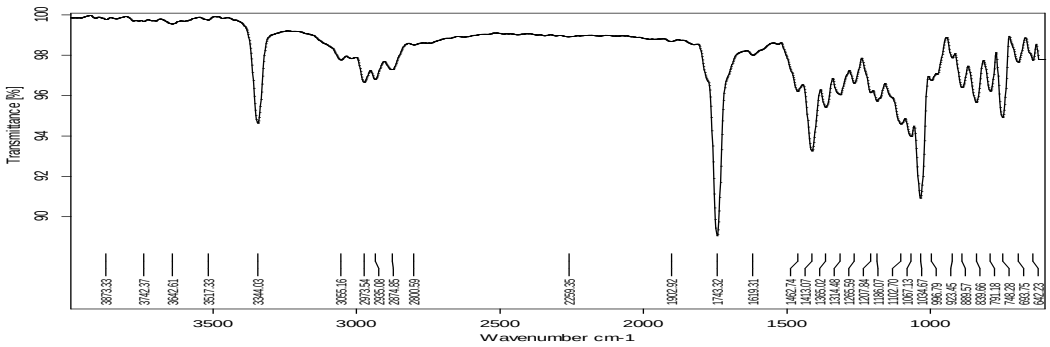


Figure 3: IR Spectrum of sample containing Etodolac and Ethyl cellulose

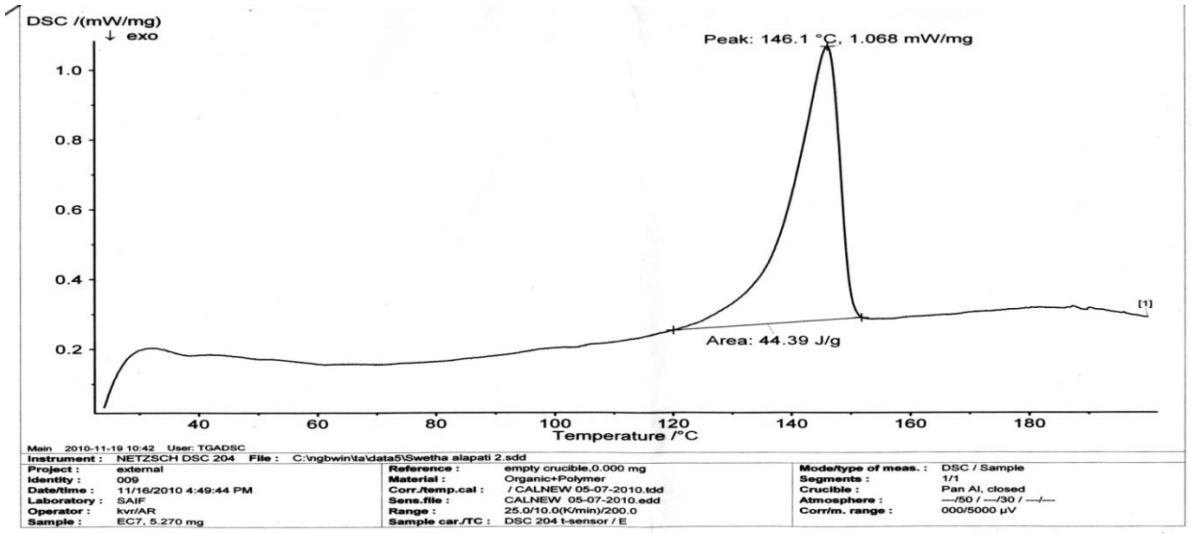


Figure 4: Thermogram of formulation EC7 (containing Etodolac and Ethyl Cellulose)

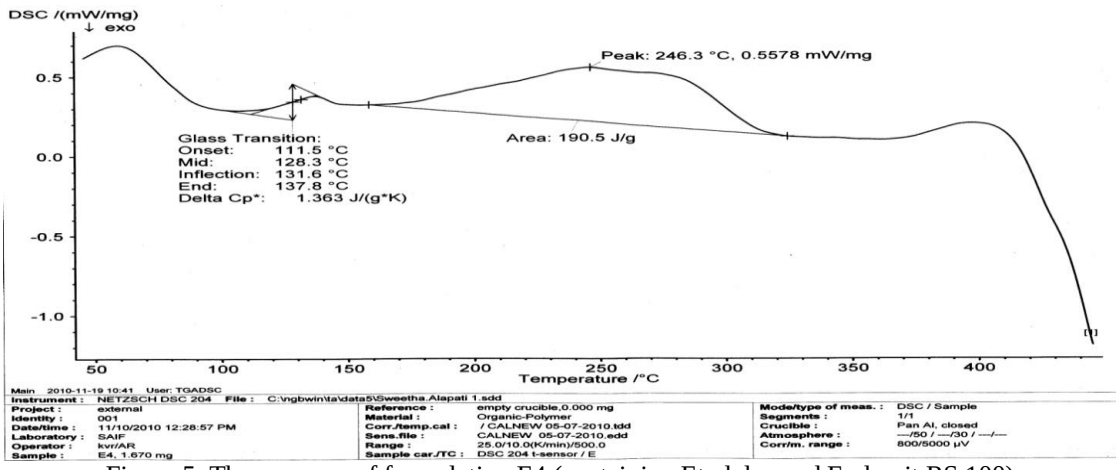


Figure 5: Thermogram of formulation E4 (containing Etodolac and Eudragit RS 100)

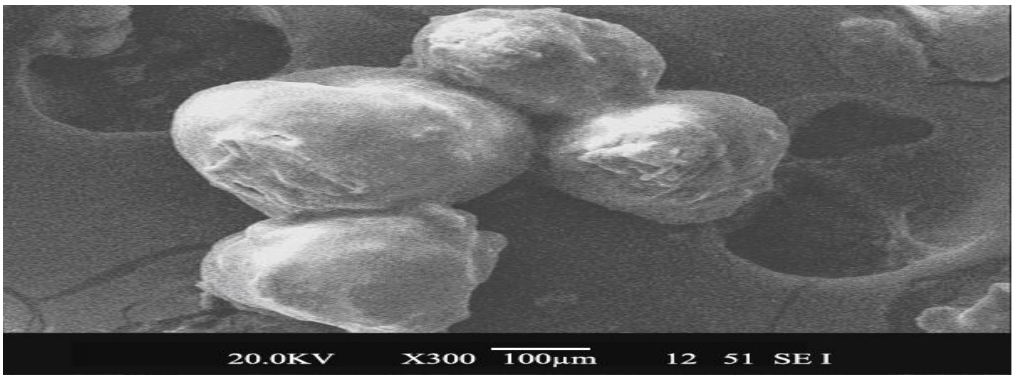


Figure 6: Scanning electron micrograph of EC4

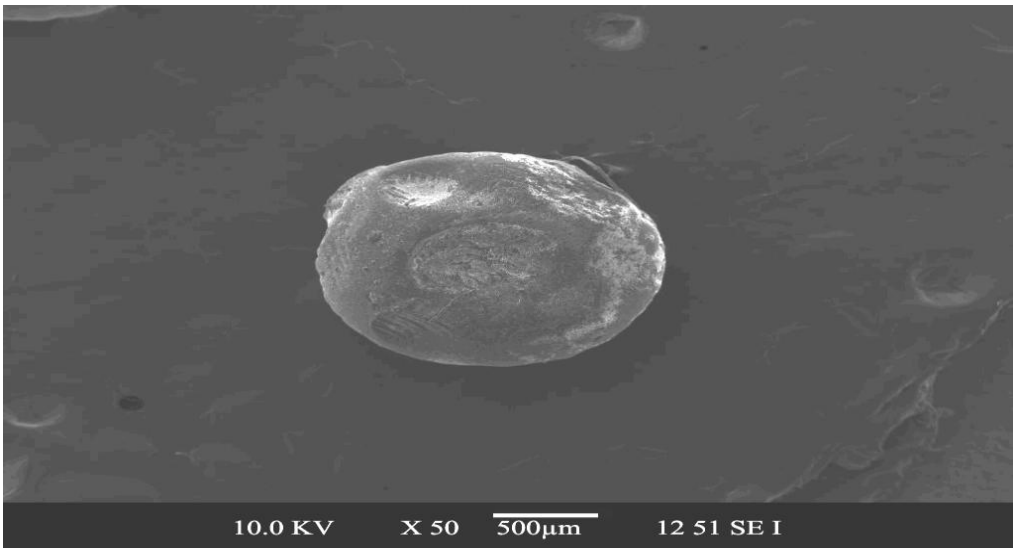


Figure 7: Scanning electron micrograph of E7

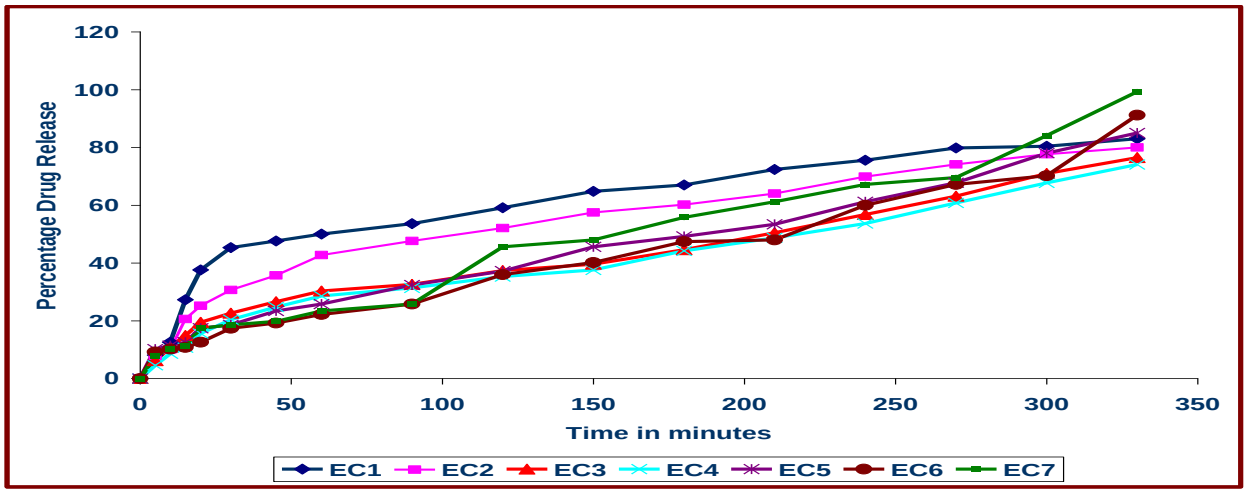


Figure 8: Drug release profile of formulated Etodolac microsponges (EC1-EC7)

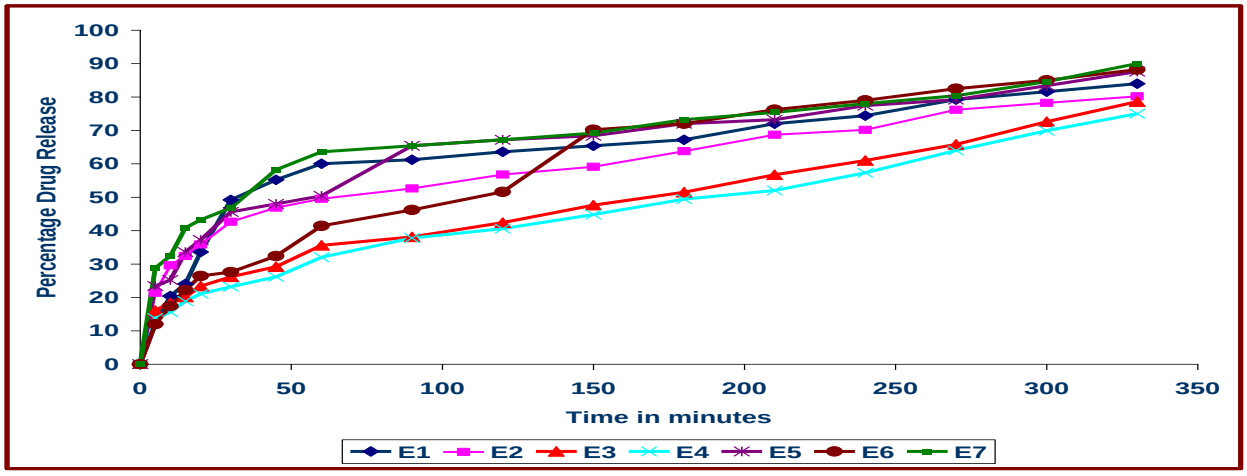


Figure 9: Drug release profile of formulated Etodolac microsponges (E1-E7)

Table 1: Formula for the preparation of Etodolac microsponges

Formulation Code	Etodolac (g)	Ethyl cellulose (g)	Eudragit RS 100 (g)	Polyvinyl alcohol (g)	Triethyl citrate (ml)	Ethyl alcohol (ml)	Water (ml)
EC1	1	1	--	0.05	1.92	20	150
EC2	1	1.5	--	0.05	1.92	20	150
EC3	1	2	--	0.05	1.92	20	150
EC4	1	2.5	--	0.05	1.92	20	150
EC5	1.5	1	--	0.05	1.92	20	150
EC6	2	1	--	0.05	1.92	20	150
EC7	2.5	1	--	0.05	1.92	20	150
E1	1	--	1	0.05	1.92	20	150
E2	1	--	1.5	0.05	1.92	20	150
E3	1	--	2	0.05	1.92	20	150
E4	1	--	2.5	0.05	1.92	20	150
E5	1.5	--	1	0.05	1.92	20	150
E6	2	--	1	0.05	1.92	20	150
E7	2.5	--	1	0.05	1.92	20	150

Table 2: Effect of drug to polymer ratio on Etodolac microsponges' properties

Formulation code	Drug to polymer ratio	Percentage yield (%)	Percentage entrapment efficiency	Mean particle size
EC1	1:1	65.0	53.0	83.46
EC2	1:1.5	62.4	57.8	82.00
EC3	1:2	70.3	59.0	83.50
EC4	1:2.5	77.7	63.0	80.24
EC5	1.5:1	91.6	70.3	65.87
EC6	2:1	68.6	74.0	62.41
EC7	2.5:1	84.2	87.6	60.08
E1	1:1	82.0	57.5	82.72
E2	1:1.5	95.0	59.0	80.06
E3	1:2	85.3	65.9	78.65
E4	1:2.5	90.0	61.0	78.21
E5	1.5:1	94.4	76.0	67.34
E6	2:1	86.4	82.1	59.99
E7	2.5:1	89.0	89.0	56.34

Table 3: Drug release kinetics

Formulation code	R^2 value			
	Zero order	First order	Higuchi	Korsemeyer-Peppas
EC1	0.8234	0.00053	0.9083	0.8831
EC2	0.9094	0.9820	0.9516	0.9514
EC3	0.9719	0.9504	0.9757	0.9731
EC4	0.9716	0.9588	0.9724	0.9629
EC5	0.9934	0.9267	0.9638	0.9738
EC6	0.9808	0.8036	0.9303	0.9553
EC7	0.9826	0.6161	0.9468	0.9655
E1	0.7681	0.9147	0.8863	0.9023
E2	0.9199	0.9655	0.9801	0.9876
E3	0.9866	0.9703	0.9820	0.9770
E4	0.9848	0.9743	0.9823	0.9815
E5	0.8718	0.9626	0.9622	0.9803
E6	0.9389	0.9908	0.9865	0.9909
E7	0.855	0.9426	0.9462	0.9756

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