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Formulation and Evaluation of Celecoxib Microspheres by Using Ethylcelluose and Eudragit S-100 in Colon Drug Delivery

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ABSTRACT

To achieve successful colonic delivery, a drug needs to be protected from absorption or the environment of the upper gastro intestinal tract and then be abruptly released into proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Most of the conventional drug delivery system for treating various disorders and diseases such as inflammatory bowel disease, colon cancer and intestinal amoebiosis have failed as drugs in its intact form as they do not reach the site of action in appropriate concentration. For an effective and safe therapy for such diseases, development of a specific drug delivery system is a challenging task. Hence we aim to develop a drug delivery system which would deliver the drug in its intact form as close as possible to target site, leading to reduction of dose related side effects. The objective of present study was to develop multiparticulate colon drug delivery system of Celecoxib. The colon drug delivery system of Celecoxib microspheres was prepared by emulsion polymerisation method by using ethyl cellulose and Eudragit S 100 polymers in varying concentration. Formulations were evaluated for percent yield, entrapment efficiency, scanning electron microscope, FTIR spectroscopy and in vitro release studies. The optimized formulations of Celecoxib microspheres shows to prolonged activity with increased stability without loosing its therapeutic activity in colon drug delivery system.

Keywords: Colon drug delivery, Celecoxib, Ethyl cellulose, Eudragit S100.

INTRODUCTION

Colon is an important site for the delivery and absorption of drugs. There are number of advantages of drug targeting to colon, the most being are, Most of the conventional drug delivery system for treating various disorders and diseases such as inflammatory bowel disease, colon cancer and intestinal amoebiosis have failed as drugs in its intact form as they do not reach the

site of action in appropriate concentration [1]. Microspheres drug administration offers a number of advantages in therapeutics, where the controlled releases of drug delivery as well as the predictable and reproducible drug release kinetics are important features of them in colon drug delivery system [2]. Celecoxib is a nonsteroidal anti-inflammatory drug (NSAIDS) widely prescribed in inflammation, pain and fever through inhibition of prostaglandin synthesis and cyclooxygenase-2 (COX-2). Celecoxib is used to decrease growths found in the intestines (colon polyps) of persons with a family history of this condition. The recommended adult oral dosage of Celecoxib is 100-200 mg twice daily[3]. The aim of present study is to develop a drug delivery system which would deliver the Celecoxib in its intact form as close as possible to target site, leading to reduction of dose related side effects. The aim of this work is to investigate the possibility of obtaining a prolonged, relatively constant effective level of Celecoxib from the Ethyl cellulose and Eudragit microspheres formulations. The present investigation is to prepare Celecoxib microspheres to improve the bioavailability by increasing residence time in colon. The main objectives of the study are to develop a stable, reproducible and patent non-infringing targeted drug delivery system for Celecoxib. The success of the project will give a reproducible method for delivering drug to the favourable site of absorption and action thus minimizing the total dose and reducing the toxic effect of the drug. It will also minimize the bioavailability problem due to degradation in acidic or alkaline environment of the gastro intestinal tract.

MATERIAL AND METHODS

Celecoxib was obtained as gift sample from Ranbaxy Laboratories Ltd, India. Ethyl Cellulose from S. D. Fine Chemicals Ltd, Mumbai. Eudragit S100 from Rohm Pharm, Germany.

Table 1: Composition of batches of Celecoxib microspheres

Batch. no	Celecoxib (Pure Drug)	Ethyl Cellulose	Eudragit S100	Dichloromethane
FC-1	1 gm	500 mg	500 mg	10 ml
FC-2	1 gm	1 gm	1 gm	10 ml
FC-3	1 gm	1.5 gm	500 mg	10 ml
FC-4	1 gm	2 gm	1 gm	10 ml
FC-5	1 gm	500 mg	1 gm	10 ml
FC-6	1 gm	500 gm	1.5 gm	10 ml
FC-7	1 gm	1 gm	2 gm	10 ml

Preparation of Microspheres:

A 1 gm pure drug of Celecoxib was accurately weighed and dissolved in the 0.1% Tween 80 were completely dissolved of the drug was prepared and 1gm of Ethylcellulose and 1gm of Eudragit S 100 was weighed and made completely dissolve in dichloromethane. Celecoxib and mixture of polymer were dispersed in 0.1% tween 80 containing 100ml of distilled water in a beaker at room temperature. The dispersion was stirred using a stainless steel half moon paddle stirrer at 1000 rpm for 15 mins. Then microspheres are under go on the ultra sonicator for 20

mins. Then hardened microspheres were then separated by cooling centrifugation for 20 mins at 4000 rpm. The hardened microspheres were then separated by centrifugation, washed four times with petroleum ether, once with acetone, three times with water, centrifuged, vacuum dried at room temperature and stored in desiccators. Microspheres were prepared using at different amounts ratio of Ethylcellulose and Eudragit S 100 polymer. Composition of batches of Celecoxib microspheres were shown on table 1.

Evaluation of Celecoxib Microspheres

Determination of percent yield

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated.

Determination of entrapment efficiency

The drug content of Celecoxib loaded microspheres was determined by dispersing 20 mg microspheres in 20 ml of methanol, which was stirred with a magnetic bead for 8 hr to extract the drug. The samples were diluted and analyzed spectrophotometrically at 255 nm and the percentage drug entrapment was calculated [4].

Particle size analysis

Particle size of prepared microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Scanning Electron Microscopy (SEM)

Morphology and surface topography of the microspheres were examined by scanning electron microscopy (SEM- Jeol, JSM-840A, Japan). The samples were mounted on the SEM sample stab, using a double-sided sticking tape and coated with gold under reduced pressure (0.001 torr) for 5 min to improve the conductivity using an Ion sputtering device (Jeol, JFC-1100 E, Japan). The coated samples were observed under the SEM and photomicrographs of suitable magnifications obtained.

***In-vitro* release study**

Dissolution studies of the Celecoxib microspheres were carried out in triplicate employing USP XIII dissolution rate test apparatus-1 (Electrolab, TDT-06T, India). Microspheres were loaded in capsule and placed into the basket of the dissolution apparatus, the pH changes were performed starting with 900ml of 0.1N Hcl (pH-1.2) for 2hr, mixed phosphate buffer containing 0.5 % Sodium Lauryl Lulphate (pH-6.8) for 2hr, followed by mixed phosphate buffer(0.5% SLS) of pH 7.5 till the end of test [5]. The temperature of the dissolution fluid was maintained at 37 ± 0.5^{0}C with a stirring speed of 100 rpm. Aliquots of the dissolution medium were at 1 hr interval for a period of 24 hr and the sampled volume of buffer maintained at the same temperature. The samples withdrawn every hour were filtered (0.22 µm, Millipore) and assayed spectrophotometrically at 255 nm. The dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

Kinetics of drug release

For finding out the mechanism of drug release from tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations [6, 7].

Zero order release equation:
Q = K0 t - - - - - - (1)
First order equation:
In Q = Kf t - - - - - - (2)
Higuchi's square root of time equation:
Q = KH t ½ - - - - - - (3)
Korsmeyer and Peppas equation:
F = (Mt/M) = Km tn - - - - - - (4)

RESULT AND DISCUSSION

Percent yield

All batches showed a percentage yield of greater than 60%, whereas four batches showed a yield of more than 70%. Percentage yield is found to be higher with formulation C5. Results showed that percentage yield increases with increase in the amount of polymer.

Entrapment efficiency

All batches show percent entrapment more than 45% and it is found that entrapment of drug increases with an increase in the amount of the polymer. Formulation F5 shows maximum entrapment whereas formulation F7 shows minimum entrapment of the Celecoxib in the polymer as shown in table 1.

Table 1: Entrapment Efficiency of Celecoxib Microspheres

S.No	Formulations	Encapsulation efficiency %
1.	F 1	53.19
2.	F 2	55.59
3.	F 3	54.76
4.	F 4	51.65
5.	F 5	64.76
6.	F6	52.99
7.	F7	48.19

Particle size analysis

Results showed that particle size of prepared microspheres was in the range of 20.57 ± 7.25 µm to 35.107 ± 15.52 µm. It was concluded that with increase in polymer concentration, particle size of prepared microspheres increases as shown in table 2.

Table 2: Particle Size Analysis of Microspheres of Celecoxib

Batches	F1	F2	F3	F4	F5	F6	F7
Particle size(µm)	47.55	52.93	63.35	71.28	82.75	73.54	69.55

Scanning electron microscopy

The scanning electron microscopy of the microspheres was shown in figure 1. The most of the microspheres were spherical in shape and size ranges from 10-40 µm. Only some spheres were

in large size. The size analysis of F5 of microspheres showed that about 75% were in the size range of 10 µm. The size distribution of the microspheres was found to be normal in F5.

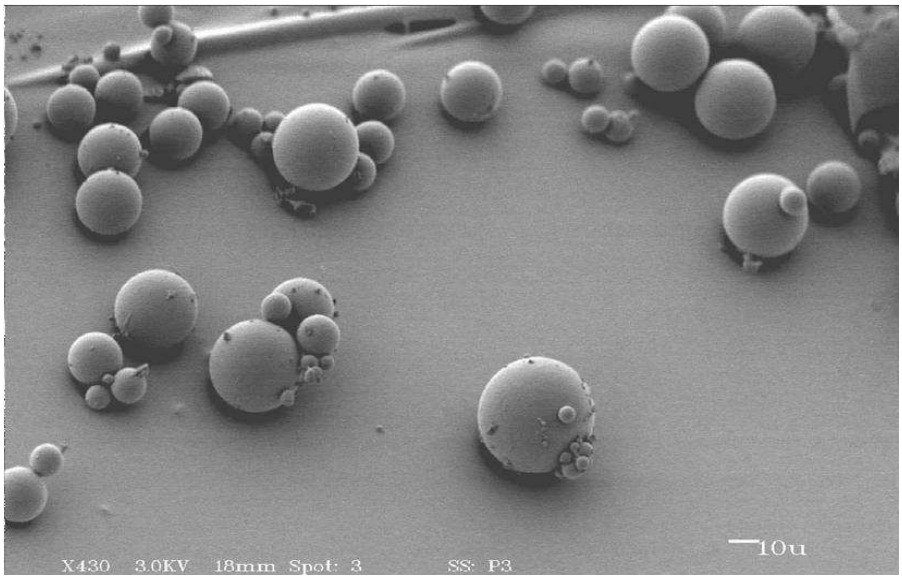

Figure 1: SEM photomicrographs of batch F5

***In-vitro* release study**

The prepared microspheres of Celecoxib release 88.67% of Celecoxib at 24 hr (F1). F2, F3 and F4 microspheres releases the 90.15% and 88.21%, 84.17% respectively. At the same time the F6 and F7 microspheres releases the 83.25% and 77.11% respectively in the *in-vitro* study of Celecoxib microspheres. The F5 releases 92.83% of the drug after 24 hr (F5) were shown on table 3 and figure 2.

Table 3: Comparative *In Vitro* Drug Release of Celecoxib Microspheres

Time	Cumulative Percentage Drug Release						
	F1	F2	F3	F4	F5	F6	F7
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	5.25	6.17	5.48	4.57	7.54	4.34	3.43
2	7.82	8.98	8.51	7.13	10.36	6.67	5.52
3	14.08	15.70	14.09	12.92	16.19	13.37	11.75
4	20.63	21.81	20.64	19.00	22.76	18.54	17.36
6	28.16	29.13	28.18	27.21	30.55	26.97	25.32
8	38.07	38.13	37.39	36.18	40.25	35.94	33.59
10	48.07	48.37	47.16	45.03	49.59	46.16	44.23
12	55.90	57.57	56.35	54.20	59.72	53.97	51.34
16	69.53	70.75	69.75	68.03	72.24	68.03	65.14
20	76.21	77.22	75.98	74.01	80.10	74.01	71.78
24	88.67	90.15	88.21	84.17	92.83	83.25	77.11

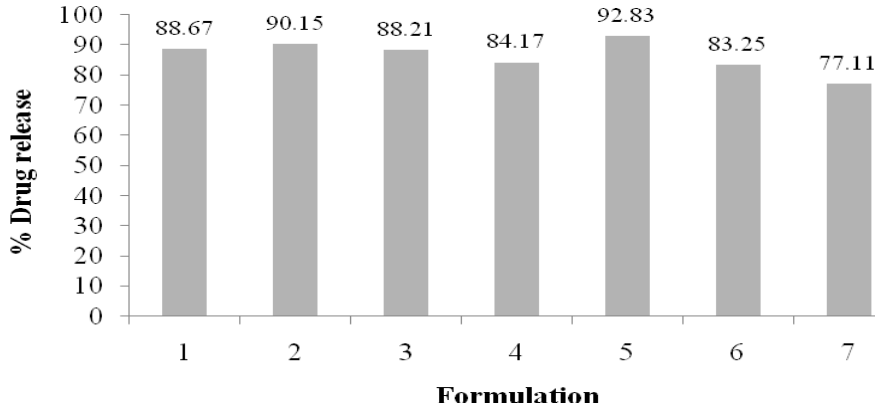

Figure 2: Comparative *In-Vitro* Dissolution Study of Celecoxib Microspheres

Kinetics of drug release

The regression coefficient for the best formulation F5 of Zero order plots were found to be 0.9814; First order plots were found to be 0.9492. F5 with regression coefficient of 0.965 followed Higuchi matrix suggesting diffusion controlled release and 0.9777 were shown on table 4.

Table 4: Correlation coefficient of kinetic modeling

Models	Correlation coefficient (r^2)
Zero order	0.9814
First order	0.9492
Higuchi	0.9650
Hoffenberg	0.9777

CONCLUSION

In the present study an attempt was made to develop a colon drug delivery system for Celecoxib by using polymer ethyl cellulose and eudragit S-100 to improve bioavailability and efficacy. The microspheres were prepared by emulsion polymerisation method and characterized by using scanning electron microscope. Formulation of Celecoxib in the form of microspheres was developed to a satisfactory level in term of drug release. The compatibility studies were done by FTIR spectroscopy. It implies that there was no interaction between drug and polymer and they are compatible with each other. Size distribution by microscopic method showed not much significant difference in formulations. The *in-vitro* release profiles of microspheres in phosphate buffer containing 0.5% SLS at 37^{o}C confirmed the controlled release of microspheres that can be targeted to colon. *In-vitro* study was done and microspheres formulation was given the satisfactory result.

In conclusion, it is possible to prepare microspheres containing Celecoxib by emulsion polymerisation method, to prolonged activity with increased stability without loosing its therapeutic activity in colon.

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REFERENCES

[1] B Arul; R Kothai; B Sangameswaran; B Jayakar. *Indian Journal of Pharmaceutical Sciences*, **2003,** 65, 6, 640-642.
[2] Balaji Narasimahan. *Advanced drug delivery reviews*, **2001,** 48, 229-247.
[3] S Hazner Dar. *International journal of pharmaceutics*, **2004,** 269, 131-140.
[4] S Freiberg; X.X Zhu. *International Journal of Pharmaceutics*, **2004**, 282, 1-18.
[5] N.K.Jain; Y.S.R Krishnaiah; S Satyanarayana. *Colon specific drug delivery system*, **2001,** 89-110.
[6] M. A. Nasra; M. A. EL-Massik; V. F. Nagger. *Asian Journal of Pharmaceutical Sciences* **2007,** 2, 1, 18-28.
[7] Anekant Jain; Yashwant Gupta; Sanjay K. Jain; *J Pharm Pharmaceutical Sciences*, **2007** 10 , 1, 86-128.