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Design and Evaluation of Dual Coated Enteric Spheres of Diclofenac Sodium

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Diclofenac sodium was formulated as dual coated enteric spheres for intestinal specific drug delivery using enteric polymers like cellulose acetate phthalate and ethyl cellulose. The dual coating was given using a new process composed of wet granulation and thermal change methods using both the polymers. The new process was analyzed for its capability to produce spheres of uniform size, good flowability, uniform drug loading, and maximum entrapment efficacy and the absence of interaction between drug and process parameters as well as polymers. *In vitro* release study was carried out in simulated gastric fluid for first 2 h and in simulated intestinal fluid for next 6 h. The best formulation B3, which contained cellulose acetate phthalate and ethyl cellulose in the concentration of 10:90 at 1:1.5 drug–polymer ratio was further evaluated using *in vivo* models for its Pharmacodynamic efficacy and ulcerogenicity.

Diclofenac sodium is a new generation non–steroidal antiinflammatory agent, which is widely used in the long-term therapy for rheumatoid arthritis. Short biological half-life of 1–2 h necessitates multiple dosing for maintaining therapeutic effect throughout the day. Albeit one among the best in long term therapy in management of arthritis, diclofenac sodium suffers from severe drawbacks like peptic ulceration and gastric bleeding[1,2]. These adverse effects create a potential need for delayed release system, which is capable of targeting the release to intestine and bypasses the stomach.

In the present work, an innovative method was employed to prepare dual coated enteric spheres of diclofenac sodium. The enteric spheres were prepared by combining wet granulation and thermal change methods[3]. Resistance for gastric erosion was offered by two polymers, cellulose acetate phthalate and ethyl cellulose. The drug was wet granulated using aqueous acacia mucilage with cellulose acetate phthalate and then coated with ethyl cellulose by thermal change method. The release retardant property of two polymers in addition to avoiding the ulcerogenicity of diclofenac sodium, also helps to maintain constant plasma concentration of the drug for prolonged period.

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MATERIALS AND METHODS

Diclofenac sodium (IP) was a generous gift provided by Pharm Fabrikon, Madurai. The polymers used such as ethyl cellulose (20 cps) and cellulose acetate phthalate were purchased from S. D. Fine Chem., Boisar.

Preparation of enteric spheres:

Enteric spheres were prepared by using a simple but innovative process that was designed by combining wet granulation with thermal change methods. Thermal dependent solubility of ethyl cellulose was advantageously clubbed with wet granulation of cellulose acetate phthalate to impart enteric release properties to the delivery system. Diclofenac sodium was mixed with cellulose acetate phthalate; the resulting mixture was granulated with 30% w/w aqueous acacia mucilage and dried at 50°. Dried granules of uniform size (No. 30/40) were further encapsulated with ethyl cellulose by coacervation-phase separation technique by thermal change method. The ethyl cellulose coating was given on drug–cellulose acetate phthalate core by using cyclohexane as solvent for ethyl

TABLE 1: COMPOSITION AND PHYSICAL CHARACTERISTICS OF THE ENTERIC SPHERES

Batch Code	Drug Polymer ratio	Composition			Average diameter (m)	Drug content (mg)*	Entrapment efficacy (%)	Angle of repose
		Drug (mg)	CAP (mg)	EC (mg)				
A 1	1 : 1	1000	-	1000	457.94	47	94	22°36'
A 2	1 : 1	1000	1000	-	498.57	46	92	22°12'
A 3	1 : 1	1000	100	900	447.50	42	84	23°31'
A 4	1 : 1	1000	300	700	431.94	47	94	22°48'
A 5	1 : 1	1000	500	500	422.01	45	90	23°11'
B 1	1 : 1.5	1000	-	1500	493.71	38	95	24°42'
B 2	1 : 1.5	1000	1500	-	506.22	37	92.5	25°81'
B 3	1 : 1.5	1000	150	1350	490.22	37	92.5	24°37'
B 4	1 : 1.5	1000	450	1050	476.76	36	90	22°46'
B 5	1 : 1.5	1000	750	750	464.35	34	85	26°51'

A1 to A5 represent various formulations at 1:1 drug-polymer ratio and B1 to B5 represent various formulations at 1:1.5 level using cellulose acetate phthalate (CAP) and ethyl cellulose (EC) at different proportions. *Indicates drug content in each batch was estimated using 100 mg of enteric spheres.

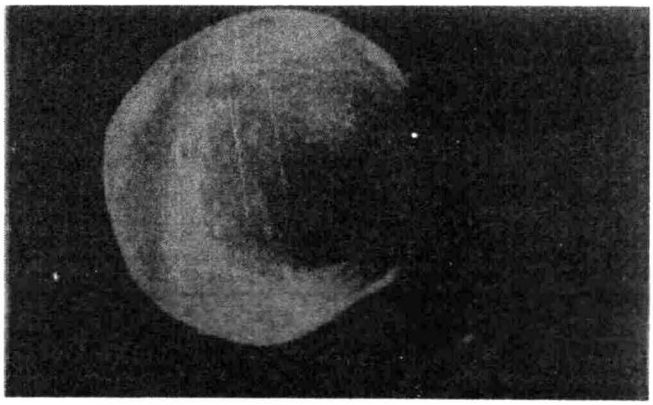
cellulose and changing the temperature from 80° to room temperature with continuous stirring at 1000 rpm. Drug–polymer ratio was kept at two levels like 1:1 and 1:1.5. Although the amount of drug loaded in each batch was constant (1 g), the concentrations of cellulose acetate phthalate and ethyl cellulose were altered at each level in order to prepare ten batches of the enteric spheres with different polymer composition (Table 1).

In vitro release studies:

In vitro drug release studies were carried out for 8 h using the rotating basket method specified in USP XXI. The volume and ionic strength of the dissolution media were selected in order to simulate the gastrointestinal environment. Two phases of dissolution studies were carried out in 900 ml of simulated gastric fluid for first 2 h and in simulated intestinal fluid for next 6 h. Samples were withdrawn and replaced with fresh media after every hour. Samples were filtered using membrane filter of nylon type with pore size of 0.45 µm and analyzed colorimetrically at 450 nm[4]. The *in vitro* release studies were carried out in triplicates.

Evaluation of enteric spheres:

Surface morphology of enteric spheres was studied using a Hitachi Gold Scanning Electron Microscope after coating the spheres with gold vapors. Morphological analysis was carried out at different magnifications (Photograph 1). Size distribution analysis was carried out by sieve analysis, which involved usage of sieves ranging from 10 to 120-mesh size. The data obtained was



Photograph 1: Close surface view of enteric spheres

Scanning electron micrograph showing close surface view of enteric spheres. All the photographs were taken using Hitachi Gold Scanning Electron Microscope at the magnification of 60 x 2.

subjected to graphical treatments in order to find the mode of size distribution[5]. Flowability of enteric spheres was tested by measuring the repose angle using funnel method. Uniformity of the drug content was confirmed by analyzing the drug content in each batch after dissolving the spheres in acetone and then extracting the drug from the organic layer using water. Drug content in aqueous layer was determined at 450 nm. Drug entrapment efficacy[6] of the process was calculated using the drug content data. Amount of drug entrapped in the spheres in each batch was compared with the amount of drug, which was intended to be loaded in order to get the entrapment efficacy of this newly designed process (Table 1).

Drug integrity was checked by carrying out the thin layer chromatographic studies[7] and IR spectral analysis for the enteric spheres of best *in vitro* formulation B3, and the results were compared with that of pure drug. Thin layer chromatographic analysis was carried out using benzene:methanol:acetone in the ratio of 7:2:3 as mobile phase and sulphuric acid in methanol as detector in the form of spraying solution. These studies were carried out in order to authenticate the non-interaction of the process parameters with molecular integrity of the drug.

Although it could be validly concluded that the prominent mechanism is erosion from the polymer characteristics, in order to verify the presumption, erosion study was carried out. In erosion studies, the enteric spheres were exposed to simulated gastric fluid for first 2 h and to simulated intestinal fluid for next 6 h and analyzed for metamorphosis of structural integrity, which was checked by taking scanning electron micrographs (photograph 2 to 5).

In vivo studies:

Gastrointestinal compatability and pharmacodynamic efficacy of the enteric spheres were analyzed by carrying out ulcerogenicity[8] and antiinflammatory[9] studies respectively using animal models. Male Wister rats weighing 120–140 g were divided into three groups each having six animals. While one group served as control the remaining three groups were administered with pure drug suspension, marketed formulation and formulation B3 (containing cellulose acetate phthalate and ethyl cellulose in the ratio of 10:90 at 1:1.5 drug–polymer ratio) through oral route. The comparative therapeutic efficacy of the drug in the formulation and in pure state could be established using carrageenan induced rat paw oedema model, where carrageenan (0.1 ml of 1 % w/w) was injected into subplanatar region of left paw after one hour of the drug dosing. The paw volume of all groups was measured after 3 h of injection of an agent that causes edema. The results were compared and expressed as per cent oedema inhibition with respect to control paw volume. After 24 h, the animals were sacrificed and the stomach was excised. The stomach was then incised and then examined for ulcer development under stereomicroscope.

RESULTS AND DISCUSSION

Surface morphology studies revealed that the enteric spheres are discrete, spherical in shape and devoid of cracks (photograph 1). Micrometric analysis revealed that the mode of size distribution was log normal in all batches with the range distribution of 422.01 to 506.22 μm. Pursuant to the results obtained from the angle of repose studies, the good flow characteristics of the enteric spheres of all batches could be confirmed. Drug content determination studies affirmed the uniform distribution of drug in all batches. Entrapment efficacy calculations revealed the capability of the process to give maximum drug loading irrespective of inter polymer ratio and drug–polymer ratio changes (Table 1).

The similarity in Rf values, ranging between 0.70 to 0.73, and the absence of secondary spots, besides ensuring the absence of drug–polymer interaction also affirmed the molecular integrity of drug, which remained unaltered due to the process parameters. The absence of interaction in the best *in vitro* formulation B3 (containing cellulose acetate and ethyl cellulose at the concentration of 10:90 at 1:1.5 drug-polymer ratio) was further confirmed by IR spectral analysis.

In vitro release studies revealed that the drug release from all batches is concentration-dependent and erosion-mediated. Graphical treatment of *in vitro* kinetic data according to the Hixson-Crowell equation revealed these facts. The order and mechanism of the release were confirmed based on the linearity of graphical expression of dissolution data to first order and erosion plots respectively (Table 2).

The extent of influence of polymer concentrations and combinations was studied comparative analysis on t_{50} values of different formulations. The batches formulated with cellulose acetate phthalate alone using wet granulation process were abruptly failed to sustain the

TABLE 2: *IN VITRO* RELEASE KINETIC DATA OF ENTERIC SPHERES

Batch Code	Correlation coefficient		Release rate (min^{-1})	Hixson Crowell Cube root Cube root dissolution rate constant	T_{50} (h)
	First order plot	Erosion plot			
A 1	–0.9428	–0.9738	0.3472	0.0770	4.26
A 2	–0.9885	–0.9848	0.7028	0.1326	2.46
A 3	–0.9832	–0.9730	0.4313	0.7992	5.20
A 4	–0.9758	–0.9497	0.4292	0.0775	4.37
A 5	–0.9669	–0.9326	0.4424	0.0782	4.26
B 1	–0.9640	–0.9820	0.2763	0.0662	4.35
B 2	–0.9959	–0.9841	0.5338	0.1160	2.58
B 3	–0.9895	–0.9750	0.3726	0.0740	6.56
B 4	–0.9750	–0.9501	0.3515	0.0684	5.29
B 5	–0.9640	–0.9306	0.3859	0.0712	4.45

A1 to A5 and B1 to B5 represent various formulations prepared using cellulose acetate phthalate (CAP) and ethyl cellulose (EC).

release in simulated intestinal fluid although they did not release the drug in simulated gastric fluid. The batches formulated with ethyl cellulose alone using thermal change process, failed not only to extend the release for 8 h but also to impede the release in acidic ambience. Among other batches prepared using the process comprised of both wet granulation and thermal change methods, the targeted results were achieved at 1:1.5 drug–polymer ratio. As expected the presence of cellulose acetate phthalate and ethyl cellulose synergistically enhanced the ability of the delivery system to impede the enteric release. The extent of this additive impact was found to be maximum in the batch B3, having high ethyl cellulose concentration at 1:1.5 drug–polymer ratio. Besides its ability to retard the enteric release, the uniformity of the release pattern observed in the simulated intestinal fluid made the system having cellulose acetate phthalate and ethyl cellulose in the concentration of 10:90 at 1:1.5 drug–polymer ratio as best choice for *in vivo* studies (Fig. 1).

Erosion studies confirmed that the prominent mechanism of release is erosion. The enteric spheres retained its structural integrity for first 2 h of its stay in simulated

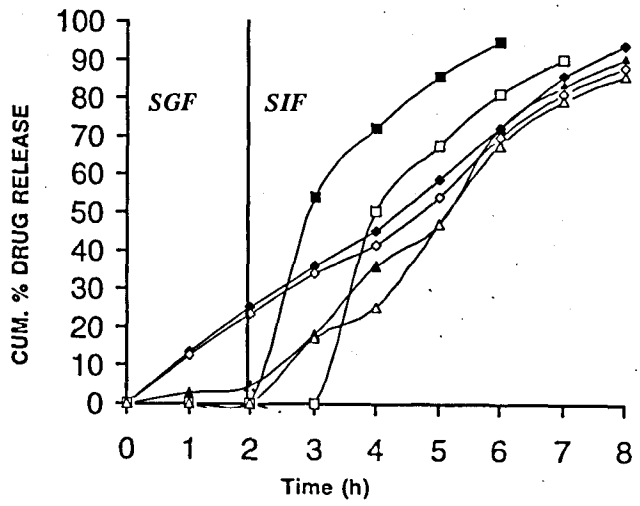
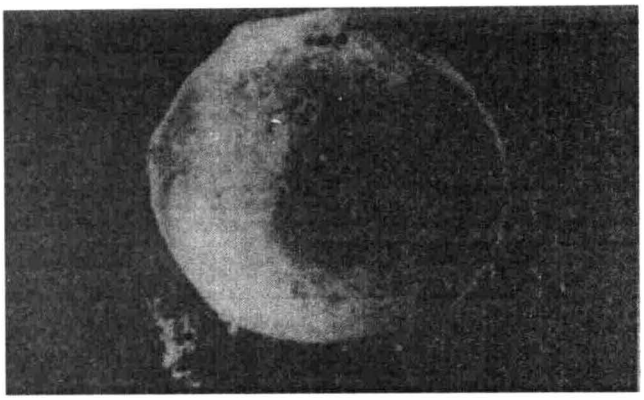


Fig. 1: Comparative *In vitro* release profiles of formulations

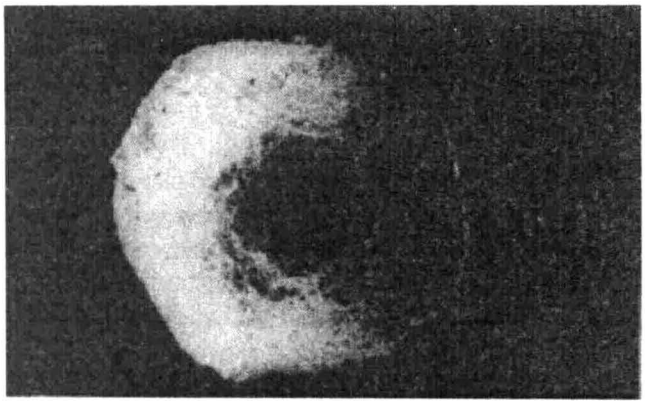
In vitro **profiles of formulations A1 (-◇-), A2 (-□-), A3 (-▲-), B1 (-◊-), B2 (-□-), B3 (-Δ-). The *in vitro* studies were performed using USP XXI basket apparatus using simulated gastric fluid for first 2 h and simulated intestinal fluid for next 6 h. The correlation coefficient was 0.9895 for the formulation B3**



Photograph 2: Structural integrity after 2 h

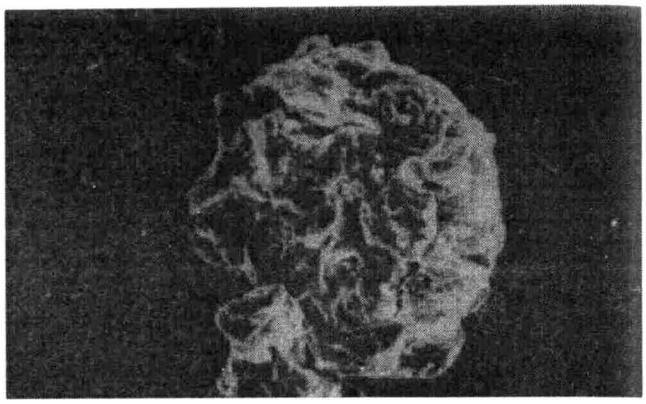
Scanning electron micrograph showing close surface view of enteric spheres after 2 h stay in simulated gastric media (60 x 2). The enteric spheres retained their structural integrity at the end of 2 h stay in acidic environment.

gastric fluid (photograph 2). When the release media was changed to simulated intestinal fluid the structural changes started to occur. After 2 h stay in simulated intestinal fluid, the delivery system was riddled by the entry of dissolution media and resulted in fluffy mass (photograph 3). Micrographs taken at the end of 6th hour, revealed the onset of degradation of the enteric spheres (photograph 4). At the end of the 8th hour, the enteric spheres completely lost its structural integrity and they may no longer have ability to retain drug molecules (photograph 5). During the stay in simulated intestinal fluid,



Photograph 3: Presence of pores at the end of 2 h stay in SIF.

Scanning electron micrograph showing close surface view of enteric spheres after 2 h stay in simulated intestinal fluid (60 x 2). The enteric spheres were riddled by the entry of dissolution media.

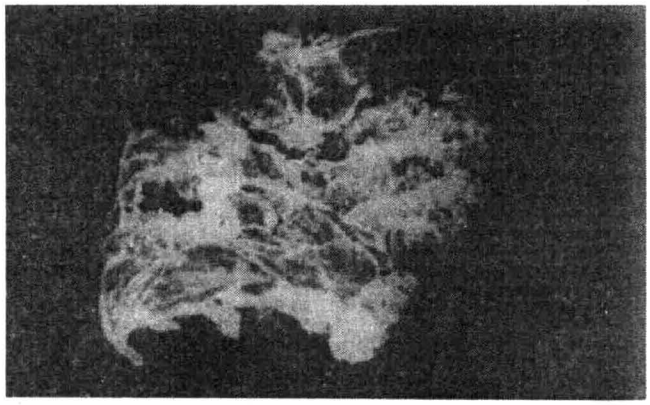


Photograph 4: Initial changes in structure of enteric spheres after 4 h stay in SIF.

Scanning electron micrograph showing close surface view of enteric spheres after 4 h stay in simulated intestinal fluid (60 x 2). The enteric spheres showed onset of degradation.

the delivery system progressively developed pores and tortuous pathways, which might have aided drug release in uniform manner.

Pharmacodynamic studies and ulcerogenetic studies affirmed the validity of the *in vitro* evaluation method followed. Although the anti-inflammatory activity of the formulation is only 3% less than that of pure drug and marketed formulation, the difference was statistically insignificant and the formulation was found to have advantage over its marketed and other conventional dosage



Photograph 5: Complete loss in structural integrity after 6 h stay in SIF.

Scanning electron micrograph showing close surface view of enteric spheres after 6 h stay in simulated intestinal fluid (60 x 2). The enteric spheres lost their structural integrity.

forms as it produced less gastric erosion (results not shown). The presence of enteric retardant polymers not only avoided gastric erosion but also might have caused negative digression in the therapeutic efficacy of the formulation.

In conclusion, formulation B3 (containing cellulose acetate and ethyl cellulose in the ratio of 10: 90 at 1:1.5 drug-polymer ratio) has achieved the targets of present study such as intestinal specific release, uniformity of drug release and non-gastric erosion and thus improves the patient compliance.

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