International Journal of Biomedical and Pharmaceutical Sciences ©2011 Global Science Books

Development and Evaluation of Colonic Drug Delivery of Aceclofenac using Pectin and Guar Gum

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ABSTRACT

The objective of the present study was to microencapsulate the anti-inflammatory drug (Aceclofenac) to provide controlled release and to minimize or eliminate local side effects by avoiding drug release in the upper gastrointestinal tract. The drug was targeted to the colon and its aligned areas for local effects. Aceclofenac was microencapsulated with guar gum or modified guar gum (carboxymethyl guar gum) and pectin using an ionotropic-gelation technique. Aceclofenac microspheres were subjected to micromeritic properties, drug loading, *in-vitro* drug release as well as SEM, DSC, FT-IR spectroscopy and a swelling study (swelling index and swelling kinetics), among others. The prepared microspheres were light yellowish in colour, free-flowing, and almost spherical in shape. The drug-loaded microspheres showed 57.28 to 81.73% drug entrapment efficiency and particle size ranged from 0.80 to 1.10 mm. The DSC study showed the possibility of a weak non-covalent interaction between drug and polymer which may be due to H-bonding or an ionic interaction. The swelling study showed a swelling index of 0.7 at pH 1.2 and 1.2 at pH 6.8; at both pHs, the swelling followed a zero-order kinetics. The FT-IR spectra showed a peak at 1742.65 cm^{-1}, which confirms the carboxymethylation of guar gum. FT-IR spectra of drug-loaded beads indicate that the drug was properly loaded. *In-vitro* drug release studies were carried out up to 8 h in 0.02M phosphate buffer (pH 6.8) and up to 2 h in 0.1 N HCl (pH 1.2). All the formulations followed a Higuchi-Matrix model of release kinetics.

Keywords: carboxymethyl guar gum, ionotropic gelation, release kinetics, zero-order kinetics
Abbreviations: CMGG, carboxy methyl guar gum; **DSC**, differential scanning calorimetry; **FTIR**, Fourier transform infrared; **GG**, guar gum; **GI**, gastro intestinal; **SEM**, scanning electron microscopy

INTRODUCTION

Colonic drug delivery can be achieved by oral or by rectal administration. Rectal administration offers the shortest route for targeting drugs to the colon. However, it can be uncomfortable for patients and compliance may be less than optimal (Watts *et al.* 1997) and the drug does not always reach the sites of colonic absorption (Hardy *et al.* 1986). Targeted drug delivery into the colon is become increasingly popular for local treatment of a variety of bowel diseases like amebiosis, colonic cancer, Crohn's disease, local treatment of colonic pathogenesis, ulceratives, and systemic delivery of protein and peptide drugs (Odeku *et al.* 2005; Philip *et al.* 2009). To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated taking into account the obstacles of the gastrointestinal tract. The various strategies developed to achieve this goal have used specific characteristics of this organ, namely pH, microflora, enzymes, reducing medium, and transit time (Friend *et al.* 1985; Park *et al.* 1993; Gazzaniga *et al.* 1994; Vyas *et al.* 2005). Various pharmaceutical approaches that can be exploited for the development of colon-targeted drug delivery systems include the use of prodrugs, pH-sensitive polymers; bacterial degradable polymers, hydrogel and matrices and multicoating time-dependent delivery systems (Masataka *et al.* 2004; Philip *et al.* 2008).

For the colonic delivery of drugs, an encapsulation polymer is designed to undergo minimal absorption and hydrolysis in the tracts of the upper gastrointestinal tract and undergo enzymatic hydrolysis in the colon, thereby releasing the active drug moiety from the carrier. Glucuronic and glycosidic polysaccharides, which are specifically degraded by colonic-glucuronidases and colonic glycosidases, respectively, permit the release of the attached drug to its pharmacological activity (Ashford *et al.* 1994; Chen *et al.* 2004). The coating of pH-sensitive polymers to the tablets, capsules, or pellets provides delayed release and protects the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction.

Aceclofenac is a non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is a newer derivative of diclofenac and has less gut complication, a short biological half life of 4 h, and a dosing frequency more than once make it an ideal candidate for modified release multiple unit preparation. To reduce the frequency of administration and to improve patient compliances, Aceclofenac is suitable for making a sustained release dosage form.

Microencapsulation is a useful method for prolonging drug release from dosage forms and reducing adverse effects. Among various microencapsulation methods, ionotropic gelation can be used to prepare microspheres of a water-insoluble drug with a water-soluble polymer for sustained release (Lakshmana *et al.* 2009; Umadevi *et al.* 2010). The oral route of drug administration has been used as it is the most natural, uncomplicated, convenient, and safer route.

In this present study our aim was to prepare, characterize and establish an *in-vitro* dissolution study of Aceclofenac microspheres using pectin, guar gum and modified

Received: 28 May, 2011. Accepted: 2 September, 2011.

Research Note

Table 1 Formulation variable and encapsulation efficiency of different microspheres.

Formulation code	Drug (mg)	Pectin (mg)	GG (mg)	CMGG (mg)	$CaCl_2$ solution (% w/v)	Encapsulation efficiency (%)
A1	125	200	50	-	10	62.52
A2	125	200	50	-	4	68.42
A3	125	175	75	-	10	66.89
A4	125	175	75	-	6.5	78.79
A5	125	175	75	-	4	71.32
A6	125	150	100	-	10	70.42
A7	125	150	100	-	6.5	81.73
A8	125	150	100	-	4	75.54
A9	125	100	150	-	10	68.32
A10	125	100	150	-	6.5	74.63
B1	125	200	-	50	10	59.58
B2	125	200	-	50	4	64.19
B3	125	175	-	75	10	68.23
B4	125	175	-	75	6.5	78.47
B5	125	175	-	75	4	71.28
B6	125	150	-	100	10	69.03
B7	125	150	-	100	6.5	80.19
B8	125	150	-	100	4	73.87
B9	125	100	-	150	10	65.11
B10	125	100	-	150	6.5	72.15

guar gum as the colon drug delivery system. The microspheres were prepared by an ionotropic gelation method. The prepared microspheres were also evaluated for drug content, SEM, size-frequency distribution, micromeritic properties, FT-IR Spectroscopy, a swelling study, a DSC study, among others. Such a formulation can only release the drug in the colon due to colonic enzymes and bacteria and not in other parts of the gastrointestinal tract.

MATERIALS AND METHODS

Chemicals

Aceclofenac (Microlabs Pvt. Ltd., Bangalore), calcium chloride (Merck Ltd., Mumbai), Na_2HPO_4 (Merck Specialties Pvt. Ltd., Mumbai), sodium hydroxide, potassium di hydrogen phosphate, iso propyl alcohol (Qualigens Fine Chemicals, Navi Mumbai), monochloro acetic acid (LobaChemie Pvt. Ltd, Mumbai), methanol (International Chemicals, Kolkata), guar gum (HiMedia laboratories Pvt. Ltd., Mumbai) and pectin (Sisco Research Lab Pvt. Ltd, Mumbai) used in the experiment were of analytical grade. Only double distilled water was used.

Preparation of carboxymethylated guar gum

Carboxymethylated guar gum was prepared according to the method of Chen *et al.* (2004) for chitosan with slight modifications. At first, 5 g guar gum and 50 ml isopropyl alcohol were placed in a 200-ml round bottom flask. Then, 13 ml of 10N aqueous NaOH was added within 25 min with constant shaking. Then 30 g of monochloroacetic acid was added over a period of 10 min. The reaction mixture was heated to 60°C with 3 h constant stirring using a magnetic bead, then filtered and washed with ethanol and then dried in a hot air oven at 55°C for 3 h.

Preparation of microspheres

At first, Aceclofenac (125 mg fixed), a specific amount of GG/CMGG and pectin (total polymer = 250 mg) was placed in a beaker. Then 10 ml 0.2N NaOH was added to the beaker with constant stirring. The mixture of drug and polymer was poured drop by drop into different concentrations of $CaCl_2$ solution as indicated in **Table 1**. After making all beads of a particular formulation (**Table 1**), particles were collected by filtration, washed, dried and desiccated at room temperature.

Scanning electron microscopy

The purpose of scanning electron microscopy (SEM) was to obtain topographical characteristics of the polymer. SEM images were taken of the best prepared sample, according to Jain *et al.* (2004). Small amount of the sample were coated uniformly with gold-palladium by using a sputter coater (Polaron SC-76430). Samples were mounted on the SEM stage and scanned using a JEOL-JSM-6360 scanning electron microscope (Jeol Datum Ltd., Tokyo, Japan) (**Fig. 1**).

Fourier Transform Infrared (FT-IR) spectral analysis

FT-IR spectral measurements of guar gum and carboxymethyl guar gum were performed using an FT-IR Spectrometer (Spectrum BX, Serial No. 78625, Perkin-Elmer® Instruments, USA) to understand whether carboxymethylation had occurred properly (**Fig. 2**).

Particle size measurement

Particle size was measured with a compound optical microscope (Zeiss Optical Microscope) attached to a camera (Milling 1991; Patel *et al*. 2005). The images obtained by the camera measured sizes (in mm) with an in-built scale in the software (Zeiss Axovision software).

Micrometric properties

Micrometric properties were measured according to Banker (1987), Milling (1991) and Patel *et al.* (2005).

1. Angle of repose

The angle of repose of different formulations was measured according to a fixed funnel standing method (n = 3):

$$\theta = \tan^{-1}\frac{h}{r}$$

where θ = angle of repose, h = height of the sample from the base, r = radius of the sample in the base.

2. Bulk density and tapped density

Bulk and tapped densities were measured using a graduated cylinder. At first, a known mass of formulation was poured into the cylinder and bulk volume was noted. Then that cylinder was tapped mechanically by a mechanical tapper for 10 min (approx. 300 times) and tapped volume was also noted. Then bulk and tapped densities were calculated. This experiment was performed in triplicate.

3. Carr's index

Compressibility index (CI) or Carr's Index value of microspheres was computed according to the following equation:

$$\text{Carr's Index (\%)} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \text{ X } 100$$

4. Hausner's ratio

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Determination of entrapment efficiency and drug loading

To initially determine drug entrapment efficiency (DEE), at first 50 mg beads were placed in a 50-ml beaker, then 10 ml of pH 3 and 0.2-0.3 ml of Tween 80 was added. The mixture was stored for 3-4 h at 50°C, then cooled; NaOH was then added to make the pH 6.8. Then 10 ml of 3% pectinase solution was added and the mixture was stored for 24 h at 37°C. The final volume was calculated. The mixture was sonicated and diluted 100 times using 0.02M phosphate buffer (pH 6.8). The absorbance was measured with a UV-spectrophotometer at 274 nm and drug content was determined using the following equations:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \text{ X } 100$$

$$\text{Drug loading (\%)} = \frac{\text{Weight of drug}}{\text{Weight of microspheres}} \text{ X } 100$$

For all formulations, the theoretical drug content was 16.6 mg in 50 mg of sample.

Swelling study

Microspheres (50 mg) were placed and tied in a muslin cloth (Chaurasia *et al.* 2006), which was placed separately in simulated gastric fluid (SGF) (pH 1.2) and simulated intestinal fluid (pH 6.8) at 37 ± 0.5°C After 30 min interval the muslin bag was taken out and the microspheres were placed on a tissue paper to soak excess amount of water. Then weight of microspheres was taken and changes in weight were measured. Then the swelling index (α) was calculated according to the following formula:

$$\alpha = \frac{W_g - W_0}{W_o}$$

where W_o is the initial weight of the microspheres and W_g is the final weight of the microspheres at every 30 min time interval. Then a graph of swelling index (α) vs time (t) was plotted.

Thermal analysis (DSC study)

The DSC thermogram was obtained by using DuPont 2100 v 4.1c DSC. The samples (pure drug, drug-loaded and blank beads, etc.) were placed in copper pan and heated at a constant rate of 20°C/min over a temperature range of 30 to 400°C under nitrogen purging. Thereby, the TGA and DSC graphs were obtained (**Table 3**).

In-vitro drug release studies

Drug release from drug loaded microspheres were investigated according to Patel *et al.* (2005) in dissolution media containing 0.02 (M) phosphate buffer (pH 6.8) and at pH 1.2. These experiments were performed using a USP-II rotating paddle-type dissolution test apparatus (Veego VDA-6D, Veego Instruments Co., Mumbai). A weighed quantity (50 mg) of sample was added to the dissolution medium containing 3% rat cecal content until pH 6.8. The amount of drug released was analyzed by a UV-VIS spectrophotometer (Thermo Spectronic-UV-1, France) at 274 nm for Aceclofenac.

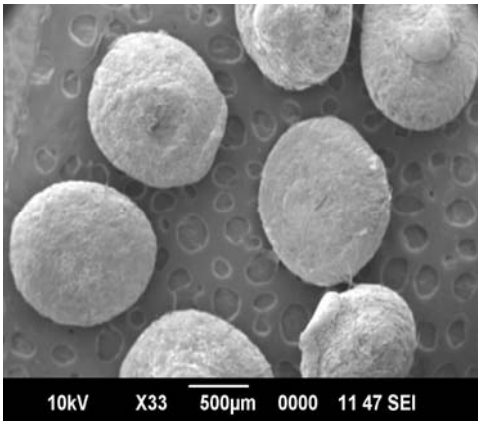

Fig. 1 SEM photograph of prepared microsphere.

Statistical analysis

All experiments were done in triplicate to produce the reproducibility in result and the data presented are the averages of mean of three independent experiments with standard deviation. The data were analyzed using Microsoft Excel XP (Microsoft Corp.). One-way analysis of variance (ANOVA) followed by Tukey's multiple range test was performed to determine the least significance difference for all the reported results. The differences were considered as significant at $P < 0.05$.

RESULTS AND DISCUSSION

Drug loading and encapsulation efficiency of Aceclofenac microspheres

Drug loading and percentage encapsulation efficiency increased when guar gum microspheres and 6.5% (w/v) $CaCl_2$ solution were used in the formulation. Encapsulation efficiency of all formulations varied from 59.58 to 81.73% (**Table 1**). Drug loading and encapsulation efficiency was good for all preparations but was best for formulations A7, B7 and A4. Trivedi *et al.* (2008) found that the encapsulation efficiency of Aceclofenac microspheres using Eudragit was 60-82%.

The percentage encapsulation efficiency was proportional to the polymer concentration up to a certain limit (Rahman *et al.* 2006). The concentration of the cross-linking agent had no significant effect on percent encapsulation efficiency (Chaurasia *et al.* 2006). In this study, for all cases, the theoretical drug loading remains fixed since in all cases the same quantity (50 mg) of microspheres was used.

Morphology

The Aceclofenac microspheres prepared by the ionotropic gelation method were almost spherical, free-flowing, and slightly yellow. SEM of the surface of Aceclofenac microspheres showed small pores/channels on the surface (**Fig. 1**). No difference was observed in the morphological properties of microspheres due to the presence of the drug, as also observed by Bigucci *et al.* (2009). Lakshmana *et al.* (2009) observed rosin microspheres to be almost spherical and with a smooth surface. A porous and spherical structure of colonic drug delivery vehicle with Eudragit was reported by Dhawale *et al.* (2010). The degree of porosity of microspheres was dependent on Eudragit concentration.

Particle size

The maximum size of particles ranged from 0.80 to 1.20 mm (**Table 2**). Particle size of microspheres increase as the amount of polymer increases (Chaurasia *et al.* 2006; Shukla *et al.* 2010). The mean diameter of guar gum cross-linked with glutaraldehyde microspheres ranged from 0.68 to 0.79

Table 2 Micromeritic properties of different microspheres (n = 3).

Formulation code	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (Ci) (%)	Hausner's ratio	Particle size (mm)
A1	20.63 ± 1.131	0.503 ± 0.026	0.604 ± 0.012	16.67 ± 0.016	1.20 ± 0.046	0.95 ± 0.13
A2	27.13 ± 0.565	0.499 ± 0.008	0.594 ± 0.016	15.97 ± 0.015	1.19 ± 0.002	0.86 ± 0.16
A3	19.87 ± 0.121	0.512 ± 0.021	0.630 ± 0.035	18.70 ± 0.040	1.23 ± 0.016	1.02 ± 0.08
A4	20.31 ± 0.628	0.508 ± 0.035	0.579 ± 0.021	12.28 ± 0.066	1.14 ± 0.006	1.01 ± 0.21
A5	21.75 ± 0.321	0.516 ± 0.012	0.609 ± 0.071	15.25 ± 0.083	1.18 ± 0.059	0.98 ± 0.06
A6	20.62 ± 0.202	0.518 ± 0.018	0.627 ± 0.042	17.36 ± 0.057	1.21 ± 0.023	1.06 ± 0.22
A7	21.69 ± 0.543	0.494 ± 0.021	0.588 ± 0.013	15.97 ±0.061	1.19 ± 0.061	1.03 ± 0.06
A8	22.74 ± 1.185	0.501 ± 0.013	0.616 ± 0.015	18.70 ± 0.021	1.23 ± 0.015	0.99 ± 0.07
A9	21.53 ± 0.181	0.572 ± 0.056	0.726 ± 0.023	21.26 ± 0.014	1.27 ± 0.004	1.12 ± 0.10
A10	22.17 ± 0.323	0.562 ± 0.075	0.663 ± 0.025	15.25 ± 0.063	1.18 ± 0.027	1.08 ± 0.11
B1	22.35 ± 1.012	0.518 ± 0.020	0.658 ± 0.045	21.25 ± 0.016	1.27 ± 0.022	0.98 ± 0.28
B2	22.69 ± 1.218	0.509 ± 0.028	0.626 ± 0.015	18.70 ± 0.005	1.23 ± 0.005	0.91 ± 0.21
B3	21.25 ± 0.163	0.522 ± 0.032	0.668 ± 0.007	21.87 ± 0.004	1.28 ± 0.015	1.08 ± 0.12
B4	24.08 ± 0.017	0.518 ± 0.019	0.622 ± 0.005	16.67 ± 0.006	1.20 ± 0.042	1.06 ± 0.08
B5	23.69 ± 0.588	0.533 ± 0.016	0.661 ± 0.019	19.35 ± 0.008	1.24 ± 0.056	1.02 ± 0.06
B6	18.73 ± 1.131	0.512 ± 0.055	0.650 ± 0.014	21.26 ± 0.056	1.27 ± 0.025	1.10 ± 0.05
B7	20.21 ± 0.089	0.528 ± 0.042	0.649 ± 0.017	18.70 ± 0.061	1.23 ± 0.040	1.08 ± 0.10
B8	21.23 ± 0.767	0.544 ± 0.021	0.702 ± 0.027	22.48 ± 0.013	1.29 ± 0.012	1.02 ± 0.12
B9	23.18 ± 0.121	0.589 ± 0.008	0.766 ± 0.034	23.08 ± 0.014	1.30 ± 0.042	1.18 ± 0.06
B10	22.78 ± 0.163	0.578 ± 0.014	0.699 ± 0.031	17.35 ± 0.063	1.21 ± 0.022	1.02 ± 0.05

Table 3 Release kinetics of aceclofenac from pectin and guar gum or carboxymethyl guar gum microspheres.

Formulation code	Zero-order		1st order		Higuchi-Matrix		Koresmeyer-Peppas	
	K	R^2	K	R^2	K	R^2	N	R^2
A1	9.313	0.814	0.016	0.978	30.95	0.967	0.317	0.961
A2	9.588	0.867	0.019	0.993	30.98	0.973	0.356	0.916
A4	12.40	0.969	0.051	0.838	36.94	0.925	1.015	0.956
A5	9.323	0.890	0.021	0.989	29.40	0.952	0.380	0.864
A7	10.13	0.866	0.020	0.968	32.98	0.987	0.382	0.984
A8	10.89	0.988	0.055	0.892	31.84	0.907	1.063	0.971
A10	8.823	0.983	0.052	0.973	25.21	0.863	0.966	0.949
B1	9.486	0.798	0.016	0.993	31.65	0.955	0.290	0.933
B2	8.988	0.890	0.021	0.984	28.85	0.986	0.400	0.958
B4	11.13	0.963	0.061	0.969	31.19	0.813	1.121	0.933
B5	9.142	0.754	0.013	0.993	31.06	0.936	0.257	0.950
B7	9.928	0.818	0.017	0.984	32.93	0.969	0.319	0.968
B8	7.398	0.843	0.018	0.996	24.13	0.966	0.328	0.916
B10	10.34	0.881	0.021	0.974	33.38	0.986	0.396	0.970

Table 4 Cumulative % release of aceclofenac formulations (n = 3).

	pH 1.2		pH 6.8 phosphate buffer containing 3% rat cecal content							
Time	1 h	2 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
A1	2.60 ± 0.05	5.25 ± 0.02	49.51 ± 0.25	55.71 ± 1.12	62.01 ± 0.95	68.42 ± 0.54	77.54 ± 0.24	84.13 ± 0.56	88.30 ± 1.24	92.51 ± 1.20
A2	7.86 ± 0.02	10.26 ± 0.10	46.56 ± 0.31	49.46 ± 0.98	56.50 ± 0.74	63.65 ± 0.24	70.93 ± 0.20	80.43 ± 0.24	88.00 ± 1.26	93.66 ± 1.42
A4	4.34 ± 0.08	6.59 ± 0.03	13.03 ± 0.08	19.80 ± 0.78	50.60 ± 0.54	58.11 ± 0.64	65.76 ± 0.36	80.04 ± 0.26	90.33 ± 1.10	94.19 ± 1.24
A5	6.19 ± 0.12	8.14 ± 0.06	41.28 ± 0.14	46.23 ± 0.56	49.20 ± 0.98	54.28 ± 0.26	63.57 ± 1.12	70.95 ± 0.24	80.52 ± 0.98	94.47 ± 1.65
A7	2.45 ± 0.15	4.94 ± 0.08	44.14 ± 0.12	54.83 ± 0.24	63.26 ± 1.12	69.32 ± 0.84	75.54 ± 1.00	84.31 ± 1.02	93.32 ± 0.74	97.38 ± 1.28
A8	8.37 ± 0.04	10.93 ± 0.14	10.77 ± 0.32	15.30 ± 0.92	32.83 ± 1.10	48.57 ± 1.10	53.82 ± 1.10	67.78 ± 1.12	75.54 ± 0.54	83.42 ± 1.24
A10	4.54 ± 0.21	6.89 ± 0.12	10.68 ± 0.13	14.98 ± 0.12	18.68 ± 0.20	30.38 ± 1.20	40.09 ± 1.24	54.44 ± 1.42	60.03 ± 0.68	70.25 ± 1.20
B1	2.73 ± 0.13	8.24 ± 0.10	54.60 ± 0.14	58.42 ± 0.45	65.02 ± 1.26	71.73 ± 1.24	78.56 ± 1.02	85.49 ± 1.00	92.52 ± 0.24	96.94 ± 1.34
B2	2.13 ± 0.14	8.34 ± 0.13	38.48 ± 0.09	43.53 ± 0.47	50.80 ± 1.26	60.27 ± 124	65.75 ± 0.98	71.20 ± 1.14	79.01 ± 0.84	86.26 ± 0.98
B4	6.22 ± 0.15	8.18 ± 0.03	10.36 ± 0.18	12.64 ± 0.58	19.11 ± 0.08	36.01 ± 1.00	42.92 ± 0.74	58.27 ± 1.12	80.19 ± 0.46	85.88 ± 0.36
B5	5.68 ± 0.08	11.14 ± 0.06	56.78 ± 0.14	63.59 ± 0.24	67.67 ± 1.14	74.65 ± 1.20	78.91 ± 0.76	86.06 ± 1.74	90.49 ± 0.26	97.81 ± 0.24
B7	2.35 ± 0.12	7.11 ± 0.02	51.87 ± 0.20	59.98 ± 0.30	65.87 ± 2.12	74.21 ± 1.00	80.34 ± 0.24	86.56 ± 1.10	95.32 ± 0.28	99.43 ± 0.54
B8	3.98 ± 0.03	10.02 ± 0.12	37.83 ± 0.14	42.60 ± 0.45	45.42 ± 1.14	50.29 ± 0.94	57.22 ± 0.46	62.21 ± 1.00	69.34 ± 1.12	74.59 ± 0.32
B10	2.08 ± 0.02	8.13 ± 0.10	43.76 ± 0.15	52.96 ± 1.10	62.34 ± 1.12	67.82 ± 1.24	73.16 ± 0.24	87.04 ± 1.24	92.82 ± 1.10	98.68 ± 1.24

mm (Mazumder *et al.* 2010). The carboxymethylated guar gum microspheres are insignificantly larger than the guar gum microspheres (1.05 ± 0.07 vs. 1.01 ± 0.07 mm; n = 10; $P > 0.05$).

Micromeritic properties of Aceclofenac microspheres

All the formulations showed an angle of repose in the range of 18.73-27.13, i.e., < 30 (**Table 2**), which shows the free-flowing nature of the microspheres. The microspheres had good packability, shown by bulk and tapped densities. Eudragit-coated Aceclofenac microspheres showed similar Carr's index, Hausner's ratio and angle of repose values (Trivedi *et al.* 2008). The mean bulk and tapped density of all formulations ranged from 0.499 to 0.589 and from 0.579 to 0.622, respectively. CI ranged from 12.28 to 23.08% and formulation A4 had the lowest CI index, indicating excellent compressibility. Hausner's ratio ranged from 1.14 to 1.30, i.e., all the formulations showed good flow properties.

Swelling study

The adhesive and cohesive properties of polymers are gene-

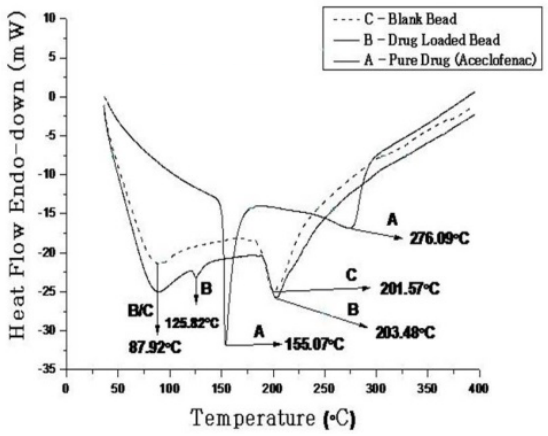

Fig. 2 DSC curve for pure drug, drug loaded bead and blank bead.

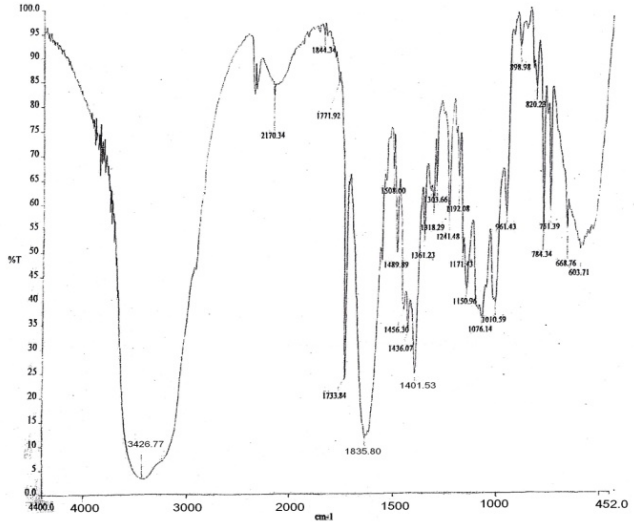

Fig. 3 FT-IR spectra of drug-loaded bead.

rally affected by their swelling behavior (Mortazavi *et al.* 1993). Swelling at pH 1.2 was less than at pH 6.8 and α at pH 1.2 was 0.7 but at pH 6.8 it was 1.2. The R^2 value at both pH 1.2 and 6.8 indicates that the swelling follows a zero-order kinetics (**Table 3**). The equilibrium swelling was dependent on the content of carboxylic acid groups and on the content of hydrophobic monomer. The incorporation of hydrophilic units increased the swelling ratio in SIF (pH 7.2), but has had an inverse effect in SGF (pH 1.2) (Davara *et al.* 2001).

In-vitro dissolution study

A very small amount of drug (minimum 5.25%, maximum 11.14%) was released from the prepared microspheres at pH 1.2 during the 2-h study. After that there was a slow but steady release reaching 70-80% after 8 h (**Table 4**). Eudragit-coated chitosan microspheres showed 95.9% release in the colon (Umadevi *et al.* 2010). Dhawale *et al.* (2010) reported 101% release of 5-fluorouracil: eudragit ratio of 1:2 at pH 7.4. Chaurasia *et al.* (2006) observed 91% drug release from guar gum microspheres in cecal content media.

DSC study

DSC is very useful in the investigation of the thermal properties of microspheres, providing both qualitative and quantitative information about the physicochemical state of a drug inside a microsphere (Dubernet 1995). Pure Aceclofenac showed a peak at 155.07°C, which is the melting point of Aceclofenac, the drug-loaded bead showed a peak at 125.82°C while the blank bead showed no peak in this region (**Fig. 2**). A weak, non-covalent interaction might have taken place between the drug and polymer due to hydrogen bonding or an ionic interaction for which a peak at 125.82°C was observed in the drug-loaded bead. No detectable endotherm is observed if the drug is present in a molecular dispersion or solid solution state in the polymeric microspheres loaded with a drug (Mu *et al.* 2001).

FT-IR study

The FT-IR spectra confirmed the carboxymethylation of guar gum, revealed by the appearance of a peak at 1742.65 cm^{-1} (C=O stretching) (**Fig. 3**). Dodi *et al.* (2011) also observed a reduced intensity of the absorption band located at 3418 due to OH stretching indicating that some OH groups were carboxymethylated. In the drug-loaded bead the broad peak around 3626 cm^{-1} indicated a hydrogen-bonded OH group. The binding between gum and drug has taken place, revealed by the abolition of the C=O peak of COOH at 1771 cm^{-1}.

CONCLUSION

Aceclofenac microspheres were successfully prepared by using the ionotropic-gelation method. Polymer variation influences particle size as well as the drug release pattern of microspheres. The release kinetics showed that drug release from Aceclofenac microspheres followed the Matrix-Higuchi model (diffusion-controlled drug release mechanism). Initially, in gastric medium (pH 1.2), the release of the drug (Aceclofenac) from microspheres was low, but at pH 6.8 all formulations showed burst release initially and then tended to release at a constant rate. As expected, the prepared microspheres could release the drug at pH 6.8, which is the pH of the colon and its aligned areas, proving to be a good candidate for site-specific drug delivery.

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