Academic Sciences

Asian Journal of Pharmaceutical and Clinical Research

Vol. 4, Issue 4, 2011 ISSN - 0974-2441

Research Article

DEVELOPMENT AND EVALUATION OF COMPRESSION COATED COLON TARGETED TABLETS OF ACECLOFENAC BY USING NATURAL POLYMERS

NAVNEET SYAN*, POOJA MATHUR

Ganpati Institute of Pharmacy, Bilaspur, Yamunanagar, Haryana, India, 135102 Email: syannavneet@gmail.com

Received: 23 Aug 2011, Revised and Accepted: 12 Sep 2011

ABSTRACT

The investigation was concerned to make a successive colon targeted delivery of compression coated aceclofenac tablets. The influence of locust bean gum and xanthan gum polymers and their various combinations was studied on drug release profile. The preformulation studies like FTIR spectroscopy and differential scanning calorimetry (DSC) showed the absence of drug-excipient interactions. The tablets were found within the permissible limits for various physicochemical parameters. Dissolution studies were performed in 0.1N HCl for 2 h, in pH 7.4 buffer for 3 h and the in pH 6.8 buffer up to 24 h. The *in vitro* studies were also performed in pH 6.8 phosphate buffer containing 4% w/v rat caecal content. The cumulative percentage release of aceclofenac after 24 h was found 61.40±1.02%, 54.43±1.86%, 46.27±1.96%, 39.37±2.70%, 49.63±2.88% (mean±S.D.), for formulation LX1, LX2, LX3, LX4 LX5 respectively. The effect of presence of rat ceacal content (4%w/v) on cumulative % drug release was observed significantly positive. The formulations containing locust bean alone showed rapid release of drug. Whereas combination of locust bean gum and xanthan gum was found sufficient to sustain the drug release for successful colon targeting. Present study on the polysaccharides demonstrated that the combination of locust bean gum and xanthan gum as a coating material proved capable of protecting the core tablet containing aceclofenac during the condition mimicking mouth to colon transit.

Keywords: Ceacal content, Colon, Phosphate Buffer

INTRODUCTION

Oral drug delivery is a widely accepted route of administration of therapeutically active moieties; the gastrointestinal tract presents several types of barriers to oral drug delivery. Colon targeted drug delivery is useful in colonic diseases treatment like IBS, IBD, Chron's disease and ulcerative colitis, oral delivery of proteins and peptides, in the diseases where a delay in systemic absorption is therapeutically desirable (angina, nocturnal asthma, arthritis).[1] The utilization of enzymes produced by the bacteria residing exclusively in the colon is a means of obtaining site specific delivery to this region.[2]

Aceclofenac is one of the emerging NSAID molecule for arthritis treatment. It is a newer derivative of diclofenac and has less gastrointestinal complications.[3,4] The short biological half-life (4 h) and frequent dosing make aceclofenac an ideal candidate for sustained release dosage forms.[5] Aceclofenac is a 2-[2-[2-[(2,6-dichlorophenyl) amino] phenyl]acetyl]oxy]-acetic acid, a highly potent member of a new class of compounds of non steroidal anti-inflammatory drug available in oral formulations for the management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-beta and TNF in the inflammatory cells.[6] The locust bean gum is natural polysaccharide having a molecular weight of 3,10,000 derived from the endosperm of the seed of the *Ceratonia siliqua linne* (Fam: leguminosae). The locust bean contains about 88% D-galacto-D-mannoglycan, 4% of pentan, 6% of protein, 1% of cellulose and 1% of ash.[7]

The physicochemical properties of galactomannan are strongly influenced by the galactose content and the distribution of the galactose units along the main chain. Longer galactose side chains produce a stronger synergistic interaction with other polymers and greater functionality.[8]

The hydrophilic polymer xanthan gum is a high molecular weight hetero polysaccharide gum produced by a pure culture fermentation of a carbohydrate with the microorganism *Xanthamonas campestris*. It has been widely used in oral and topical formulations, cosmetics and foods as suspending or stabilizing agent, and release control agent in hydrophilic matrix formulations.[9]

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms.[8] The objective in the present study was development of colon targeted drug delivery system containing natural gums as release retardant in different concentration ratios, in upper GIT, but is degraded by microbial flora in colon.

MATERIALS AND METHODS

Aceclofenac and locust bean gum were obtained as a gift sample from Ovation Remedies, Kala-Amb (H.P.) and HI-Media Laboratories Pvt. Ltd., Nasik respectively. Croscarmellose sodium was obtained as gift sample from Mapple biotech Pvt. Ltd. Xanthan gum purchased from S.D. fine chemicals Pvt. Ltd. Microcrystalline cellulose, magnesium stearate and talc used were of analytical grade. Healthy male albino rats were obtained by animal house of department, Kurukshetra University Kurukshetra, weighing 150-200g.

Preparation of core tablets

Each core tablet (avg. wt. 125 mg) for *in vitro* studies consists of aceclofenac (100 mg), microcrystalline cellulose (19 mg), croscarmellose sodium (3mg), talc (2 mg) and magnesium stearate (1 mg). The materials were weighed, mixed and passed through a mesh (250mm) to ensure complete mixing. The tablets were prepared by compressing thoroughly the mixed materials using 6 mm round, flat and plain punches on an eight station rotary tablet punching machine (Fluid Pack machinery, Ahemdabad), optimizing the hardness and die cavity of the machine. Table 1 exhibits formulation of core tablets.

Table 1: Formula for core tablet

Sr. No.	Ingredients	Amount(mg)
1	Aceclofenac	100
2	Microcrystalline cellulose	19
3	Croscarmellose sodium	3
4	Magnesium stearate	1
5	Talc	2
6	Total weight	125

Preparation of compression coated tablets

The formulated core tablets were compression coated with different quantities of coating material such as locust bean gum and xanthan gum taken in LX1, LX2, LX3, LX4 and LX5 (4:0, 3:1, 1:3, 0:4, 2:2) respectively. The microcrystalline cellulose is added in the formulation as a direct compression aid to produce sufficient

hardness. The compression coating was provided by placing 40 % quantity of coating material in the die cavity, and then the core tablet was carefully positioned in the centre of the die cavity and was filled with the other 60 % of the coating material. The coating material was compressed around the core at an applied force of 5,000 kg using 13 mm round, flat and plain punches, optimizing the hardness. Table 2 exhibits formulation of compression coated tablets.

Evaluation of tablets

Preformulation studies were also carried out to check the compatibility between drug and various polymers by using FTIR and DSC studies. The prepared core tablets of aceclofenac were evaluated for hardness (Pfizer hardness tester) and disintegration study for fast disintegrating core matrix. Content uniformity of all the formulations (three tablets each) were calculated by the method as specified in I.P. Compression coated tablets were evaluated for hardness, friability (Roche's friabilator), weight variation and *in vitro* release studies.

***In vitro* drug release studies [10]**

The compression coated aceclofenac tablets were evaluated for their integrity in the physiological environment of stomach and the small intestine under conditions mimicking mouth to colon transit. These studies were carried out using a USP XXII/XXIII dissolution rate test apparatus (Apparatus 1, 100 rpm, 37 °C). The tablets were tested for drug release for 2 h in 0.1N HCl (900 mL) as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with pH 7.4 phosphate buffer (900 mL) and tested for 3 h because the average small intestine transit time is about 3 h. Then further release studies up to 24 h were carried out in pH 6.8 phosphate buffered saline (PBS). At the end of time periods, the samples of 1 mL were taken separately, suitably diluted and analyzed for aceclofenac content using double beam UV spectrophotometer at 273 nm. The susceptibility of the locust bean gum and xanthan gum coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 mL of pH 6.8 PBS containing 4% w/v rat caecal contents. The caecal contents were obtained from male albino rats after pretreatment for 7 days with locust bean gum dispersion which provided the best condition for the *in vitro* evaluation of locust bean gum. Thirty min before the commencement of drug release studies, five rats were killed by spinal traction. Their abdomen were opened, the caecum were isolated, ligated at both ends, dissected and immediately transferred into pH 6.8 PBS which is previously bubbled with CO_2

Table 2: Formula for compression coat mixture

Sr. No.	Ingredients	LX1(4:0)	LX2(3:1)	LX3(1:3)	LX4(0:4)	LX5(2:2)
1	Locust bean gum	340	255	85	0	170
2	Xanthan gum	0	85	255	340	170
3	MCC	55	55	55	55	55
4	Magnesium stearate	2	2	2	2	2
5	Talc	3	3	3	3	3
6	Total weight	400	400	400	400	400

Table 3: Preformulation flow parameters of granules

Batch code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Compressibility index (%)	Angle of repose
LX1	0.642	0.750	1.17	14.28	20.80
LX2	0.603	0.689	1.14	12.48	21.90
LX3	0.680	0.790	1.16	13.92	23.10
LX4	0.587	0.671	1.14	12.51	18.72
LX5	0.580	0.665	1.15	10.52	19.80

Table 4: Physical characteristics of compression coated tablets of aceclofenac

Formulation code	Friability*	Hardness before coating**	Hardness after compression coating**	Disintegration Time** (min.)	Content Uniformity** (%)
LX1	0.21	2.74±0.34	6.68±0.44	200.31 ± 5.68	95.8 ± 0.541
LX2	0.15	2.88±0.23	6.84±0.37	210.30 ± 3.77	97.83 ± 0.907
LX3	0.10	2.76±0.14	6.36±0.71	198.33 ± 3.20	98.23 ± 0.251
LX4	0.10	2.90±0.83	6.54±0.18	211.50 ± 1.87	100.2 ± 0.642
LX5	0.09	2.33±0.65	6.22±0.21	210.66 ± 3.50	98.86 ± 0.950

All values are expressed as Mean ± SD,* n=10, **n=6

The caecal bags were opened; their contents were individually weighed, pooled and then suspended in PBS to give a final dilution of 4% w/v. As the caecum is naturally anaerobic, all the operations were carried out under CO_2. The studies simulating the drug release in colon were carried out in USP XXII/XXIII dissolution rate test apparatus (Apparatus I, 100 rpm, 37 °C) with slight modification. A beaker (capacity 150 mL, internal diameter 55 mm) containing 100 mL of dissolution medium immersed in vessel containing 600 ml water, which is in turn placed in the water bath of dissolution apparatus. The coated tablets were placed in the basket containing pH 6.8 phosphate buffered saline along with the rat caecal contents. The experiments were carried out with the continuous CO_2 supply into the beaker to simulate anaerobic environments of caecum. The drug release studies were carried out for 24 h (as usual colonic transit time is 20-30 h) and 1 mL of samples were taken at different time intervals. The volume was made up to 10 mL with PBS, centrifuged and the supernatant was filtered through a bacteria proof filter and this filtrate was analyzed for aceclofenac spectrophotometrically. The above study was carried out on all the aceclofenac tablets coated with different coat compositions (LX1, LX2, LX3, LX4, LX5) and also without rat caecal content in pH 6.8 PBS (control).

RESULT AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for aceclofenac using locust bean gum and xanthan gum as carrier. The release of such a small percent of drug from the surface of the matrix tablets in the physiological environment of stomach and small intestine is a serious consideration for drugs showing deleterious effects on stomach and small intestine. The drug delivery system targeted to colon should remain intact in stomach and small intestine, but should release the drug in colon.

FTIR spectra of pure aceclofenac and its physical mixture are shown in figure 1, 2. The results of physical mixtures of drug and various excipients revealed no considerable changes in the IR peaks of aceclofenac, thereby indicating the absence of any interaction between drug and polymers used. The results of DSC studies are given in figure 3, 4. Pure aceclofenac showed a sharp endotherm at 155.83 °C corresponding to its melting point (100, 101). The mixture showed melting endotherm at 149.85 °C. There was no appreciable change in the melting endotherms of the physical mixture with excipients as compared to pure drug. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between drug and excipients used in the preparation. All the batches were evaluated for pre-compression parameters for characterization of flow properties (Table 3). The physical properties and hardness of the tablets were found in the range of 2-3 kg/cm² for core tablets and 6-7 kg/cm² after coating. Percentage weight loss in the friability test was less than 0.7% in all the batches. All the batches contained aceclofenac within 100±5% of the labeled amount. Overall, the prepared tablets batches were of good quality with respect to hardness, friability and drug content (Table 4). Disintegration time for core tablets was 1 min showing sufficient fast release property of core tablets. The combined action of the super disintegrants (sodium starch glycollate) and microcrystalline cellulose (used as a diluent and direct compression vehicle) might have contributed to such a fast disintegration. Thus the core tablets of aceclofenac formulated in the study were found to have the required characteristics for colon targeting in the form of a locust bean gum compression coat over the drug core.

Table 5: Cumulative % drug release data of compression coated tablets of aceclofenac

Time (h)	LX1	LX2	LX3	LX4	LX5
0	0	0	0	0	0
2	8.43±0.55	8.03±0.20	7.93±0.72	6.77±0.32	8.47±0.65
5	22.57±1.16	17.70±0.46	7.17±0.55	9.07±0.83	9.47±0.81
6	25.53±1.50	19.23±0.35	17.60±0.92	15.77±1.90	18.50±1.75
8	28.60±1.10	26.57±0.93	21.43±1.15	18.39±1.73	23.40±1.85
10	36.47±0.71	35.33±0.85	30.43±3.80	21.60±2.11	32.23±1.90
12	41.20±0.92	38.37±1.16	33.47±1.10	26.23±1.85	34.20±0.90
14	44.43±0.95	41.80±0.40	37.33±3.25	28.23±0.90	39.23±0.60
16	46.23±1.00	44.23±2.40	39.53±2.71	30.20±2.90	41.53±1.50
18	47.83±1.00	46.10±2.05	40.67±2.00	33.17±1.90	43.33±1.77
20	49.70±1.31	47.40±0.70	43.50±2.18	36.50±2.21	45.13±1.90
22	54.63±2.25	50.30±1.21	44.53±1.96	37.10±2.00	46.43±1.02
24	61.40±1.02	54.43±1.86	46.27±1.96	39.37±2.70	49.63±2.88

All values are expressed as Mean ± SD, n=3

Table 6: Cumulative % drug release data of compression coated tablets of aceclofenac in presence of 4% rat ceacal content

Time (h)	LX1	LX2	LX3	LX4	LX5
0	0	0	0	0	0
2	8.43±0.32	7.87±0.06	6.27±1.82	6.67±2.45	9.57±0.71
5	22.00±0.26	20.23±0.19	11.30±1.21	8.67±2.50	19.53±1.86
6	28.23±0.12	26.46±1.96	22.20±2.01	18.54±2.57	23.63±2.21
8	36.30±1.61	32.07±0.75	35.37±1.70	31.57±1.27	34.27±0.95
10	43.17±1.11	42.53±1.21	37.77±0.15	36.17±1.90	41.17±2.01
12	57.50±3.82	56.50±1.64	42.07±1.95	40.23±2.00	51.17±2.36
14	61.13±1.26	58.53±1.89	47.83±1.10	43.13±0.55	55.83±1.99
16	72.53±1.05	70.33±0.71	54.60±2.71	50.70±2.29	67.79±1.74
18	81.17±3.10	80.87±2.20	57.33±1.75	53.47±2.25	73.54±1.86
20	88.20±1.68	84.37±0.86	60.03±3.10	56.63±2.35	76.06±1.97
22	89.60±1.55	86.73±1.80	63.17±2.05	60.53±2.06	80.44±2.20
24	91.50±0.82	88.17±1.90	71.90±1.41	67.73±2.10	86.71±2.01

All values are expressed as Mean ± SD, n=3

The core tablets of aceclofenac were compression coated with a coat formulation that contained various quantities of locust bean and xanthan gum. The cumulative amount of aceclofenac released from LX1, LX2, LX3, LX4 and LX5 (4:0, 3:1, 1:3, 0:4, 2:2 of LB:XG) was 22.57%, 17.7%, 7.18%, 9.07% and 9.47% respectively after 5 h of the dissolution study in simulated gastric and intestinal fluids. Thus the locust bean gum and xanthan gum in the form of a compression coat, has potential to protect the drug from being released in the physiological environment of stomach and small intestine. To assess the integrity of the coats, drug release studies were carried out without the addition of rat caecal contents into pH 6.8 phosphate buffer. At the end of the 24 h of the dissolution study LX1, LX2, LX3, LX4 and LX5 were found intact and the cumulative mean percent drug released was 61.4±1.02%, 54.53±1.86%, 46.27±1.96%, 39.37±2.7% and 49.63±2.88%, respectively (Table 5, Figure 5). This indicates that until the coat will degraded, the gum will not permit the release of the bulk drug present in the core.

The drug delivery systems targeted to the colon not only protect the drug from being released in the physiological environment of stomach and small intestine, but also help a dosage form to release the drug in colon. It was reported earlier that rat caecal content medium at 4% w/v level after 7 days of enzyme induction provide the best conditions for assessing the susceptibility of locust bean gum to colonic bacterial degradation . Hence, *in vitro* drug release studies were carried out in pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents.

When the *in vitro* studies were carried out in the presence of rat caecal content medium, the cumulative percent drug released from aceclofenac tablets coated with coat formulation LX1 was found to be 91.5±0.82 and the coat remained intact. The coat (LX4) was almost degraded in the presence of rat caecal contents thereby releasing the drug into the dissolution medium. Since the xanthan gum content of coat formulation LX2 (85 mg) was lesser compared to coat formulations LX3 (255 mg) and LX4 (170 mg) and the coat might

have been completely hydrated and subsequently form smallest path length among all three formulations for movement of aceclofenac from core tablet towards the dissolution medium and resulting in the release of about 83.3±4.1% of aceclofenac (Table 6, Figure 6). The results showed that tight control of drug release from compression coated formulation LX3 and LX4 might have facilitated the colonic bacterial action on swollen locust bean gum and resulted in the degradation of the formulation thereby releasing the drug in the physiological environment of colon. The compression coated formulation LX2 was completely degraded in simulated colonic fluids whereas LX3 and LX4 formulation partially degraded in simulated colonic fluids.

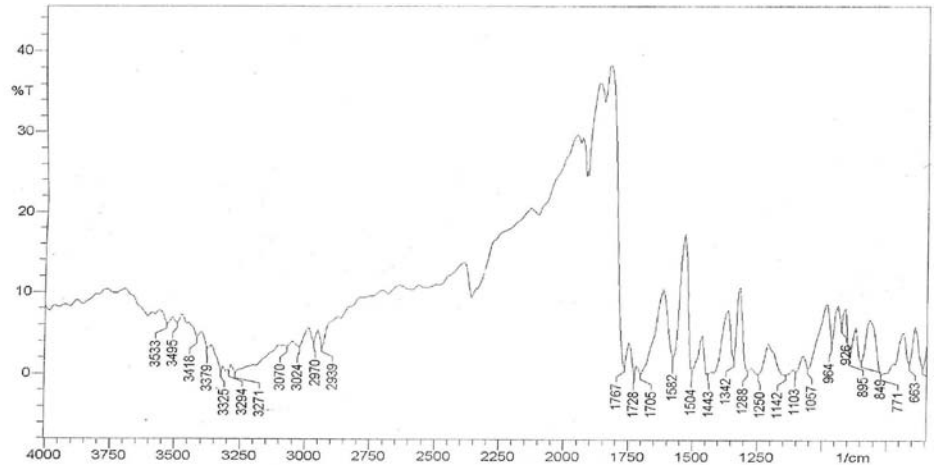

Fig. 1: FTIR spectra of pure aceclofenac

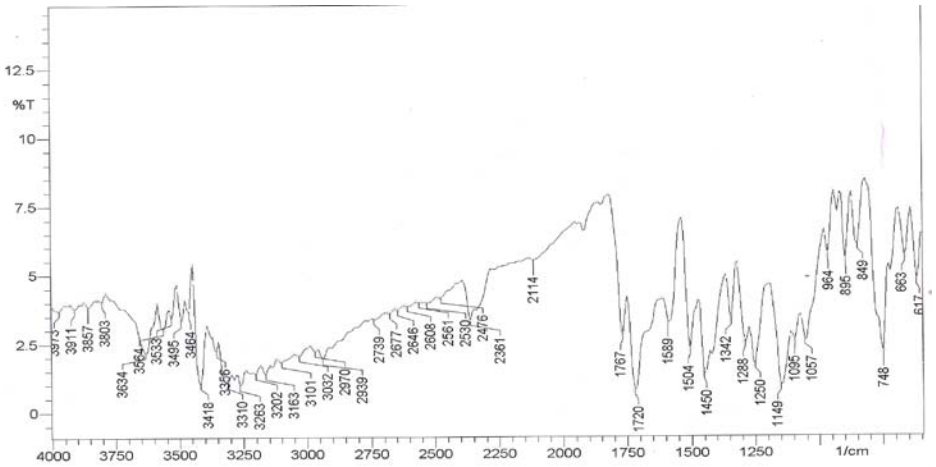

Fig. 2: FTIR spectra of mixture of drug and polymers

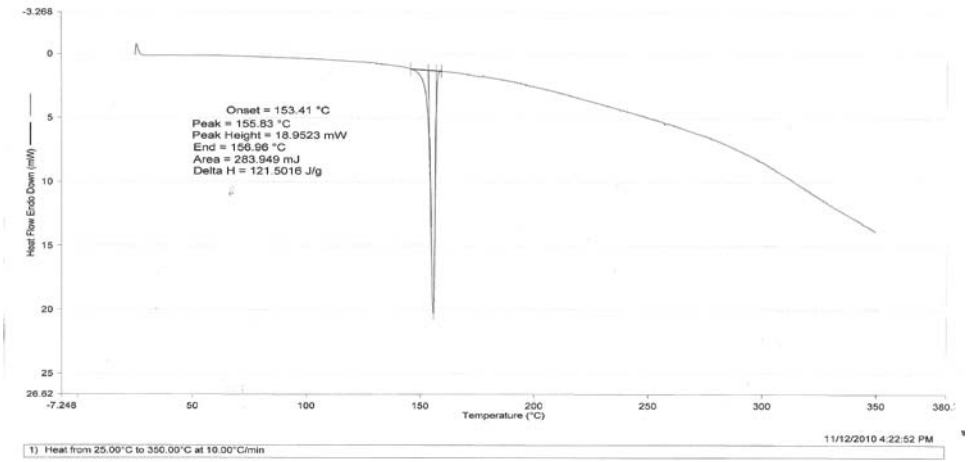

Fig. 3: DSC graph of pure aceclofenac

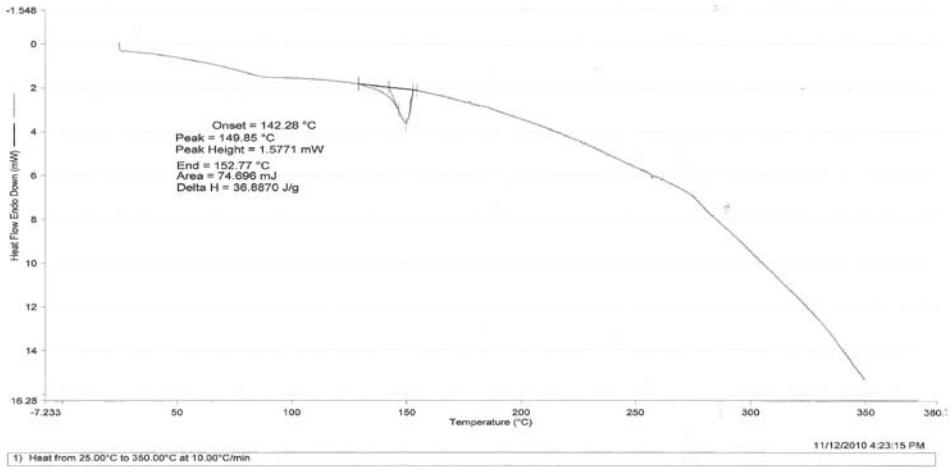

Fig. 4: DSC graph of mixture of drug and polymers

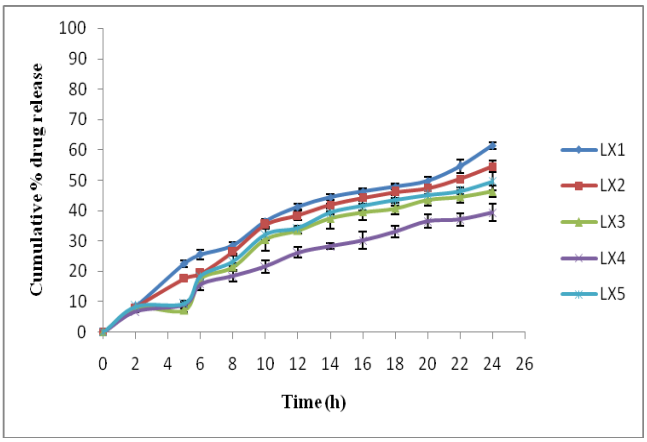

Fig. 1: Dissolution release profile curve for compression coated tablets of aceclofenac in the absence of rat ceacal content

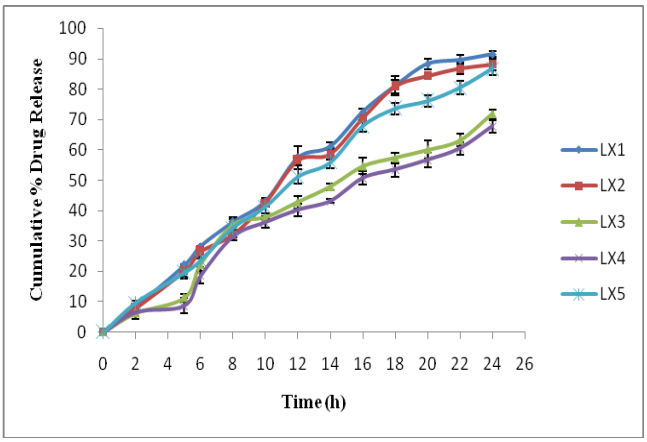

Fig. 5: Dissolution release profile curve for compression coated tablets of aceclofenac in the presence of 4% rat ceacal content

CONCLUSION

The results of the study indicate that aceclofenac tablets compression coated with both LX3 and LX4 (3:2, 2:3 of LB: XG) would be potential formulations in delivering the drug to the colon.

The percent drug released from aceclofenac core tablets coated with coat formulation LX3, LX4 was found to increase from 6 hr onwards indicating the commencement of disruption of the hydrated gum coats. The percent of drug released after 24 hr of testing was 83.3±1.8%, 75.58±2.3% and the tablet coat was found to be broken at one point making way for the release of the drug. The percent drug released from aceclofenac core tablets coated with coat formulation LX4 was found to be 74.04±1.3%.

ACKNOWLEDGMENT

The authors greatly acknowledge Ovation Remedies, HI-Media Laboratories and Mapple Biotech Pvt. Ltd. for providing free gift samples. The authors acknowledge Center for Pharmaceutical

Nanotechnology, NIPER for carrying out DSC of formulated batches. Authors are also thankful to Professor Jagmohan Oberoi for his technical assistance and timely suggestions.

REFERENCES

1. Kinage K, Nandgude T, Bhise K, Deshmukh P. Study and development of colon targeted drug delivery system of locust bean gum and xanthan gum. Int J Green Pharm. 2007; 1(1): 33-36.
2. Macleod GS, Fell JT, Collett JH, Sharma HL, Smith AM. Selective drug delivery to the colon using pectin:chitosan:hydroxypropyl methylcellulose film Coated tablets. Int J Pharm. 199; 187: 251-257.
3. Mutalik S, Naha A, Nayak U, Ranjith AK, Musmade P, Krishan M, Parambil A, et al. Preparation, *in vitro*, preclinical and clinical evaluations of once daily sustained release tablets of aceclofenac. Arch Pharm Res. 2007; 30(2): 222-234.
4. British Pharmacopoeia. The Stationary office, MHRA, British Pharmacopoeial Commission office, Vol. 1, London, (2005).
5. Mutalik S, Krishnan M, Reddy MS, Kushtagi P, Nayak U, Parambil A, Ranjith AK, Udupa N. Chitosan and enteric polymer based once daily sustained release tablets of aceclofenac: *in vitro* and *in vivo* studies. AAPS Pharm Sci Tech. 2008; 9(2): 651-659.
6. Ghosh S, Barik BB. Preparation and evaluation of aceclofenac sustained release formulation and comparison of formulated and marketed product. Int J Medi Medi Sci. 2009; 1(9): 375-382.
7. Chellan VR, Chithambaram M, Joseph AJLJ, Thengungal KR. An *in vitro* and *in vivo* investigation into the suitability of bacterially triggered delivery system for colon targeting. Chem Pharm Bull. 2002; 50(7): 892-895.
8. Venkataraju MP, Gowda DV, Rajesh KS, Shivakumar HG. Xanthan and locust bean gum (from *Ceratonia siliqua*) matrix tablets for oral controlled delivery of propranolol hydrochloride. Asian J Pharm Sci. 2007; 2 (6): 239-248.
9. Santos H, Veiga F, Pina, ME, Sousa, JJ. Compaction, compression and drug release properties of diclofenac sodium and ibuprofen pellets comprising xanthan gum as a sustained release agent. Int J Pharm. 2005; 295: 15-27.
10. Krishnaiah YSR, Bhaskar Reddy PR, Satyanarayana V, Karthikeyan RS. Studies on the development of oral colon targeted drug delivery systems for metronidazole in the treatment of amoebiasis. Int J Pharm. 2002; 236: 43-55.