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Formulation and *in Vitro* Investigation of Polysaccharides Based Drug Delivery Systems for targeting Aceclofenac to the Colon

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ABSTRACT

The present study was aimed to develop aceclofenac compression coated tablets by using locust bean gum and guar gum mixture in the ratio 1:1 along with xanthan gum as coating carrier materials. The core tablet containing 100mg of aceclofeanc were compression coated with a coat weight of 400mg containing gum (LBG:GG) mixture and XG in the ratio 6:1, 5:2, 4:3 and 3:4. The developed coated tablets were evaluated for hardness, friability, weight variation and content uniformity. Drug release studies were carried out in pH 1.2 for 2h, pH 7.4 for 3h and then in pH 6.8 up to 24h with or without rat caecal content to mimic the physiological conditions from the mouth to colon. The formulation released 0 to 4.72 % of drug in first 5 h and released 33.19% to 52.97% of the drug at the end of 24 h in control study. The increase in drug release was observed from all the formulations in presence of 4% rat caecal content indicating susceptibility of gum mixture to the rat caecal content. The in vitro release studies revealed that, gum mixture and HPMC in the ratio 5:2 were found to be suitable for targeting aceclofenac to the colon without being released significantly in upper part of gastrointestinal tract. FTIR studies indicated no drug and excipients interactions.

Keywords: Aceclofenac, colon specific drug delivery systems, locust bean gum, guar gum, xanthan gum and colon targeting.

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INTRODUCTION

Colon specific drug delivery systems (CDDS) were developed to reduce side effects and achieve high local drug concentration at the afflicted site in the colon, hence optimal therapeutic effectiveness and good patient compliance [1-3]**.** It has been proved effective in treating colonic diseases such as inflammatory bowel diseases and colon cancer or improving absorption of protein or polypeptide drugs. A colonic drug delivery system is expected to protect the drug during the transit time in the gastrointestine and to allow its release only in the colon [3]. Conventional oral dosage forms are ineffective in delivering drugs to the colon due to absorption and /or degradation of the active ingredient in the upper part of the gastrointestinal tract [4-5]. Therefore, colon-specific drug delivery systems, which can deliver drugs in an appropriate concentration in the colon without releasing them in the upper part of GI tract, can be expected to decrease the side-effects of the drug and improve the quality of life for the patients suffering from colon-specific diseases.

The various approaches that have been studied for targeting orally administered drugs to the colon include use of pH sensitive polymers**,** time dependent dosage forms and the use of carriers degraded by enzymes produced by colonic bacteria [6-9]. Amongst all these approaches used for colon targeting, a microbially controlled delivery system is the most appealing as it relies on the unique enzymatic ability of the colonic micro flora and enables a more specific targeting independent of pH variation along the GI tract [10-12].

In the present study was aimed to design a novel locust bean gum based compression coated tablet formulations for targeting drugs to the colon and to evaluate its colon site specificity. The developed compression coated tablet formulation, using aceclofenac as the model drug, consisted of two parts, i.e., a fast disintegrating aceclofenac core tablets and outer enzyme controlled compression coating layer of GG:LBG mixture along with XG which could prevents or reduces immature drug release in the upper part of gastro intestinal tract and releases the drug in the colon after oral administration.

MATERIALS AND METHOD

Materials

Aceclofenac was obtained as a generous drug gift sample from Bioforce Pharma, New Mumbai. Locust bean gum was obtained as a gift sample from lucid colloids Pvt. Ltd., Mumbai, India. Guar gum and xanthan gum was purchased from SD fine chemicals, mumbai. Cross linked polyvinyl pyrollidone (Cross PVP) and spray dried lactose was obtained as a gift sample from M/s Arbindo Pharma Ltd., Hyderabad., India. Starch, talc and magnesium stearate used for the preparation of tablets were purchased from commercial source Loba chemicals, Mumbai, India.

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Preparation of aceclofenac compression coated tablets

Table 1 Composition of Fast Disintegrating Aceclofenac Core Tablets

Ingredients	Quantity (mg)
Aceclofenac	100
Spray dried lactose	38
Sodium starch glycollate	7.5
Magnesium Stearate	3.0
Talc	1.5
Total Weight (mg)	150

The fast disintegrating aceclofenac core tablets were prepared by direct compression technique by using the formula as shown in table 1. All the ingredients were thoroughly mixed with mortar and pestle passed through the mesh to ensure complete mixing. The powder quantity weighing 150mg was taken and compressed into tablets using 6mm round; flat and plain punches on a single station tablet punching machine (Cadmach, India). The developed core tablets were compression coated with the different granular coat formulation containing LBG:GG mixture and XG in different ratios as shown in table 2. For compression coating on core tablet, about 50% of coat material was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manually, which was then filled with the remainder 50% of the coat material. The coating material was then compressed around the core tablet by using 10 mm round and plain punches.

Characterization of aceclofenac core and compression coated tablets

The developed aceclofenac core and compression coated tablets were studied for their compressional characteristics like weight variation, hardness, friability and drug content uniformity using reported procedure [13,14]. The hardness tablets were measured using Pfizer tablet hardness tester. Friability was determined on 10 tablets by using Roche friability testing apparatus. For weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance.

Estimation of drug content

To ensure uniformity in drug content both aceclofenac core tablets as well as compression coated tablets were tested for their drug content. The 10 tablets were finely powdered, and quantity of the powder equivalent to 100 mg of aceclofenac was accurately weighed and dissolved in 50 ml of pH 7.4 phosphate buffer contained in 100ml volumetric flask with intermittent shaking to ensure complete solubility of the drug. The solution then made up to 100ml with phosphate buffer pH 7.4 and mixed thoroughly. The solution were filtered, suitably diluted and drug content was estimated by UV spectrophotometer at 276nm (Shimadzu, Japan).

In vitro drug release studies

The ability of the prepared compression-coated tablet formulation to prevent or to remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by in vitro drug release in USP XXIII dissolution rate test apparatus (apparatus type 1,100rpm, 37±0.5ºC) for 2 h in pH 1.2 (900ml), as the average gastric emptying time is 2h, then the dissolution media is replaced with pH 7.4 phosphate buffer (900ml) and dissolution was continued for another 3 h as the usual small intestine transit time is 3-5 h and dissolution were continued in phosphate buffer pH 6.8 until completion of 24 h as the usual colon transit time is 20-30h. At the end of the time periods 5 ml sample were taken, suitably diluted and analyzed for percentage of drug release by UV spectrophotometer at the λ_{max} value of 276 nm (Shimadzu, Japan).

In vitro drug release studies in rat caecal colonic fluid

The in vitro drug release studies simulating in rat caecal colonic fluid were carried out in USP dissolution rate test apparatus (Apparatus 1 (basket type), 100rpm, 37^0C) with slight modifications as reported by Krishnaih and et al (10). A beaker (capacity 200ml, internal diameter) containing 150 ml of 4% rat cecal content medium in the phosphate buffer pH 6.8 immersed in water maintained in 1000 ml vessel, which in turn, was in the water bath of the apparatus. The swollen formulation after completing the dissolution studies in 0.1M HCl (2 hr) and phosphate buffer pH 7.4 (3 hr) were placed in the basket of the apparatus and immersed in the rat cecal content medium contained in 200 ml beaker and dissolution studies continued until completion of 24 h. As the cecum is naturally anaerobic, the experiment was carried out with continuous supply of carbondioxide into the beaker. At the end of the time periods 5ml samples were withdrawn, suitably diluted, centrifuged to remove debris and analyzed for percentage of drug release by UV spectrophotometer at the λ_{max} value of 276 nm.

Fourier Transform infrared (FTIR) spectral studies

FTIR spectroscopic data was taken to confirm the chemical stability of the aceclofenac in the core and compression coated tablets. FTIR spectra of the neat drug aceclofenac, optimized batch aceclofenac compression coated tablet formulation LGX52 (before storage and after storage) and placebo tablet formulation were obtained. The FTIR spectra scanning was acquired in the range of 400-4000 cm^{-1} with a resolution of $1cm^{-1}$ using KBr pellet method by spectrophotometer (Shimadzu, FTIR 8400S, Japan).

RESULTS AND DISCUSSION

Dissolution of fast disintegrating aceclofenac core tablets

The outer compression coat of LBG:GG mixture and XG combination functions as a controlling mechanism of aceclofenac release from compression coated tablets, therefore the aceclofenac core tablets were prepared with required fast disintegration and dissolution characteristics. Tested in USP disintegration tester (Elico, India), the core tablets were found to

disintegrate within 1min showing required fast disintegration characteristics. Because core tablets contains a super disintegrant cross PVP and water soluble directly compressible diluent spray dried lactose which might have contributed for such a fast disintegration of core tablets, over 99% of drug dissoluted in pH 1.2 buffer within 30min. The fast disintegrating and dissolution of the core tablet prevent it from being the rate limiting factor for release of aceclofenac from compression coated tablets formulation soon after degradation of locust bean gum present in the coat.

Physical characterization of Aceclofenac core and compression coated tablets

Table 2. Composition of coat formulations for aceclofenac core tablets.

Ingredients	Quantity (mg) present in coat formulations			
	LGX61	LGX52	LGX43	LGX34
Locust bean gum	150	125	100	75
Guar gum	150	125	100	75
Xanthan gum	50	100	150	200
Starch Paste	40	40	40	40
Talc	5	5	5	5
Magnesium Stearate	5	5	5	5
Core : Coat ratio	1 : 4	1 : 4	1 : 4	1 : 4
LBG-GG Mixture : HPMC ratio	6 : 1	5 : 2	4 : 3	3 : 4
Coat Weight (mg)	**400**	**400**	**400**	**400**

The compressional force was adjusted to give a core tablets with approximately 3.54 ± 0.28 kg/cm^2 hardness. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of 150mg is ± 10%. Average weight of the core tablet was 150mg the average percentage deviation of core tablet was found to be 2.97 ± 1.41 which is with in the official limit. The core tablet formulations passed the test for friability (0.657%) and core tablets showed 102.54 ± 0.68 % of labeled amount of drug indicating uniformity of drug content in the aceclofenac core tablets (Table 3).

Table 3. Physical characteristics of aceclofenac core and compression coated tablets

Formulations Code	Hardness (Kg/cm^2 ± SD)	Friability (%)	Drug Content (% ± SD)	Weight Variation (% ± SD)
Core tablet	3.54 ± 0.28	0.657	102.54 ± 0.68	2.97 ± 1.41
LGX61	5.45 ± 0.51	0. 324	98.24 ± 1.55	1.27 ± 3.10
LGX52	5.58 ± 0.24	0.417	98.18 ± 0.94	0.68 ± 2.59
LGX43	5.18 ± 0.51	0.384	97.72 ± 0.97	1.35 ± 4.05
LGX34	5.76 ± 0.47	0.392	97.76 ± 0.71	1.57 ± 4.49

The aceclofenac core tablets compressions coated with different coat formulartion containing LBG:GG mixture in the ratio 1:1 along with XG in different ratios as shown in table 2 and were evaluated for various quality control tests. All the coated tablet formulation showed a hardness value in the range of 5.18 ± 0.51 to 5.76 ± 0.47 kg/cm^2 indicating tablets are of

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adequate strength. In a weight variation test, the average percentage deviation of all batches of the tablets was found to be in the range of 1.27 ± 3.10 to 2.68 ± 2.59 % which is within the pharmacopoeial limit; hence all the compression coated tablets passed the test for uniformity of weight as per official requirements. The percent drug content was found to be in the range of 97.72 ± 0.97 % to 98.24 ± 1.55 %. In the present study, the percentage friability of all the batches formulation was in the range of 0.159 to 0.443 %, indicating tablets are of sufficient strength to withstand the stress of transportation and handling. All the aceclofenac compression coated tablets complied with the in-house specification for weight variation, drug content, hardness and friability as shown in Table 3.

FTIR Studies

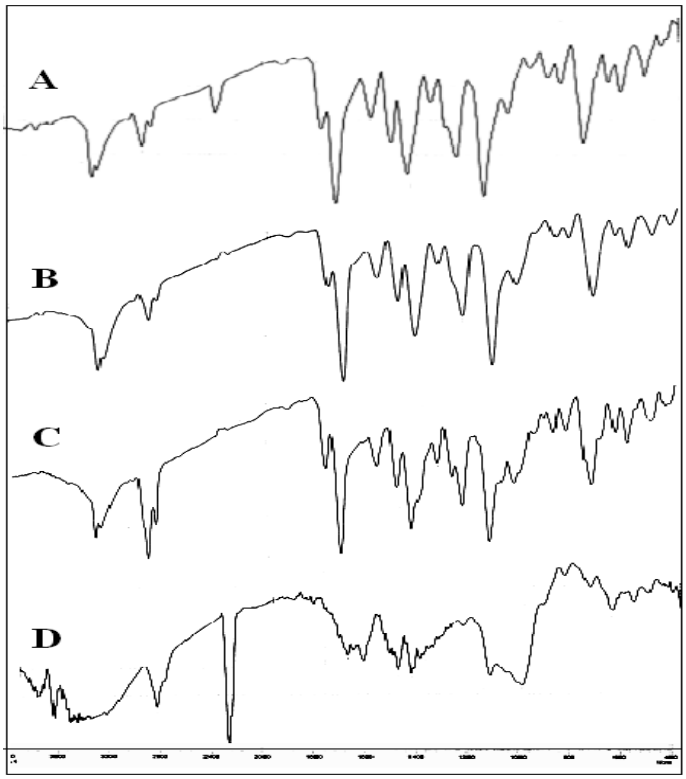

Figure1: FTIR spectra of aceclofwenac (A), core formulation (B), coated tablet formulation LGX52 (C) and placebo formulation LGX52 (D).

The FTIR spectra of pure drug aceclofenac (A), core formulation (B), compression coated tablet formulation LX52 (C) and placebo formulation LX52 (D) are shown in Fig. (1). In FTIR spectra of aceclofenac, bands at 3386 cm^{-1} due to N-H stretching frequency of secondary amine. The absorption bands at 3311 cm^{-1} and 2923cm^{-1} resulted from N-N stretching and C-H stretching of CH_2 group, respectively. The bands at 1716cm^{-1} is due to C=O stretching and C=C stretching was observed at 1579, 1500, and 1438cm^{-1}. The C-Cl stretching vibration observed at 750 cm^{-1}. In case of aceclofenac core and compression coated tablets of LX52 formulation, all the bands that are observed in aceclofenac have again appeared, indicating the absence of

chemical interaction between aceclofenac and LBG or other tablet ingredients in the core as well as compression coated tablets.

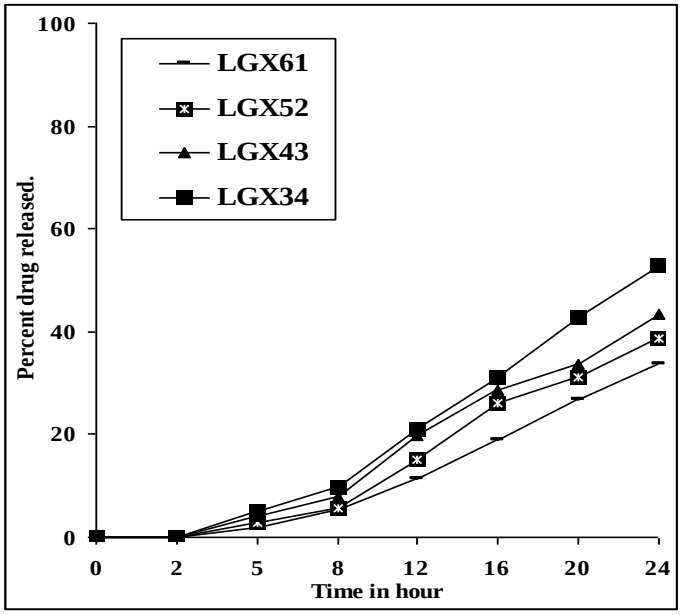

Figure 2: In vitro release profile of aceclofenac from compression coated tablet formulation without rat caecal medium (n=3).

In vitro drug release studies

The ability of aceclofenac compression coated tablets to remain intact in the physiological environment of stomach and small intestine was assessed by conducting in vitro drug release studies in 0.1N HCL for 2h and in phosphate buffer pH 7.4 for 3h and continued for another 19 h in phosphate buffer pH 6.8 with and without rat caecal content in dissolution medium to assess the ability of the compression coated tablets to release drug in the physiological environment of colon target area.

The percent drug released from the formulations LGX61 LGX52 LGX43 and LGX34 was found to be 5.18%, 1.22%, 1.12% and 0%, respectively, in the initial 5 h of dissolution study in simulated gastric (2h) and intestinal fluids (3h). Thus, it is evident from the data that the LBG:GG mixture along with XG as compression coat has the potential to control the premature drug release in physiological environment of stomach and small intestine. The drug release in first 5h decreases as the proportion of XG content in the coat increases. To assess the integrity of coat, the drug release studies were continued up to 24 h without the addition of rat caecal contents to dissolution medium. At the end of 24 h of dissolution studies, the mean percent drug released from LGX61 LGX52 LGX43 and LGX34 was 52.95%, 43.25%, 38.56%, and 33.19% respectively, as shown in fig. (1). All the formulations were found to be highly swollen but remained intact at the end of 24 h. The drug release was found to be incomplete from all the formulations in the physiological environment of colon target area. This indicates that the biodegradable polysaccharide materials LBG and GG mixture present in the coat is not

degraded and until the coat is degraded, the gums content present in the coat will not permit the release of the remaining drug present in the core in to the dissolution medium.

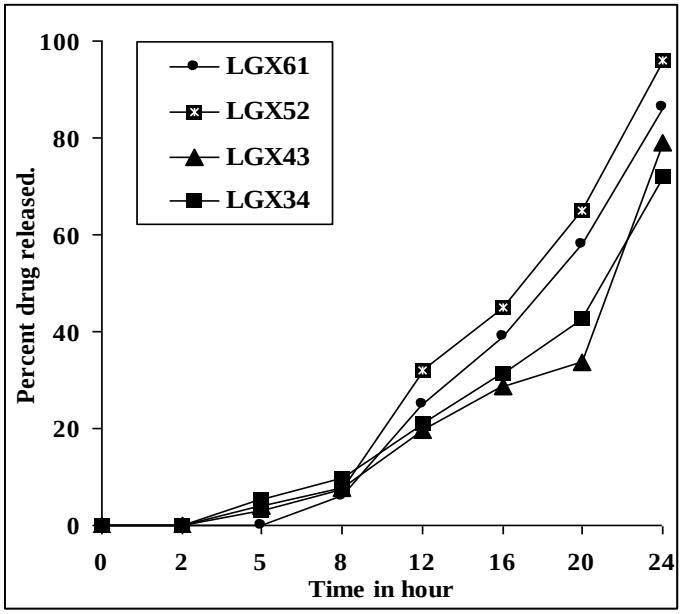

Figure 3: In vitro release profile of aceclofenac from compression coated tablet formulation in 4% w/v rat caecal medium (n=3).

The colon specific drug delivery systems should not only retard the drug release in the stomach and small intestine, but they also should give majority of drug release in the target area. Hence to assess the ability of the coat to release the drug in physiological environment of colon, the in vitro drug release studies were carried out in pH 6.8 phosphate buffer saline solution containing rat caecal contents. When the dissolution studies were carried out in the presence of 4% w/v of rat ceacal content medium, the mean percent drug released from coat formulation LGX61 and LGX52 was found to be 86.27% and 96.13%, respectively at the end of 24 h as shown in fig 2. The drug release was found to be increased from the coat formulation LX61 and LX52 indicating degradation of the LBG content present in the coat by the rat caecal enzymes. The coat formulation LGX43 and LGX34 released 79.65% and 72.45% of the drug at the end of 24h. It is evident from the data that the release was found to incomplete from the coat formulation LGX43 and LGX34. The study shows that as the proportion of XG content increases in the coat formulations LGX43 and LGX34 the drug release was decreased significantly in the physiological environment of colon. This might be due to high proportion of XG content in the coat shell which might have formed a highly viscous gel layer along with LBG:GG mixture around the core tablet which reduced the penetration of dissolution fluid in to the core tablet there by reducing drug release from the formulation in to dissolution medium.

CONCLUSION

In conclusion, the required fast disintegrating and dissoluting aceclofenac core tablets compression coated with LBG:GG mixture and XG in the ratio 5:2 found to be suitable for

targeting aceclofenac to the colon, which released only 1.12% of drug in the physiological environment of stomach and small intestine and released more then 96.13% of the drug in the physiological environment of colon. Further, FTIR studies indicated no drug and excipients interaction.

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REFERENCES

[1] Friend DR. Adv Drug Deliv Rev 1991; 7:149-199.
[2] Friend DR. Adv Drug Deliv Rev 2005; 57: 247-265.
[3] Lee VHL, Mukherje SK. Encyclopedia of pharmaceutical technology. Marcel Dekker: New York, 2002, 871-885.
[4] Valluri R, Siddaramaiah Pramod K. J Mater Sci Mater Med 2008; 19: 2131-2136.
[5] Mayur MP, Tejal JS, Avani FA. Pharm Dev Technol 2009**;** 14: 62-69.
[6] Sinha VR, Mittal BR, Bhuttani KK, Rachna K. Int J Pharm 2004; 269: 101-108.
[7] Ashford M, Fell J, Atwood D, Woodhead, P. Int. J Pharm 1993; 91: 241-245.
[8] Khan MZI, Prebeg Z, Kurjakovic N. J Control Release 1999; 58:215-222.
[9] Davis SS, Hardy JG, Fara JW. Gut 1986; 27: 886-892.
[10] Krishniah YSR, Satyanarayan S, Rama Prasad YV, Narasimha RS. Int J Pharm 1998: 171: 137-146.
[11] Potts JE, Clendigs RA, Ackard WB, Wigisch WD. In Guillet, J. (Ed), Polymer science and technology, Plenum Press, New York, 1973, 61-79.
[12] Huang SI, Bansleben DA, Knox JR. J Appl Polym Sci 1979; 23:429-437.
[13] Banker GS, Anderson LR. The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, India, 1987; 293-345.
[14] Government of India Ministry of health and family welfare. The Pharmacopoeia of India. Controller of Publications, Delhi, 2007.