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Original Article

STUDIES ON DEVELOPMENT OF ORAL COLON TARGETED DRUG DELIVERY SYSTEM OF LOCUST BEAN AND XANTHAN GUMS

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Abstract

Colon drug delivery system of Aceclofenac was attempted using locust bean and xanthan gum. The influence of buffer pH and drug/polymer ratio on the drug release was studied. Dissolution studies were performed in HCl buffer pH1.2, Phosphate buffer pH 7.4 and Phosphate buffer pH 6.8. The results were then compared by pretreatment of all formulations with HCl buffer pH1.2 for 2 hours followed by next 3 hours in Phosphate buffer pH 7.4 and then in 100 ml Phosphate buffer pH 6.8 that contained 4% w/v rat caecal contents for further 19 hours. The rapid release of drug was seen from formulation having 100% locust bean gum. Whereas, it was relatively slow for matrices containing optimum concentration of xanthan gum and locust bean gum. Thus it can be concluded that locust bean and xanthan gums have good potential to act as carrier for developing Colon drug delivery system.

Key words: Colon specific drug delivery, *Locust bean gum*, *Xanthan gum*, aceclofenac.

INTRODUCTION

Oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery (Chourasia M. K., 2003). Colon targeting is advantageous in treating diseases of colon (irritable bowel syndrome, inflammatory bowel disease, including Chron's disease and ulcerative colitis), oral delivery of proteins and peptides where a delay in systemic absorption is therapeutically desirable (nocturnal asthma, arthritis, angina) (Yang L., 2002).

Aceclofenac is a non-steroidal anti-inflammatory drug that acts especially on inflammatory sites and there by decreases the inflammation. The various strategies for targeting orally administered drug to the colon include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bio-adhesive systems and osmotic controlled drug delivery systems. Due to the poor site specificity of pH dependent systems because of large variation in the pH of the gastrointestinal tract and also the poor site specificity of the timed release dosage form because of large variation in gastric emptying time made the exploitation of the bacterial enzyme localized in the G. I. tract as one of the better approach for colon drug delivery system. Several studies were undergone on the basis of the activity of colonic bacteria on polysaccharide based carrier system. The different polysaccharides that are used under evaluation as carriers for colonic drug delivery includes pectin and its salts (Sarasija S., 2000, Ashford M., 1993), chondroitin sulphate (Ramaprasad Y. V., 1996), amylose (Friend D. R., 2001), inulin HP (Krishnaiah Y. S. R. *et al*, 2003), guar gum (Krishnaiah Y. S. R. *et al*, 2002), locust bean gum (Raghavan C. V., 2002), chitosan (Tozaki H., *et al*, 1997).

The Locust bean gum is neutral polysaccharides having a molecular weight of 3,10,000 derived from the endosperm of the seed of the *Ceratonia siliqua linn* (Fam: Legminosae). The *Locust bean* contains about 88% D-galacto-D-mannoglycan, 4% of pentan, 6% of protein, 1% of cellulose and 1% of ash. *Xanthan gum* is high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone ß-D-glucose residues) and a trisaccharide side chain of ß-D-mannose-ß ß-D-glucuronic acid-∝-D-mannose attached with alternate glucose residues of he main chain (Wilding I. R., 2001).

The objective of present study was to develop colon drug delivery system containing natural gums that retard drug release in upper GIT, but are degraded by microbial flora in colon.

MATERIALS AND METHODS

Aceclofenac was obtained as a gift sample from Aarti Drugs Ltd., Mumbai. *Locust bean gum*, *Xanthan gum*, Microcrystalline Cellulose, Magnesium Stearate, Talc, Sodium Starch Glycollate, Methanol purchased from Loba Chemie, Mumbai. Healthy male albino rats supplied by National Institute of Toxicology, Pune, India, weighing 150-200 gm.

Preparation Of Core Tablet and Compression Coated Tablets

All the ingredients were weighed accurately and were mixed. The mixture equivalent to 100 mg of aceclofenac (i.e. 125 mg) was weighed and then compressed by eight stations Tablet punching machine (Tablet punching machine, Karnavati minipress D-II link) using 8 mm flat punches, optimizing the hardness and die cavity of the machine. Table 2 exhibits formulation of core tablets.

Compression Coating of Core Tablet

All the ingredients of each coat formulation were weighed accurately and were mixed. 40% weight of Coating mixture then kept in die cavity of eight stations Tablet punching machine (Tablet punching machine, Karnavati minipress D-II link). using 11 mm flat punches, the core tablet was placed on it at center, remaining 60% of coating mixture was added to the die cavity and tablets were compressed with maximum hardness of, Table 3 exhibits formulation of compression coated tablets.

***In Vitro* drug release studies (Krishnaiah Y. S. R., *et al*,**

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2002)

The compression-coated tablets of Aceclofenac of each formulation were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. These studies were carried out using a USP XXIII dissolution rate test Type 1 (Electrolab Dissolution test apparatus Model TDT-082) at 100 rpm at 37°C. The tablets were tested for drug release for 2 hr in 900 ml of 0.1 N HCl. The dissolution medium was replaced with 900 ml pH 7.4-phosphate buffer and tested for drug release for next 3 hours. 5 ml samples were withdrawn at the prescribed time intervals, suitably diluted and analyzed for *Aceclofenac* content at wavelength of 275 mm using a double beam UV/VIS Spectrophotometer (JASCO V 530).

The susceptibility of locust bean gum coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 ml of pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents. The experiment was carried out under the approval of local ethics committee according to the CPSCEA as accepted principles for the use of experimental animals. The caecal contents were obtained from healthy male albino rats after pre-treatment for 7 days with locust bean dispersion. Earlier studies have shown that the presence of 4% w/v rat caecal contents in pH 6.8 obtained after 7 days of pre-treatment of rats with 1 ml of 2% w/v aqueous dispersion of guar gum provide the best condition for in vitro evaluation of guar gum (Rama Prasad Y. V., 1998). Five rats were killed by spinal traction 30 min before the commencement of drug release studies. The abdomen were opened, the caecal were isolated, ligated at both ends, dissected and immediately transferred into Phosphate buffer pH 6.8 that was previously bubbled with Co_2. The caecal bags were opened; their contents were individually weighed, Pooled and then suspended in Phosphate buffer to give a final caecal dilution of 4% w/v. As the caecum is naturally anaerobic, all these operations were carried out under continuous supply of Co_2.

The drug release studies were carried out in USP XXIII dissolution rate test Type 1 apparatus at 100 rpm at 37°C with slight modification. A beaker (capacity 150 ml, internal diameter 55 mm) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which was, in turn, in the water bath of the apparatus. The dissolution basket each containing one tablet were then immersed in the dissolution media to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes. 5 ml of sample was pipetted out after time interval, centrifuged and the supernatant was filtered through a bacteria-proof filter and the filtrate was analyzed for *Aceclofenac* content at 275 mm as described above. The above study was carried out on all the *Aceclofenac* tablets coated with different coat formulation LX1, LX2, LX3, LX4 with and without caecal matter in pH 6.8 Phosphate buffer (control).

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for *Aceclofenac* using *Locust bean* 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 (Anti cancer drugs in the treatment of colon cancer). The drug delivery system targeted to colon should remain intact in stomach and small intestine, but should release the drug in colon.

TABLE1: CORE TABLET FORMULATION

Sr. no	Ingredients	Core tablet
1	Aceclofenac	100
2	Microcrystalline Cellulose	20
3	Sodium starch glycholate	3
4	Magnesium stearate	0.5
5	Talc	1.5
6	Total weight	125

TABLE 2: COMPRESSION COATED MIXTURE FORMULATION

Sr. no	Ingredients	LX1	LX2	LX3	LX4
1	*Locust bean gum*	250	200	150	100
2	*Xanthan gum*	0	50	100	150
3	Microcrystalline Cellulose	45	45	45	45
4	Magnesium Stearate	3	3	3	3
5	Talc	2	2	2	2
6	Total weight	300	300	300	300

Fast-disintegrating aceclofenac were prepared by incorporating super disintegrant such as sodium starch glycollate. The hardness of the core tablets of *Aceclofenac* was found in the range of 2.4-3.1 kg. The core tablets of *Aceclofenac* were also found to comply with the friability test since the weight loss was found less than 0.57 %. The core tablets were found to disintegrate within 30 sec showing the required fast disintegration characteristics. The combined action of the super disintegrant (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.

The core tablets of *Aceclofenac* were compression coated with a coat formulation that contained various quantities of locust bean and *Xanthan gums*. The cumulative amount of *Aceclofenac* released from LX1, LX2, LX3 and LX4 (1:0, 4:1, 3:2, 2:3 of LB:XG) was 22.09, 16.95, 11.32 and 9.9% respectively after 5 hr of the dissolution study in simulated gastric and intestinal fluids. Thus, *Locust bean gum* and *Xanthan gum* in the form of a compression coat, has potential in protecting 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 to pH 6.8-phosphate buffer. At the end of the 24 hr of the dissolution study, LX1, LX2, LX3 and LX4 were found intact and the cumulative mean percent drug released was 51.27±0.8, 45.78±0.5, 35.27±1.1 and 28.49±1.0, respectively. This indicates that until the coat is degraded, the gum will not permit the release of the bulk of the drug present in the core.

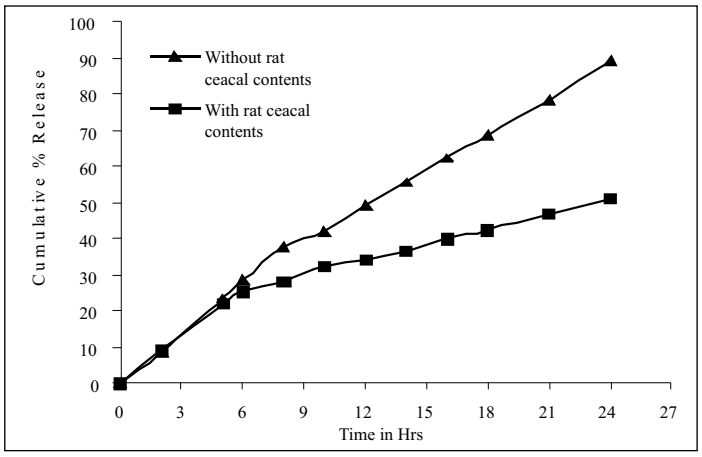

***Figure 1**: Cumulative Mean % Release of Aceclofenac from compression-coated LX1 in dissolution study with and without rat caecal contents*

The drug delivery systems targeted to the colon should not only protect the drug from being released in the physiological environment of stomach and small intestine, but also have 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 guar gum to colonic bacterial degradation[15]. Hence, in vitro drug release studies were carried out in pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents.

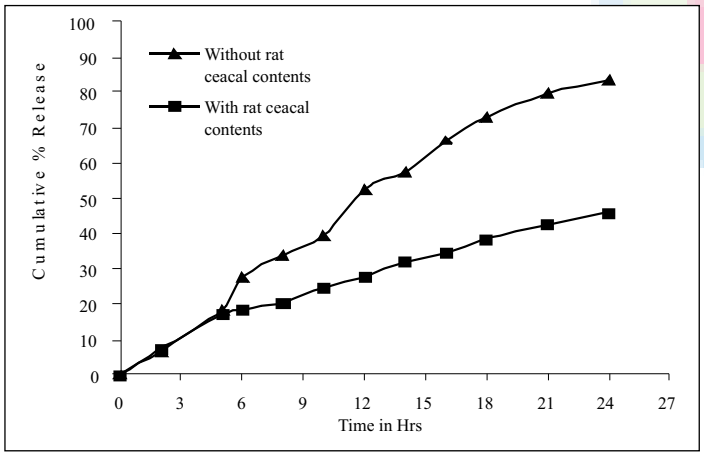

***Figure 2:** Cumulative Mean % Release of Aceclofenac from compression-coated LX2 in dissolution study with and without rat caecal contents*

When the *in vitro* dissolution 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 only 89.5±2.1 and the coat remained intact.

The percent drug released from aceclofenac core tablets coated with coat formulation LX2, LX3 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%.

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 (50 mg) was lesser compared to coat formulations LX3 (100 mg) and LX4 (150 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*. The results show 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.

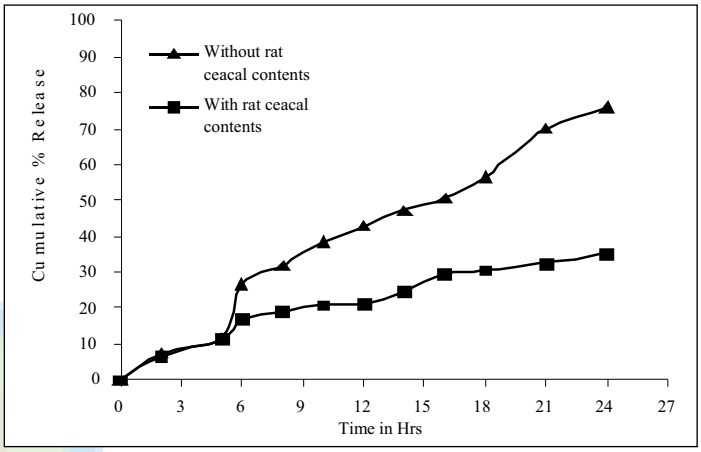

***Figure 3:** Cumulative mean % Release of Aceclofenac from compression-coated LX3 in dissolution study with and without rat caecal contents*

The compression coated formulation LX2 was completely degraded in simulated colonic fluids whereas LX3 and LX4 formulation partially degraded in simulated colonic fluids.

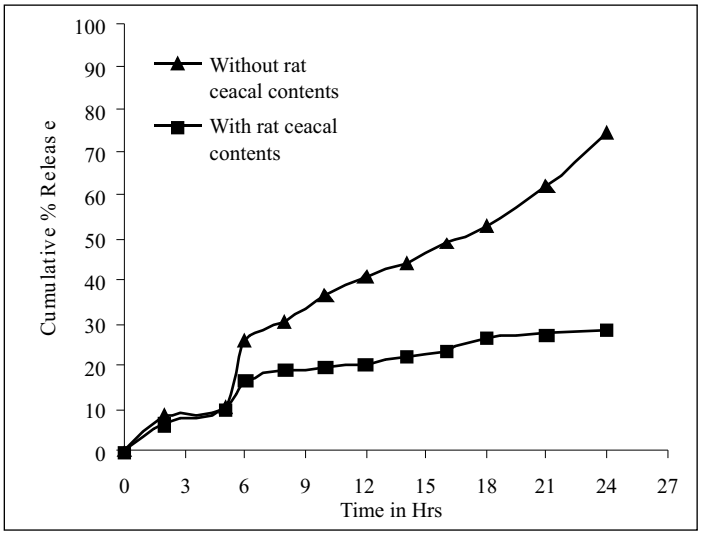

***Figure 4**: Cumulative mean % Release of Aceclofenac from compression-coated Lx1 in dissolution study with and without rat caecal contents*

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.

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