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Natural polysaccharides based compression coated tablets for colon targeted delivery of naproxen for the treatment of colitis

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ABSTRACT

The present work is aimed to develop colon targeted compression-coated matrix tablets of naproxen using guar gum (GG) and xanthan gums (XG) as coating materials. It was found that the compression-coated tablets released 0 to 7.82% of drug in the physiological environment of stomach and small intestine and 66.40% to 97.82% of drug was released in simulated colonic fluid. The DSC and FTIR studies indicated that the drug is intact in the formulations and no possibility of interaction between the naproxen and other formulation excipients was observed. The formulation showed no change in physical appearance, physical parameters, drug content and in vitro release pattern after storage at 40 ^{o}C/75% RH for 3 months. The presence of XG in the coat retarded the release of the drug in first 5 h, but in alkaline pH, enhancement in drug release rate was observed due to swelling of xanthan gum and increased susceptibility of guar gum with time resulting in a loose porous gel structure, leading to faster drug release of more then 95% in the colonic area.

Keywords: Colon targeting, guar gm, xanthan gum, naproxen, compression coating.

INTRODUCTION

Naproxen is a potent commercially available NSAID that is used to treat rheumatoid arthritis, osteoarthritis and colitis (1) (Espinar *et al.*, 1991). There have been some trials to deliver naproxen to the lower intestine and upper colon to treat intestinal diseases such as colitis and chron's diseases (2,3,4) (Larsen *et al.*, 1989; Rao *et al.*, 2003; Rodriguez, 1997). However, delivery of naproxen was limited because of its undesirable gastrointestinal toxicity such as gastrointestinal intolerance and ulceration when given orally. A formulation of naproxen with negligible to no drug release in upper part of gastrointestinal tract and controlled release in colonic region would achieve therapeutically effective concentration of drug locally in colon. At the same time, such formulations would minimize systemic or upper GI tract related side effects of naproxen (5) (Rubinstein, 2005).

Colon targeted drug delivery systems 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 (6,7) (Friend, 1991; Friend, 2005). 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 (8,9) (Krishniah *et al.,* 2002; Ashford *et al.,* 1993). A colonic drug delivery system is expected to protect the drug during the transit time in the gastro-intestine and to allow its release only in the colon. The various approaches that have been studied for targeting orally administered drugs to the colon include use of pH-sensitive polymers (10,11) (Khan *et al.,* 1999; Davis *et al.,* 1986), time-dependent dosage forms (12,13) (Van den Mooter *et al.,* 1995; Sinha *et al.,* 2002) and the use of carriers degraded by enzymes produced by colonic bacteria (14) (Krishniah *et al.,* 1998). Of these approaches, the use of materials that are degraded by the colonic microflora has been found to be the most promising because of their site specificity (14,15) (Krishniah *et al.,* 1998; Huang *et al.,* 1979). These polymers shield the drug from the environment of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organisms or degradation by enzymes (16) (Mathews, 1999). Among the strategies, compression coated systems seem to be superior in preventing premature drug release in stomach and small intestine. On the other hand, the compression coated systems, usually in tablet form, is convenient to manufacture, and no special coating solvents or coating equipments are needed for coating process (9) (Ashford *et al.,* 1993).

In the present work, core tablets were compression-coated with a mixture of guar gum and xanthan gum for colon specific delivery of naproxen. The Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) was used analyze the drug-polymer interactions. The effect of ratio of GG and XG on drug release in upper part of gastrointestinal tract and colon was investigated

MATERIALS AND METHODS

Naproxen obtained as a gift sample from Divi's Laboratories Pharma Ltd. (Hyderabad, India). Guar gum and xanthan gums were purchased from Loba Chemicals, (Mumbai, India). Crosslinked poly(vinyl pyrrolidone) (Cross PVP) and spray dried lactose was obtained as a gift samples from M/s Arbindo Pharma Ltd. (Hyderabad, India). Lactose, Sodium lauryl sulphate, Talc and Magnesium stearates were purchased from Loba Chemicals (Mumbai, India)

Evaluation of powder materials and Granules

Before compression, the powder material for core tablets and granular materials were evaluated for their physical parameters. Angle of repose was determined by funnel method, bulk density and tapped density were determined by cylindrical method and Carr's index was calculated.

Preparation of naproxen core tablets

The core tablets (average weight 180 mg) were prepared by direct compression technique. A weighed quantity of drug, cross PVP, sodium lauryl sulphate, lactose, talc and magnesium stearates were thoroughly mixed with mortar and pestle and passed through the mesh (# 250) to ensure complete mixing. The powder weighing 180 mg was taken and compressed into tablets using 8 mm round, flat and plain punches on a single station tablet punching machine (Cadmach, India). The composition of core tablets is given in Table 1.

Table 1. Composition of core tablets

Ingredients	Quantity (mg)
Naproxen	150
Cross PVP	09
Sodium lauryl sulphate	09
Spray dried Lactose	7.5
Talc	2.7
Magnesium stearate	1.8

Preparation of compression-coated tablets

The formulated core tablets were compression-coated with the different granular coatings of GG and XG in different ratios with a coat weight of 400 mg. For compression coating, about 45% (180 mg) of granular material was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manualy, which was then filled with the remaining 55% (220 mg) of granular material. The coating material was then compressed around the core tablet by using 12 mm round, flat and plain punches. The composition of compression-coat granular material is shown in Table 2.

Table 2. Composition of compression coatings

Ingredients	Quantity (mg)					
	XG1	GG2	GX3	GX4	GX5	GX6
Guar gum	350	--	300	250	200	150
Xanthan gum	--	350	50	100	150	200
Starch	40	40	40	40	40	40
Talc	6	6	6	6	6	6
Magnesium Stearate	4	4	4	4	4	4

Evaluation of core and compression coated tablets

The prepared core and compression-coated tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity using reported procedure. For estimating weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance (Elico, Mumbai, India). The thickness of the tablet was measured by using a micrometer screw gauge. The hardness of five tablets was measured using Monsanto hardness tester. Friability was determined on 10 tablets using Roche friability testing apparatus for 4 min at 25 rpm.

Estimation of drug content

The core and compression-coated tablets were tested for their drug content. The 10 tablets were finely powdered and quantity of the powder equivalent to 180 mg of naproxen was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of Phosphate buffer pH 7.4 and allowed to stand for 10 h with intermittent shaking. The solution was made up to 100 ml with phosphate buffer pH 7.4. The solutions were filtered and drug content was estimated using UV-spectrophotometer (Shimadzu, Japan) at 331 nm.

Fourier Transform Infrared spectroscopic studies

The FTIR study was carried out for naproxen, physical mixture of core tablet and the tablet formulation GX6. The FTIR spectrum was acquired in the range of 400-4000 cm^{-1}.

Differential scanning calorimetric analysis

The possibility of interaction between naproxen and polymers was assessed by carrying out thermal analysis on pure drug, guar gum, xanthan gum and powdered sample of tablet GX6. The DSC thermograms were obtained at a scanning rate of 10 ^{o}C/min over a temperature range of 30-300 ^{o}C.

In vitro drug release in gastric and intestinal fluid

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 using dissolution tester (100 rpm, 37±0.5ºC) for 2 h in pH 1.2, followed by dissolution in phosphate buffer pH 7.4. At different time intervals, 5 ml sample were taken and analyzed for drug release using UV spectrophotometer at 331 nm.

In vitro drug release in rat caecal content fluid

The in vitro drug release studies were carried out using dissolution tester (100 rpm, 37 ^{o}C) with slight modifications. A beaker containing 150 ml of 4% rat cecal content medium was immersed in the water maintained in dissolution vessel. The swollen formulation after completing the dissolution in 0.1M HCl (2 h) and phosphate buffer pH 7.4 (3 h) were placed in the basket and immersed in the rat cecal content medium. As the cecum is naturally anaerobic, the experiment was carried out with continuous supply of carbon dioxide. At different time intervals, 2 ml sample was taken and analyzed for drug content using UV-spectrophotometer at 331 nm.

Stability studies

To assess the long-term stability of the prepared formulations, the optimized GX5 tablets were stored at 40 ^{o}C /75 RH for three months and were observed for any physical change and dug contents. At the end of the three months, tablets were also subjected to drug release studies. The initial (zero time) results were compared with post-stability testing period results.

RESULTS AND DISCUSSION

The value of angle of repose of powder blend was 32.67 indicating reasonable flowability (Table 3). The values of angle of repose for all the coat formulations were in the range of 25 to 30, indicating good flowability. Carr's index for core tablet powder blend was 19.2 indicating fair flowability and all the coat formulations were in the range of 4.0 to 11.5, indicating excellent flow property.

Table 3. Pre-compression properties of core powder and compression coat granular formulation.

Formulation Code	Angle of Repose (θ)	Bulk Density		Carr's Index (%)
		Un-tapped	Tapped	
Core	32.67^{o}	0.3846	0.4761	19.218
XG1	31.82^{o}	0.4000	0.4347	7.982
GG2	32.34^{o}	0.3846	0.4347	11.525
GX3	29.53^{o}	0.4545	0.4761	4.536
GX4	28.77^{o}	0.4166	0.4347	4.163
GX5	28.77^{o}	0.4545	0.4761	4.536
GX6	29.35^{o}	0.4081	0.4255	4.089

Evaluation of core tablets

The core tablets were prepared by direct compression technique using crosslinked PVP and sodium lauryl sulphate to aid fast disintegration of the core tablet and water soluble spray dried lactose as a direct compression aid. Average weight of the core tablet was fixed at the lowest possible level (180 mg) to accommodate maximum amount of coat material over the core tablet and the average percentage deviation of core tablet was within the official limit. The core tablets were found to disintegrate within 2 min showing required fast disintegration characteristics. The core tablet formulations passed the test for friability with 0.71 % and they showed 99.5 % of labeled amount of drug, indicating uniformity of drug content (Table 4).

Table 4. Evaluation of core and compression coated tablets

Formulations	Tablet Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
Core Tablet	181	2.80	0.71	99.51
XG1	583	5.92	0.15	94.66
GG2	582	4.96	0.67	97.09
GX3	587	5.23	0.48	98.54
GX4	581	5.30	0.41	99.51
GX5	583	5.54	0.34	99.02
GX6	585	5.81	0.32	97.57

Evaluation of compression-coated tablets

The compression-coated tablets were subjected to various evaluation tests, such as uniformity of weight, drug content, hardness, friability and in vitro dissolution. All the formulation showed uniform thickness, weight, drug content (94.66 % to 99.51 %), hardness (4.96 to 5.92 kg/cm^2). Hardness of the tablets increases as the proportion of xanthan gum in the coat formulation increases. The percentage friability of all the batches was below 1%, indicating that the friability is within the limits (Table 4).

FTIR Studies

The FTIR spectra of naproxen (A), drug free GX5 tablets (B), core tablet (C) and compression-coated tablet GX5 (D) is shown in Figure 1. From the spectra, it is clear that the characteristic peaks at 3190 (-OH stretching), 2933 (-CH stretching of CH_3 groups), 1724 (C=O stretching), 1461 and 1368 (C=C stretching) and 1024 (C=O stretching) are seen in the spectra of naproxen. Whereas in spectra of core tablet and compression-coated tablet GX5, the same peaks of naproxen were appeared with slight modifications indicating no chemical interaction between naproxen and polymers.

DSC analysis

The typical DSC thermograms of naproxen (A), guar gum (B), xanthan gum (C), drug free GX5 tablets (D) and drug loaded GX5 tablets (E) are shown in Figure 2. A sharp endothermic peak corresponding to melting point of naproxen was found at 157.5 ^oC, the endothermic peaks at 108, 112 and ^oC are related to guar gum, xanthan gum and drug free GX5 tablets, whereas, the drug loaded formulation GX7 has shown a drug endothermic at 155 ^oC. This slight shift in endothermic peak may be attributed to bound water present in the polymers. The results of the DSC study indicate that the drug is intact in the formulations.

Fig 1. FTIR spectra of naproxen (A), drug free GX5 tablets (B), core tablet (C) and compression-coated tablet GX5

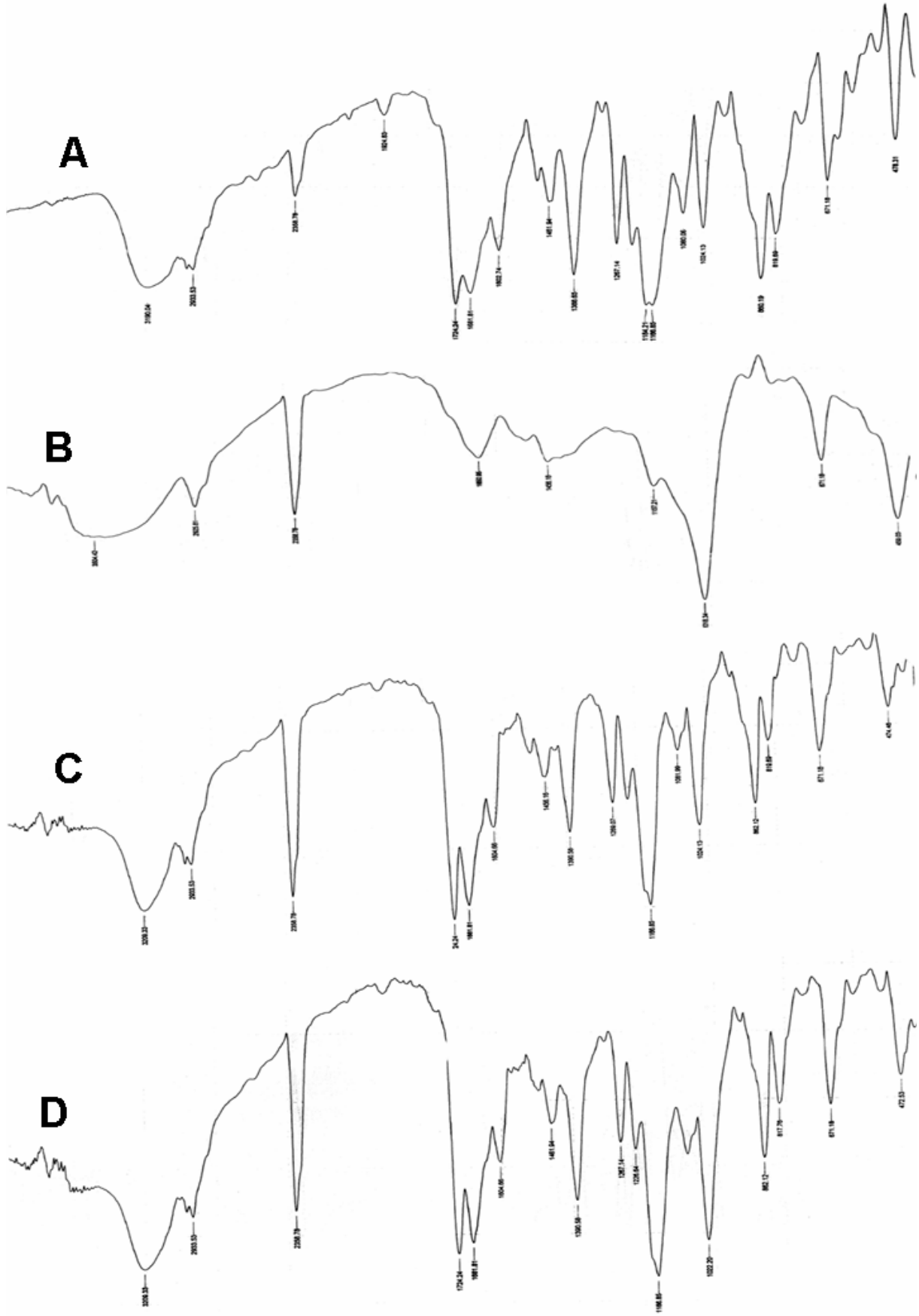
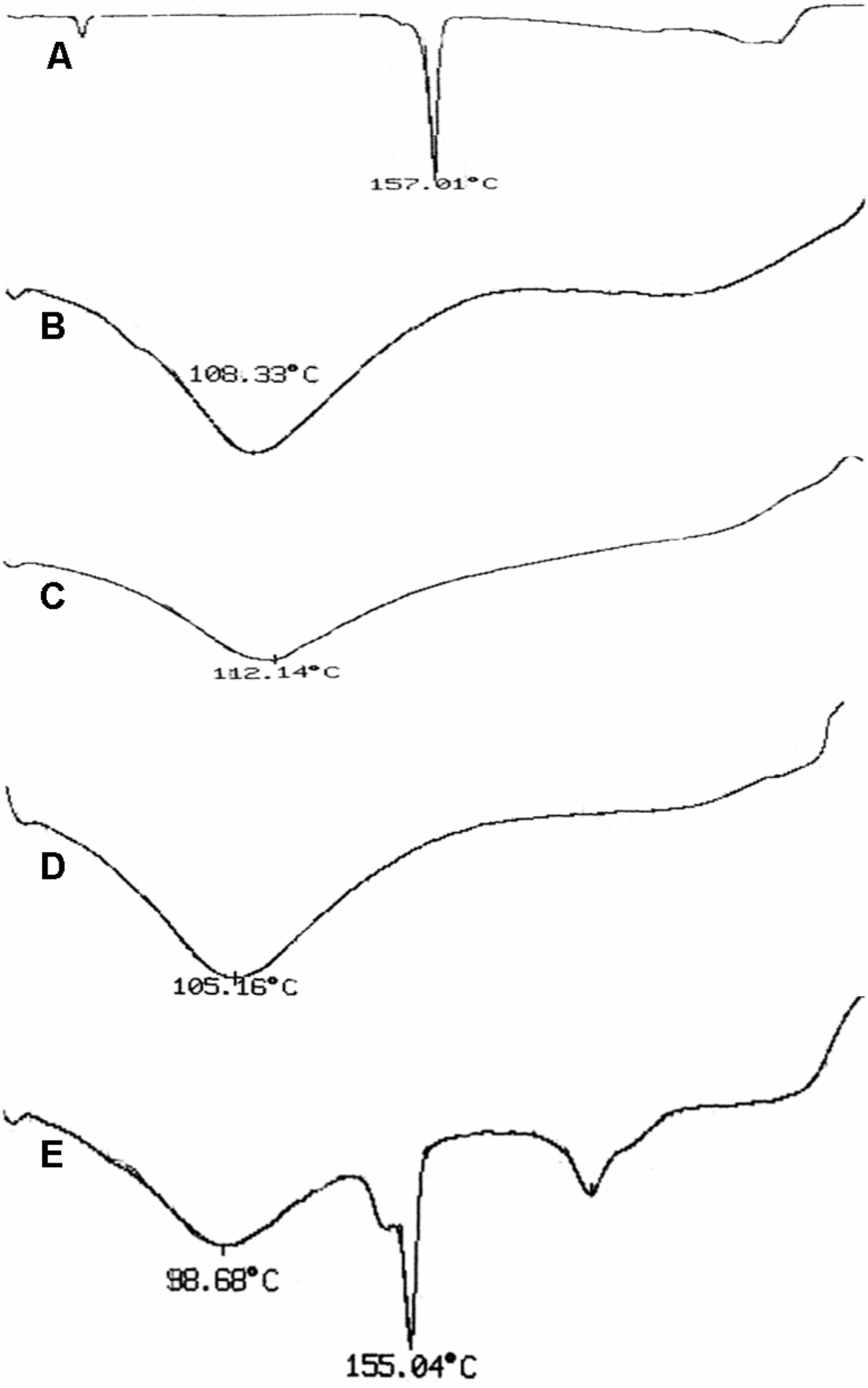


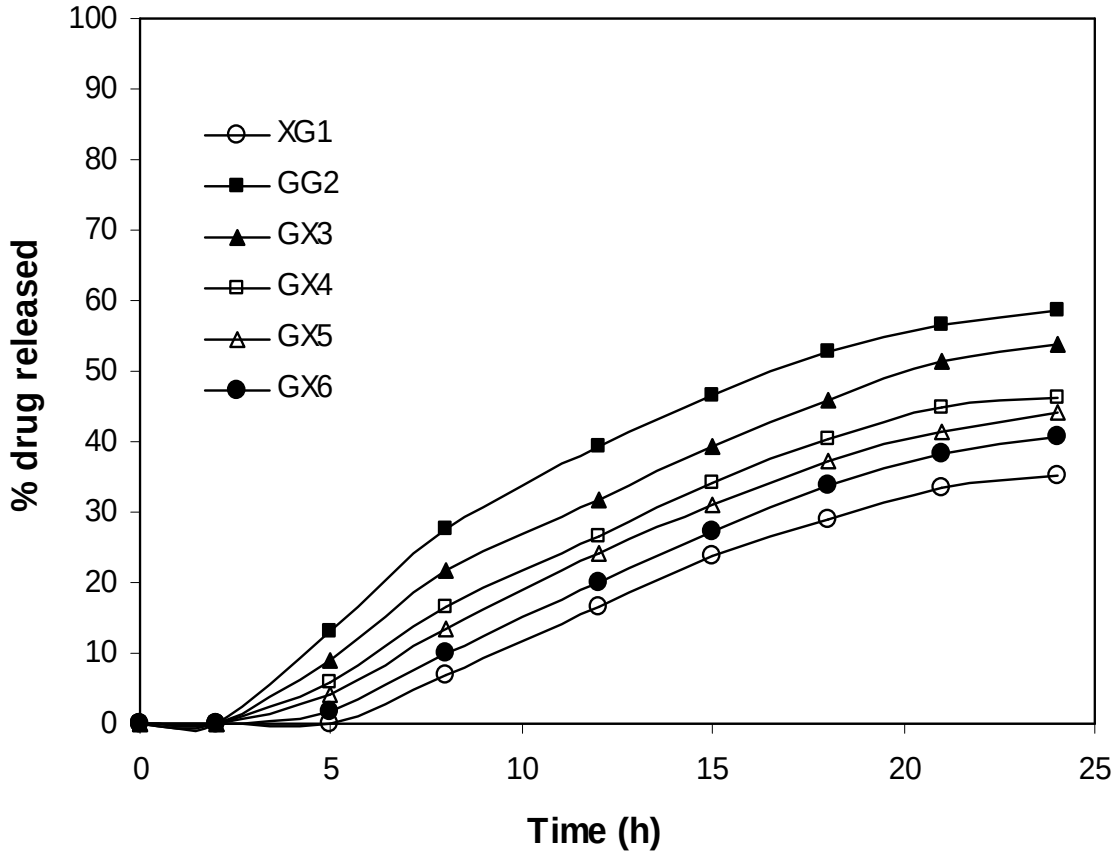
Fig 2. DSC thermograms of naproxen (A), guar gum (B), xanthan gum (C), drug free GX5 tablets (D) and drug loaded GX5 tablets (E).



In vitro drug release studies

Figure 3 shows the results of in vitro drug release studies without rat caecal contents. The drug release from the formulation XG1 coated with XG alone takes place at a highly retarded rate. The amount of drug released from XG1 was 2.6 % in simulated gastric (2 h) and intestinal fluid (3 h), the tablets remains intact and drug released at the end of 24 h was 35.21 %. The decreased drug release in the colonic area from XG1 might be due to swelling of the polymer forming a thick viscous stiff gel layer around the core tablets on being exposed to the dissolution fluids. This viscous gel layer will retard penetration of dissolution fluids into core tablets and reduce the diffusion of drug from the core tablets. On the other hand, at the end of the 5 h, the percent drug released from the formulation GG2 was 13.1 %, and 58.69 % at the end of 24 h. The formulation GG2 fails to retard drug release in physiological environment of stomach & small intestine and drug release was incomplete in physiological environment of colon, this might be due to high proportion of guar gum present in the coat and absence of rat caecal content in the dissolution fluid. The percentage of drug released from formulations GX3, GX4, GX5 and GX6 was 9.1 %, 5.8 %, 3.1 % and 1.8 % respectively after 5 h. This indicates that GG and XG mixture as a compression coat is capable of minimizing the drug release in the physiological environment of stomach and small intestine. The percent of drug released at the end of 24 h from formulation GX3, GX4, GX5 and GX6 was 53.64 %, 46.37 %, 44.20 % and 40.57 % respectively. This indicates that until the coat is degraded, the gum will not permit the release of the remaining drug present in the core.

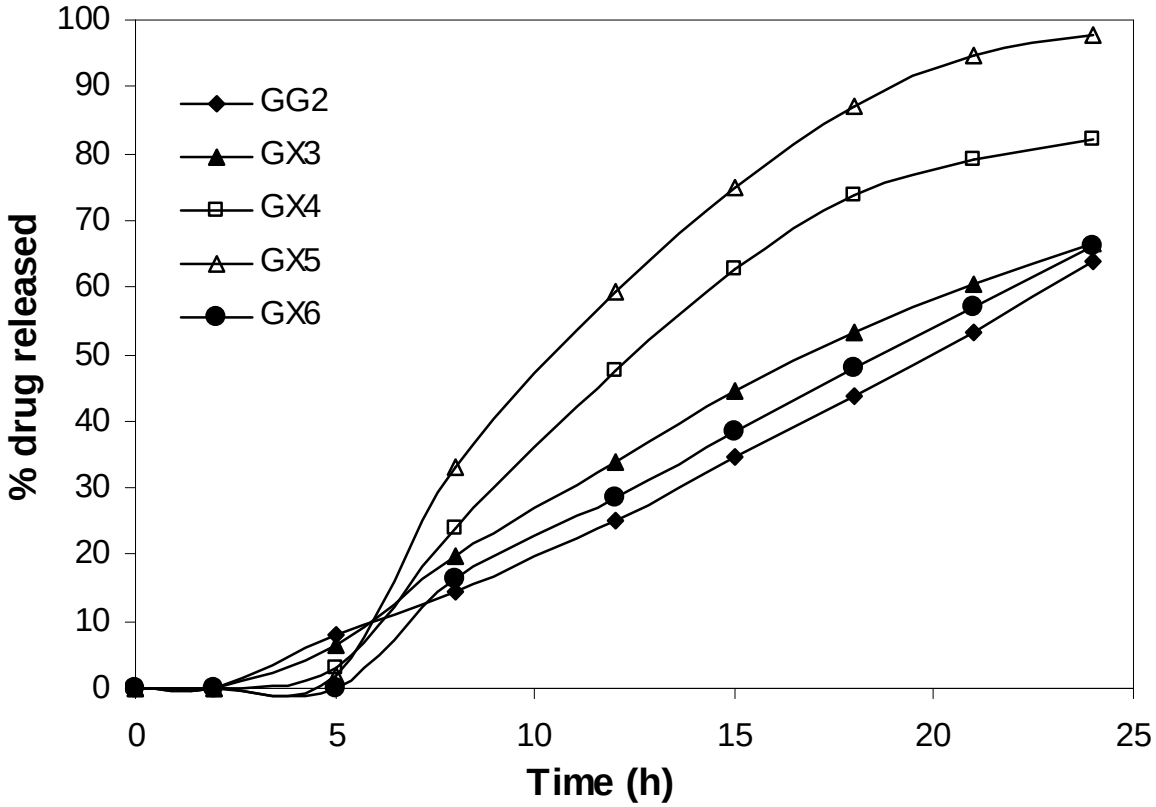
Fig 3. *In vitro* drug release profiles of tablets without rat caecal content.



The drug delivery systems targeted to colon should not only protect the drug being released in the stomach and small intestine, but they also should release and sustain the drug release in the colon. Hence, in vitro drug release studies were carried out in phosphate buffer containing rat caecal contents. Figure 4 represents the drug release profiles of tablets in the presence of 4 % w/v

of rat ceacal content medium. The percent drug released from GG2 and GX3 was found to be 63.95 % and 66.52 % at the end of 24 h. The presence of higher amount of guar gum in the coat might have not allowed its complete degradation during the testing period of 24 h. There was not much difference in the amount of drug released from the dissolution studies carried out in presence or absence of rat caecal content medium from GG2. This shows that the drug release is due to mechanical diffusion of the naproxen from the formulation, not due to action of colonic bacteria. But, there was a difference in the amount of drug released in presence or absence of rat caecal content from GX3, which may be due to lower proportion of guar gum as compared to formulation GG2. This clearly shows that the increase in drug release is due to action of colonic bacterial enzymes present in the simulated colonic fluid on the swollen guar gum, but the release was incomplete due to high proportion of guar gum in the formulation GX3. Thus, it is evident that unless the coat is completely degraded by colonic bacteria, drug release may not increase. Hence, the content of guar gum was further reduced in the coat formulation GX4, GX5 and GX6. The percent of drug released from GX4 and GX5 after 24 h was 81.99 % and 97.82 % respectively and the tablet coat was found to be completely degraded making way for the release of the drug from the core. From formulation GX6, an increase in percent drug released was not observed and at the end of 24 h, 66.40 % of drug was released.

Fig 4. Drug release profiles of tablets in the presence of 4 % w/v of rat ceacal content.



The coat formulation of GX6 was found to be highly viscous, swollen and intact which was not completely degraded in the presence of rat caecal contents there by not releasing the drug from the tablets in rat caecal content medium. Since the xanthan gum content of the coat formulation GX6 was high as compared to GX3, GX4 and GX5, the coat might have not completely hydrated due to reduced diffusion of simulated colonic fluid into the formulation and subsequently degraded by the caecal enzymes at a slower rate resulting in the release of only 66.40 % of drug from GX6 formulation in the colon.

Stability studies

The stability studies were carried out on selected formulation GX5 at 40 ^{o}C/75 % RH for 3 months. After three months, the formulation was observed for physical change, drug content and subjected to in vitro drug release studies. No change in physical appearance, physical properties and in drug content was observed. Also there was no significant difference in the percent of naproxen released from formulation GX5 when compared with that released from the same formulation before storage.

CONCLUSION

In conclusion, the tablets GX5 released only 1.40 % of drug in the physiological environment of stomach and small intestine and released more then 95 % of the drug in the colon. The presence of XG in the coat reduces the initial premature drug release in the upper part of GIT and ensures complete release of drug in the colon due to increased susceptibility of guar gum to degradation by bacterial enzymes present in dissolution fluids. Based on these results, the compression-coated tablets GX5 is most likely to provide targeted delivery of naproxen to colon.

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