Acta Pharmaceutica Sciencia
52: 281-294 (2010)

Formulation and evaluation of compression coated piroxicam tablets for colon specific drug delivery

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Abstract

The aim of the present study was to prepare and characterize compression coated piroxicam tablets using guar gum/ hydroxypropylmethylcellulose for effective delivery of drug to the colon. *In vitro* drug release studies were performed in the dissolution media with and without rat caecal contents. Results showed an enhanced release in rat caecal content when compared to formulation studied in dissolution media without rat caecal content, because of microbial degradation of polymer. The rate of drug release is dependent upon the coat thickness and amount of guar gum/ hydroxypropylmethylcellulose used in the formulations. Combination of guar gum and hydroxypropylmethylcellulose K4M provided better protection of the drug, showing increased release lag time and controlled release rate. The nature of the drug transport was found to be non-Fickian (super case-II). Release of drug from tablets began after a time delay as a result of hydrogel swelling/retarding effect, followed by zero-order release for most of the formulations studied. The *in vitro* drug release studies and *in vivo* X-ray studies indicated that optimized formulation was a promising system to provide targeting of piroxicam to the colon.

Keywords: Guar gum, Piroxicam, Colonic drug delivery, Rat caecal contents

Introduction

The overall goal for optimum therapy is to match the needs of the patient while improving the efficiency and safety of the administered drugs. Various drug delivery approaches have always played a challenging and crucial role in ensuring and predicting the delivery of promising and successful drugs to the target site of delivery in the human body. For sustained as well as controlled release systems, the oral route of administration has received the most attention. This is because of greater flexibility in dosage form design for the oral rather than the parenteral route. Colon-specific drug-delivery systems offer several potential therapeutic advantages. In a number of colonic diseases such as inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, irritable bowel syndrome, colorectal cancer, and constipation it has been shown that local is more effective than systemic delivery.

Colon-specific drug delivery systems, which can deliver drugs to the lower gastrointestinal tract without releasing them in the upper GI-tract, can be expected to decrease the side-effects of the drugs and improve the quality of life for patients suffering from colon specific diseases (Fujino et al. 1995).

Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity, much greater response to absorption enhancers, and the presence of

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large amounts of enzymes for polysaccharides (e.g., β -D-glucosidase, β-D-galactosidase, amylase,large amounts of enzymes for polysaccharides (e.g., β -D-glucosidase, β-D-galactosidase, amylase (Sinha and Kumria 2001). Various systems have been developed for colon-specific drug delivery. These include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time dependent release systems, and enzymatically controlled delivery systems (Leopold 1999). Enteric coated systems are the most commonly used for colonic drug delivery, but the disadvantage of this system is that the pH difference between small intestine and colon is not being very well-defined. These delivery systems do not allow reproducible drug release. The restraint of time dependent release system is that it is not able to sense any variation in the upper gastro-intestinal tract transit time, any variation in gastric emptying time may lead to drug release in small intestine before arrival to colon. Apparently, the most convenient approach for site-specific drug delivery to colon is enzymatically controlled delivery systems. No drug release can occur unless the system arrives to the colon (Sinha and Kumria 2001, Yang et al. 2002, Chourasia and Jain 2003). All these considerations have led current research developments to use polysaccharides, which are non-toxic and for which degradation is colon-specific.

Several polysaccharides are being investigated as carriers for colon-specific drug delivery. The polysaccharides that are under active investigation for colon-specific drug delivery include pectin and its salts (Ashford et al. 1993 and 1994, Rubinstein et al. 1993, Wakerly 1996a and 1996b, Munjeri et al. 1997), chondroitin sulfate (Rubinstein et al. 1992a and 1992b), amylose (Milojevic et al. 1995), dextran (Hovgaard and Brøndsted 1995) and chitosan (Tozaki et al. 1997). It was reported that the guar gum is a potential carrier for colon-specific drug delivery (Rama Prasad et al. 1998, Krishnaiah et al. 1998a and 1998b). The degradation of guar gum in simulated colonic fluids by the action of bacterial enzymes is well documented.

Guar gum is a galactomannan material composed of linear chains of (1→ 4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units linked by (1→ 6). The colon contains enzymes (galactomannanases) capable of degrading guar gum to short chain fatty acids. Both matrix tablets and compression coated tablets have been administered in humans.

Tablets composed primarily of guar gum and the dexamethasone was dosed orally in humans and their transit and disintegration followed using gamma scintigraphy (Kenyon et al. 1997). Some drug was released from the tablets prior to colonic arrival but the majority of drug was released in the large intestine and release was generally correlated with tablet disintegration. A similar study resulted in the same results although no drug was used in the formulations (Krishnaiah et al. 1998a). The results generated in these two studies suggested that a compression coating approach could improve targeted release (Krishnaiah et al. 1999).

The use of guar gum as a compression coating to delay release of a drug has been studied recently. Following in vitro studies (Krishnaiah et al. 2002); a guar gum based colon targeted oral delivery system for the drug 5-fluorouracil was tested in a group of 12 healthy volunteers (Krishnaiah et al. 2003a). The results from this study are consistent with delivery of 5-fluorouracil to the large intestine: t_{max} increased from 0.6±0.01 h (immediate release tablets) to 7.6±0.1 h. There was no drug detected in the plasma until approximately 5 h had elapsed. In most instances, assuming normal transit patterns, the tablets are located in the colon at this time. Similar data have been obtained with several other drugs mebendazole, metronidazole, celecoxib, and tinidazole (Krishnaiah et al. 2002a, 2002b, 2002c, 2003b).

A growing proportion of elderly patients suffer from diseases like osteoarthritis or rheumatoid arthritis and inflammatory bowel disease and they require nonsteroidal antiinflammatory drug (NSAID) therapy for the

treatment of it. But NSAIDs are well known for their gastrotoxic and duodenotoxic effects. Piroxicam, a nonsteroidal antiinflammatory drug exhibits better tolerance than aspirin, indomethacin and naproxen.

In the present investigation attempts were made to minimize the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon by applying guar gum/HPMC K4M as a compression coat over the piroxicam core tablets. Compression-coated tablets were developed for targeting of piroxicam for local action in the treatment of colonic inflammation.

Material and Methods

Piroxicam (USP) was obtained from Vilin pharmaceuticals, Roorki, India as a gift sample. Guar gum (viscosity of 1% w/v aqueous dispersion 2300 cps at 25°C), was obtained from Dabur, India and were of pharmacopoeia quality. Hydroxypropylmethylcellulose (HPMC) obtained from Lupin, Pune, India. Other materials used were microcrystalline cellulose (Avicel pH-101), sodium starch glycolate, sodium lauryl sulphate, magnesium stearate, talc, barium sulphate and methanol, were of pharmacopoeia quality.

Preparation of Piroxicam core tablets

Each core tablet (average weight 80 mg) for *in vitro* drug release studies consisted of piroxicam (20 mg), microcrystalline cellulose (MCC, 46 mg), sodium starch glycolate (6 mg), sodium lauryl sulphate (5 mg), talc (2 mg) and magnesium stearate (1 mg). Sodium starch glycolate and sodium lauryl sulphate were added to get fast disintegration tablets (disintegration time < 1 min) of piroxicam. The materials were weighed, mixed and passed through a≠60 mesh to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 6 mm round, flat and plain punches on a single station tablet machine (Cadmach, India). Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the core tablets.

Compression coating of core tablets

The core tablets were compression coated with different quantities (Table 1) of coating material containing of guar gum/HPMC with different coat weights (i.e. the coat weights were either 200 or 175 mg). Microcrystalline cellulose was included in the coat formulations to impart enough hardness, since guar gum alone gave very soft coats. Half the quantity of the coating material was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed using 9 mm round, flat and plain punches. In this study, we used a high molecular weight HPMC in combination with guar gum to enforce the mechanical resistance of the tablet during its transit in the GI tract.

Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution rates in different media were performed on the compression coated tablets.

Thickness of the core and coated tablets were measured using Digital Micrometer (Digital Caliper, Aerospace, India). Hardness of randomly selected tablets was tested using Monsanto hardness tester. Friability of core tablets and compression coated tablets were carried out on a Roche friabilator (Electrolab, Mumbai, India) using 20 accurately weighed tablets.

Table 1. Composition of guar gum/HPMC K4M coats used to cover piroxicam core tablets

Ingredients	Quantity (mg) present in the coat formulation											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Guar gum	170	160	150	140	120	110	100	90	80	85	90	95
HPMC K4M	-	-	-	-	-	-	-	-	20	15	10	5
Microcrystalline cellulose	25	35	45	55	50	60	70	80	70	70	70	70
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	175	175	175	175	175	175	175	175

Determination of drug content in tablet formulations

Both the core tablets and compression-coated tablets of piroxicam were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 50 mg of piroxicam were accurately weighed, transferred to a 100 mL volumetric flask containing 50 mL of methanol and allowed to stand for 5 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with methanol. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer (Systronics 2202, Hyderabad, India) at 333 nm. The drug concentration was calculated from the calibration curve.

Drug release studies

The release of piroxicam from compression coated tablets was carried out using USP basket-type dissolution apparatus (Electro lab, TDT-08L, USA) at a rotation speed of 100 rpm, and a temperature of 37±0.5°C.

For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid without pepsin (SGF, pH 1.2) for the first 2 h as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with enzyme-free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 h, as the average small intestinal transit time is about 3 h, and finally enzyme-free SIF (pH 6.8) was used for 19 h to mimic colonic pH conditions.

Drug release was measured from compression coated piroxicam tablets, added to 900 mL of dissolution medium. Samples withdrawn at various time intervals were analyzed spectrophotometrically at 333 nm. All dissolution runs were performed in triplicate.

Drug release studies in the presence of rat caecal contents

The ability of the compression-coated tablets to release piroxicam in the physiological environment of colon was assessed by continuing the drug release studies in rat caecal content medium. The rat caecal content medium was prepared as described previously (Rama Prasad et al. 1998). The care of the rats was in accordance with the institutional guidelines. The drug release studies were carried out using USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37±0.5°C.) with slight modifications (Krishnaiah et al. 1998b). A beaker (capacity 250 mL) containing 100 mL of rat caecal content medium was immersed in the water maintained in the 1000 mL vessel, which, in turn, was in the water bath of the apparatus. The swollen formulations after completing the dissolution study in SGF (pH 1.2) (2 h) and in the SIF (pH 7.4) (3 h) were placed in the baskets of the apparatus and immersed in the rat caecal content medium. As the caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers. At various time intervals, 2 mL of the dissolution sample was withdrawn without a pre-filter and replaced with 2 mL of fresh SIF

(pH 6.8) bubbled with CO_2, and the experiment was continued for another 19 h as the usual colonic transit time is 20-30 h.

To the samples, 2 mL of methanol was added to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes. The volume was made up to 10 mL with SIF (pH 6.8), centrifuged and the supernatant was filtered through a bacteria-proof filter and the filtrate was analyzed for piroxicam content at 333 nm. The above study was carried out on the piroxicam tablets coated with different coat compositions (F4, F7, F8 and F11) and also without rat caecal contents in SIF (pH 6.8) (control study).

In vivo X-ray studies

X-ray imaging was used to monitor the tablets throughout the GI system. Three healthy human volunteers, with age 22-30 yrs, and 50-80 kg body weight, were participated in *in vivo* studies. They were non-alcoholics, non-smokers and have not taken any drugs. The purpose of the study was fully explained and volunteers had given their written consent. Each subject ingested barium sulphate containing guar gum/HPMC K4M compression coated tablets orally with 200 mL water, after an overnight fast. The tablets were visualized using X-ray. Abdominal radiographs were taken after 30 min, 3, 6, 8, and 24 h in all subjects. The volunteers served with food, 2 h (breakfast), and 4 h (lunch) after the administration of the tablet (Demiroz et al. 2004).

Evaluation of Release rate kinetics

Data obtained from in vitro release studies were fitted to various kinetic equations to find out the mechanism of piroxicam release from compression coated tablets. Release kinetic study was done by using kinetics equation of Higuchi's square root method which gave value of cumulative percent of drug release *vs.* square root of time. When cumulative percentage drug released *vs.* time is plotted then it is zero order and if log cumulative percent of drug remaining to be released *vs.* log of time is plotted then it gives first order release.

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer-Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line.

$$M_t/M_\infty = Kt^n$$

where, $Mt/M\infty$ is fraction of drug released at time '*t*', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1 (Peppas 1985).

Stability studies

The stability studies were carried out according to ICH to asses the drug formulation stability. Optimized F11 formulation was sealed in aluminum packaging laminated with polyethylene. Samples were kept at 40°C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

FTIR studies

The infrared spectra of piroxicam, physical mixture of drug (piroxicam) and excipients and placebo were recorded between 400 to 4000 cm^{-1} on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer BX-I system, USA).

Results And Discussion

Results of piroxicam core tablet characteristics

Piroxicam powder was compressed directly into a core tablet by using direct compression vehicle such as microcrystalline cellulose. The mean drug content of the piroxicam core tablets was found to be 99.2 ±1.76 of the labeled amount indicating uniformity of drug content in the formulation (Table 2). The hardness of the core tablets of piroxicam was found to be in the range of 3.2±0.64 kg/cm^2. The core tablets of piroxicam were also found to comply with the friability test since the weight loss was found to be 0.4%. The tablets thickness was found to be 2.08±0.008 mm. The core tablets were found to disintegrate within 40s showing the required fast disintegration characteristics. The combined action of the super disintegrant (sodium starch glycolate) and microcrystalline cellulose might have contributed to such a fast disintegration property. Thus the core tablets of piroxicam formulated in the study were found to have the required characteristics for compression coating with guar gum/HPMC K4M. The core tablets containing 20 mg of piroxicam were tested in SGF (pH 1.2), SIF (pH 6.8) and SIF (pH 7.4) for their dissolution rates. Figure 1 shows the dissolution results of piroxicam core tablets. The core tablets dissolved faster in SIF pH 6.8 and 7.4 and reached 100% in less than 60 min and dissolution rate was slower in SGF (pH 1.2) and 100% drug release was reached in 3 h.

Table 2. Physical properties of piroxicam core and compression coated tablets

Formulation Code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Friability (%)	Drug Content (%)
Core	3.2±0.64	81.5±1.68	0.40	99.2
F1	5.2±0.35	286.4±3.12	0.33	95.8
F2	5.1±0.42	282.6±2.54	0.17	103.2
F3	5.0±0.25	288.0±2.68	0.34	96.6
F4	5.4±0.64	285.3±1.86	0.26	103.0
F5	4.4±0.58	258.5±1.63	0.54	97.2
F6	4.8±0.46	256.7±2.02	0.58	99.9
F7	5.0±0.86	260.1±2.36	0.45	100.6
F8	5.2±0.46	259.6±1.74	0.38	95.0
F9	6.0±0.52	257.0±2.86	0.52	98.0
F10	6.0±0.76	258.0±3.02	0.68	95.6
F11	5.5±0.62	262.5±2.56	0.46	96.0
F12	5.3±0.28	256.0±1.28	0.34	97.1

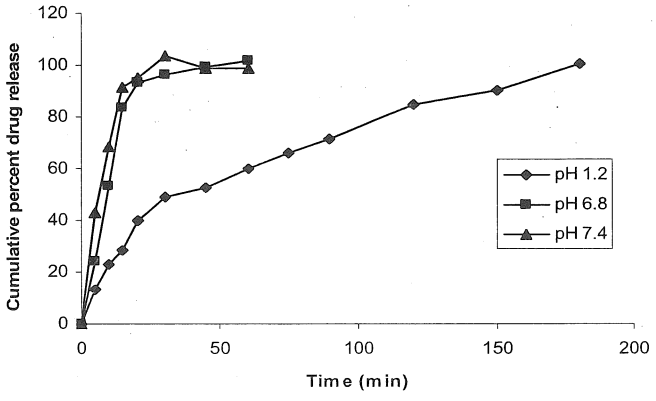


Figure 1. Dissolution profile of piroxicam core tablets in SGF (pH 1.2), SIF (pH 6.8) and SIF (pH 7.4) solutions (USP Apparatus 2 and 50rpm)

Compression-coated piroxicam tablets characteristics

The coat formulation containing various proportions of guar gum was prepared. The compression-coated tablets were prepared by applying maximum compression force and the hardness of the tablets was found to be in the range of 4.4–6.0 kg/cm^2. Thickness of the coat of compression-coated piroxicam tablets, which contained 200 and 175 mg coat weights over the core tablets (diameter 6 mm and thickness 2.08±0.008 mm), was measured using a digital caliper. The mean thickness of the compression-coated tablets was found to be 5.74±0.023 and 4.64 ±0.009 mm for formulations containing 200 and 175 mg coat weights respectively (the coating was even over the surface of the core tablet). Thus, the observed coat thickness for compression-coated tablets of 200 mg and 175 mg coat weight were 1.83±0.011 and 1.28±0.005 mm respectively.

The physical properties of guar gum/HPMC compression coated tablets are given in Table 2. It was found that crushing strength of compression coated tablets was dependent on amount of guar gum/HPMC polymers. When HPMC in polymer mixture increased the crushing strength of coated tablets increased. HPMC provides mechanical strength to the tablets. All tablets complied with the pharmaceutical quality control standards.

Dissolution results of compression coated piroxicam tablets

The cumulative mean percent piroxicam released from tablets coated with 200 and 175 mg coat weights of formulations containing varying amounts of guar gum (from F1 to F7) was found to vary from 4.09±1.02 to 10.32±2.68 after 5 h of testing in simulated gastric and intestinal fluids. The cumulative mean percent drug released for formulation containing different amounts of combination of guar gum and HPMC K4M (F9, F10, and F11) was found to vary from 8.73±2.14 to 9.85±1.75 after 5h dissolution testing (Figure 2a, 2b, and 2c). This indicates that a minimal amount of the drug is released from the guar gum/HPMC K4M compression coated formulations in the physiological environment of stomach and small intestine. Thus, guar gum in the form of coat is capable of protecting the drug from being released completely in the physiological environment of stomach and small intestine.

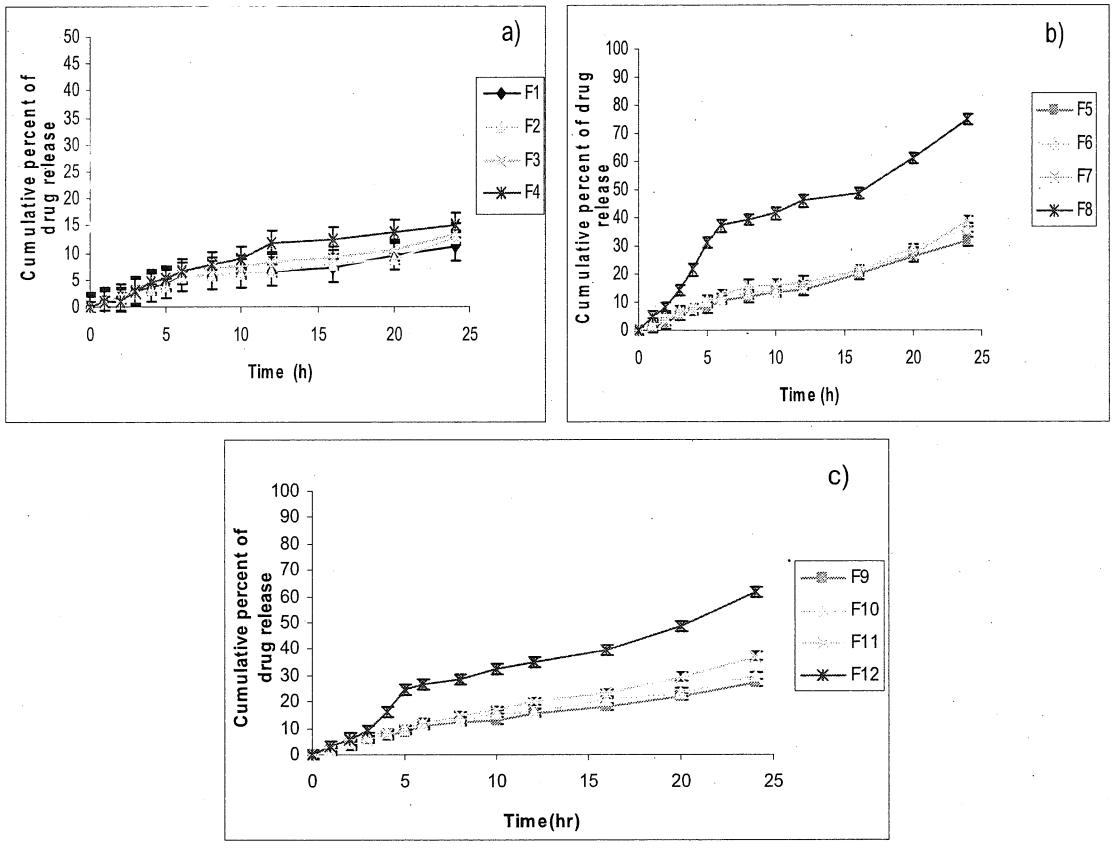


Figure 2. Cumulative percentage drug release (mean ± S.D, n=3) versus time profile for piroxicam core tablets compression coated with a) guar gum (coat weight 200mg) b) guar gum (coat weight 175mg) and c) combination of guar gum and HPMC K4M (coat weight 175mg).

On exposure to the dissolution fluids, the gum gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core tablets. On coming into contact with biological fluids, guar gum swells up and the drug release takes place by diffusion. Mechanical erosion of the swollen guar gum layer follows. Unless the swollen gum layer erodes, further hydration and swelling of the guar gum does not take place. On reaching the colonic environment, the swollen guar gum layer would be acted upon by the colonic bacterial enzymes and release the drug contained in the swollen guar gum layer (Ram Prasad et al. 1998).

To estimate the integrity of the coats, the drug release studies were further continued for 19 h by replacing the dissolution medium with SIF (pH 6.8). At the end of the experiment, the cumulative mean percent drug released from coat formulations F1, F2 F3 and F4 was between 11.32±1.02 and 15.07±2.54 and the coats were intact. This indicates that the gum will not permit the release of the bulk of the drug core until the coat is broken. The percent drug release for the formulations F5, F6, F7, F9, F10, and F11, was found between 27.23±1.65 and 38.77±0.95 after 24 h study. However, the tablets with coat formulation F8 and F12 were found to release 31.47 and 24.63 % respectively after 5 h and 74.79±0.79 and 61.45±1.65 after 24 h study. This may be due to lesser gum content of the coat which was unable to remain intact and not protecting the drug from being released.

Thus the F8 and F12 were not studied further in rat caecal contents. The formulations F1, F2, and F3 were also not studied in the rat caecal contents because very less amount of drug released after 24 h study. Even though F4 formulation releasing tiny amount (15.07±2.54 percent) of drug after 24 h, it was further studied in caecal contents to know the effect of coat thickness i.e.1.83±0.011 mm coat thickness (200 mg coat weight) compared with 1.28±0.005 mm coat thickness (175 mg coat weight).

Dissolution results of compression coated piroxicam tablets in 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 release the drug in colon after enzymatic degradation by colonic bacteria. Hence, in vitro drug release studies were carried out for selected formulations in SIF (pH 6.8) containing 4% w/v of rat caecal contents. At the end of 24 h of testing which includes testing in simulated gastric and intestinal fluids, the percent drug released from piroxicam tablets coated with coat formulation F4 was found to be only 41.41±2.68 (Figure 3). The presence of higher amount of guar gum (200 mg) in the coat with resultant thicker coat (1.83±0.011 mm) might not have allowed the disintegration of the coat during the time period of testing. This also indicates that the drug will not be released unless the coat is broken.

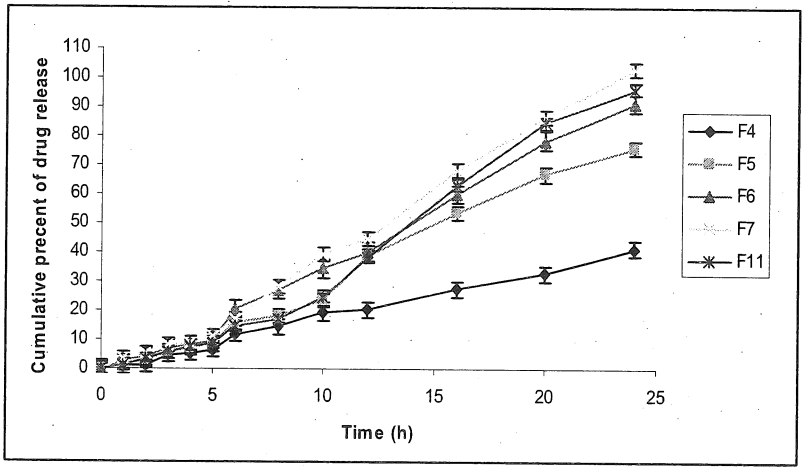


Figure 3. Cumulative percentage drug release (mean ± S.D, n=3) versus time profile for compression coated piroxicam tablets in SGF (2 h), SIF (pH 7.4) (3 h), and SIF (pH 6.8 containing 4% rat caecal contents) (19 h).

The percent drug released from tablets coated with coat formulation F5 was found to increase from 10 h onwards indicating the commencement of breaking of gum coats. The percent drug released after 24 h of testing was 75.95±1.46 and the tablet coat was found to be broken at one point making way for the release of the drug. In case of tablets coated with coat formulations F6 and F7, a significant increase in percent drug released was observed from 8 h onwards and at the end of the experiment 91.24±2.68 and 103.02±2.55 piroxicam was released. The coat was completely degraded by the rat caecal enzymes thereby releasing the drug into the dissolution medium. Since the coat weight and thickness of coat formulations F6 and F7 were lesser (175 mg, 1.28±0.005 mm) compared to coat formulation F4 (200 mg, 1.83±0.011 mm), the coat might have been completely hydrated and subsequently degraded by the caecal enzymes at a faster rate.

Guar gum, when formulated as single polymeric system, bursting of tablets was seen. This might be due to the rapid swelling of hydrophilic polymer. When it was mixed in larger concentration release was lowered, the reason for this can be decrease in the porosity. As we increase the concentration of guar gum, on

swelling, tortuocity increase due to which the channels get zigzag type and drug is not able to come out of the system. To control the initial bursting and also to improve the mechanical strength it was mixed with HPMC K4M polymer. The percent drug release from F11 formulation at the end of 24 h study in presence of rat caecal content was found to be 96.09±1.46. Better controlled release was observed in the system containing Guar gum and HPMC K4M.

Tablet containing two polymeric systems shows much more promising release than the single polymeric system. From this we concluded that by taking single hydrophilic polymer also release can be retarded but addition of another polymer which can control its release is necessary.

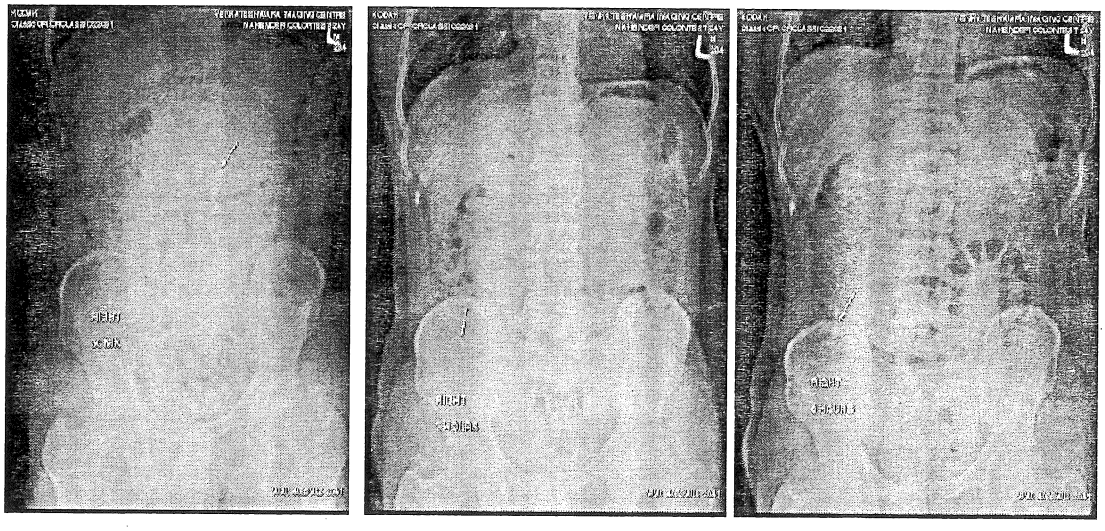
It is evident from the results of the drug release studies in the presence and absence of rat caecal contents that the drug release occurred by the degradation of guar gum coats by the enzymes present in the caecal matter.

X-ray studies

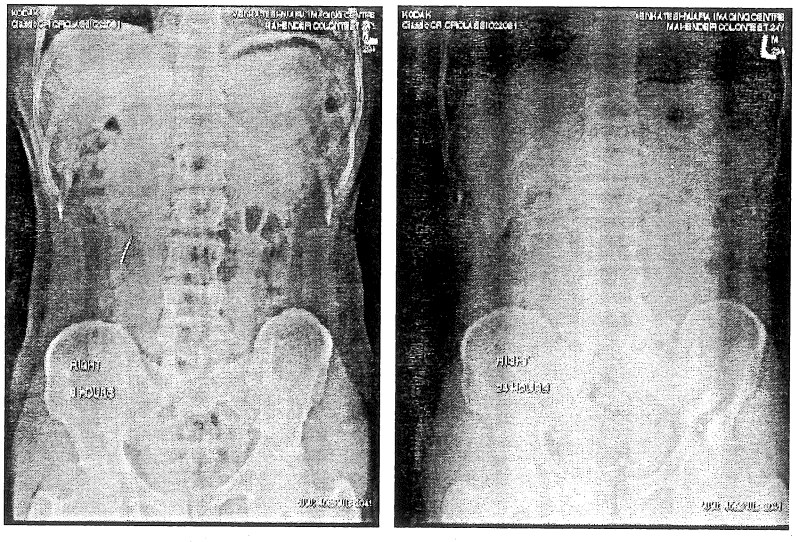
X-ray studies were carried out on the tablets, in order to see the compression coated tablets throughout the GI system. Barium sulphate was used as the marker. The position of the tablets in the body was monitored at different time points. The abdominal radiographs showed that, the tablets remained intact in the stomach in all subjects. The transit time of the tablets throughout the GI system was variable. The position of tablets at different time points is shown in Table 3 and the X-ray images of tablet throughout the GI system are shown in Figure 4.

Table 3. The position of the tablets throughout the GI tract at certain time points

Subjects	30 min	3h	6h	8h	24h
1	Stomach	Cecum	Ascending colon	Ascending colon	Not observed
2	Stomach	Cecum	Ascending colon	Ascending colon	Sigmoid colon
3	Stomach	Ileocecal Junction	Ascending colon	Ascending colon	Not observed



a) 30 min: Stomach b) 3 h: Caecum c) 6 h: Ascending colon



d) 8 h: Ascending colon f) 24 h: Not detected

Figure 4. The localization of the tablet in the gastrointestinal tract

The *in vivo* results showed that the tablets (F11 formulation) reached the colon without disintegrating in the upper region of the GI system in all subjects. From the abdominal radiographs, taken at different time points, the tablets entered the colon, varying between 3-6 h for all volunteers after tablet administration. The X-ray images showed that the tablets slowly disintegrated throughout the colon after reaching it. These results are in agreement with the results of Ashford et al (1993), who observed that the gastric emptying times of 0.6–2.9 h, small intestinal transit times of 1.8–8.5 h and colonic arrival time of 3.2–9.8 h while evaluating pectin as a compression coat for colonic drug delivery, using gamma scintigraphy.

Kinetic results

The mechanism and kinetics of drug release of piroxicam is determined by the application of korsmeyer-peppas model, higuchi's model, zero order and first order kinetics as shown in Table 4. Most of the tablet formulation follows the zero order release as their r^2 values are between 0.9748 and 0.9921. The mechanisms of drug release are non-Fickian diffusion (super case-II), since they fitted well with Korsmeyer–Peppas models (r^2 in the range of 0.9684–0.9913 with n value above 1 (Peppas, 1985). This indicates that drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.

Table 4. Regression coefficient (R^2) values of drug release data obtained from various kinetic models and n value according to Korsmeyer-Peppas.

Formulation code	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	n
F4	0.9897	0.9711	0.9718	0.9684	1.2322
F5	0.9846	0.9591	0.9303	0.9823	1.2383
F6	0.9921	0.9063	0.9413	0.9688	1.1886
F7	0.9915	0.7856	0.9334	0.9711	1.1610
F11	0.9748	0.8444	0.8972	0.9913	1.3729

Stability studies

The optimized pellets from batch F11 were charged for stability studies. There was no change in physical appearance, color. Formulations were analyzed at the end of 3 months for the assay and dissolution studies. Average drug content of the tablets were found to be 95.5±0.6 % of the labeled claim. In vitro dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of 3 months.

FTIR Studies

The IR spectra of pure piroxicam drug showed the characteristic absorption bands are as follows: tertiary amine at 3337.9cm^{-1}, aromatic C-H stretching at 3102, 3067 cm^{-1}, aliphatic CH_3 stretching at 2931, 2879cm^{-1}, C-H stretching of pyridine at 3067, 3031cm^{-1}, amidic keto group showed absorption band at 1629 cm^{-1}, sulphoxide stretching at 1065, 1039 cm^{-1}, and 2-substituted pyridine bending mode at 772-731cm^{-1}.

No drug-polymer interaction was observed in the FTIR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture.

Conclusion

Guar gum and HPMC K4M in combination, in the form of compression coated tablets is capable of protecting piroxicam from being released in the in the upper region of GI system, i.e. stomach and small intestine. The *in vitro* drug release studies *and in vivo* X-ray studies indicated that optimized formulation was a promising system to provide targeting of piroxicam to the colon. The release pattern of the above

formulation was best fitted to Korsmeyer-Peppas model and zero-order model. Mechanism of drug release followed was non-Fickian (super case-II) transport mechanism.

Acknowledgement

The authors would like to thank the T. Jayapal Reddy, management of St.Peter's Institute of Pharmaceutical Sciences, Warangal, Andhra Pradesh, India for their kind support throughout the work.

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Received: 12.06.2009
Accepted: 20.05.2010