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Research Article

FORMULATION AND EVALUATION OF FENOPROFEN CALCIUM COMPRESSED COATED TABLETS FOR COLON SPECIFIC DRUG DELIVERY

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ABSTRACT

Compression coating was one of the strategies used for delivering drugs to the colon. Colon specific drug delivery of Fenoprofen calcium (FC) systems based on guar gum and HPMC as compression coated tablets were evaluated using *in vitro* and *ex-vivo* methods. HPMC was included in this study to control the solubility of Guar gum and premature drug release in stomach and small intestine. Dissolution studies in pH 6.8 phosphate buffered saline containing 4% w/v rat caecal contents have demonstrated the susceptibility of guar gum to the colonic bacterial enzymatic action with subsequent drug release. The results of the *in vitro* study indicated that the optimized formulation (F18) containing 60% of guar gum was able to release less than 1% of drug in the environment of stomach, small intestine and released 98% of drug in the targeted area. *In-vivo* X-ray studies also established that the designed dosage form reached the targeted site. An envelope consisting of Guar Gum and HPMC over the core tablets of FC could be a promising drug delivery system for arthritis management by avoiding serious gastrointestinal adverse reactions associated with the conventional oral therapy.

Key Words: Compression coating, Guar gum, Colon specific drug delivery, Rat caecal contents caecal contents.

INTRODUCTION

Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides[1-6].Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects .Different approaches are designed based on prodrug formulation, pH-sensitivity [7], time-dependency (lag time)[8], microbial degradation and osmotic pressure etc to formulate the different dosage forms like tablets, capsules [9], multiparticulates, microspheres, liposomes for colon targeting. The efficiency of drug delivery system is evaluated using different in vitro and in vivo release studies.

The development and the design of colon-specific drug formulations represents a technological challenge as these dosage forms must pass through the upper gastrointestinal (GI) tract in intact form before delivering the drug to the colon. Colon-specific drug delivery does not appear to make much sense at first because of the small area of absorption and the strong barrier properties of the colonic epithelium. Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' or a sustained/prolonged release once they reach the colon.

However, the colon has some unique features, which make this organ attractive for site-specific drug delivery. On the one hand, the peptidase activity in the large intestine is significantly lower than that in the stomach and the small intestine and the colonic transit time is much longer than that of the upper GI tract. This allows the delivery of unstable peptide drugs and drugs with a low permeability to this lower intestinal region. On the other hand, the topical treatment of colonic disorders may lead to the reduction of both drug dose and side effects. Fenoprofen calcium (FC) is a propionic acid derivative and is a protypical NSAID used to reduce fever, mild to moderate pain, inflamatory diseases like osteo, rheumatoid, juvenile arthritis and ankylosing spondylitis [10-18].

MATERIALS

Fenoprofen Calcium as a model drug(Gift sample from suven life sciences, Hyderabad, india) Sodium Starch Glycolate (Amishi drugs and chemicals, Ahmedhabad, india), Magnesium Stearate, Talc, Sodium Lauryl Sulphate (S.D.fine chemicals pvt Ltd, Mumbai,india), Guar gum and Hydroxy propyl methyl cellulose (HPMC K15M) (Dr.Reddy's laboratories, Hyderabad, India).

METHODS

Preparation of fast disintegrating FC core tablets

The core tablets were prepared by direct compression method according to the formulae shown in Table 1. After number of trials were made in order to reach an optimum and rapid disintegration and dissolution. Each core tablet (average weight 250mg) consists of fenoprofen calcium (200mg), microcrystalline cellulose (MCC, 32.5nmg), sodium lauryl sulphate (2.5mg), talc (2.5mg) and magnesium stearate (2.5mg),sodium starch glycolate (4%,10mg) were added to obtain fast disintegration of tablets (disintegration time <1min) of fenoprofen calcium. The materials were weighed, blended and passed through a mesh (#60) to ensure proper mixing. Talc and Magnesium stearate were added to the powder blend and compressed into the tablets by using 9 mm round, flat and plain punches on a 16 station tablet machine (Cadmach Ltd, India) [17-22].

Preparation of FC compression coated tablets

The prepared FC core tablets were subjected to compression-coating with guar gum. By using 12mm round, flat and plain punches half the amount required for the coat was placed in the die then the core tablet was carefully positioned in the center of the die and then the other half was added. The powder were compressed around the core using constant compression force of 5kg/cm^2. 250,300,350,400 and 450 mg different coat weights were used as shown in Table 2.

Estimation of drug content

The core and compression-coated tablets of FC were tested for their drug content. The 10 tablets were finely powdered, and quantity of the powder equivalent to 250 mg of fenoprofen calcium was accurately weighed and transferred to 250 ml volumetric flasks containing 50 ml of pH-6.8 phosphate buffer and allowed to stand for 8 hour with intermittent shaking to ensure complete solubility of the drug. The solution then made up to 100ml volume with pH-6.8 phosphate buffer and mixed thoroughly. The solution were filtered, diluted and drug content was estimated by UV-spectrophotometer at 272 nm.The drug concentration was calculated from the calibration curve [21-25].

In vitro drug release studies

Drug release studies of FC core tablets

The core tablets containing 200 mg of fenoprofen calcium were tested in SGF (0.1N HCL), SIF (pH 6.8), and SIF (pH 7.4) buffer solutions for their dissolution rates

Table 2: Composition of guar gum coats used to cover the FC core tablets

Formulation	Guar gum (mg)	Microcrystalline cellulose (mg)	Magnesium stearate(2%) (mg)	Talc (1%) (mg)	HPMCK15M	Total coat weight (mg)
F1	150	92.5	5	2.5	-	250
F2	175	67.5	5	2.5	-	250
F3	200	42.5	5	2.5	-	250
F4	180	111	6	3	-	300
F5	210	81	6	3	-	300
F6	240	51	6	3	-	300
F7	210	129.5	7	3.5	-	350
F8	245	94.5	7	3.5	-	350
F9	280	59.5	7	3.5	-	350
F10	240	166.5	8	4	-	400
F11	280	121.5	8	4	-	400
F12	320	76.5	8	4	-	400
F13	270	166.5	9	4.5	-	450
F14	315	166.5	9	4.5	-	450
F15	360	166.5	9	4.5	-	450
F16	260	166.5	9	4.5	10	450
F17	250	166.5	9	4.5	20	450
F18	240	166.5	9	4.5	30	450
F19	230	166.5	9	4.5	40	450

Dissolution studies were performed using USP dissolution test apparatus II with 50 rpm at 37±0.5 ^{0}C). At various time intervals, a sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at 272 nm.

Drug release studies of compression coated FC tablets

The release of FC from compression coated tablets was carried out using USP basket-type dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 100 rpm, and a temperature of 37±0.5 ^{0}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 (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 simulated intestinal fluid (SIF, pH 6.8) was used for 19 h to mimic colonic pH conditions.

Drug release was measured from compression coated FC tablets. A sample of 5 ml was withdrawn and replaced with equal volume of fresh medium.Analyzed spectrophotometrically at 272 nm. All dissolution runs were performed in triplicate [24-35].

Drug release studies in the presence of rat caecal contents

Preparation of rat caecal contents

The susceptibility of guar gum coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 mL of SIF (pH 6.8) containing 4% w/v of rat caecal contents. The caecal contents were obtained from male albino rats after pre-treatment for 7 days with guar gum dispersion. Presence of 4% w/v rat caecal contents in SIF (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 conditions for *in vitro* evaluation of guar gum [36-41].Thirty minutes before the commencement of drug release studies, rats were killed by spinal traction. The abdomen was opened, the caecal were isolated, ligated at both ends, dissected and immediately transferred into SIF (pH 6.8), previously bubbled with CO_2.The caecal bags were opened; their contents were individually weighed, pooled and then suspended in SIF (pH 6.8) to give a final caecal dilution of 4% w/v. As the caecum is naturally anaerobic, all these operations were carried out under CO_2 [36-41].

Dissolution study procedure

***In vitro* drug release studies in artificial rat caecal content fluid**

The in vitro drug release studies were carried out using USP dissolution rate test Apparatus 1[44], 100rpm, 37^{0}C with slight modifications. A beaker (capacity 250ml) containing 100 ml of 4% rat ceacal content medium was immersed in the phosphate buffer pH 6.8 maintained in 1000-ml vessel, which in turn, was in the water bath of the apparatus. The tablet 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 ceacal content medium contained in 250 ml beaker. The drug release studies were carried out for 19 h (usual colonic transit time is 20–30 h) and 1 ml samples were taken at different time intervals without a prefilter and replaced with 1 ml of fresh SIF (pH 6.8) bubbled with CO_2. To the samples, 1 ml of ethanol was added to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes [36]. 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 fenoprofen calcium content at 272 nm as described above. The above study was carried out on F16 ,F17 ,F18 and F19 formulations.Control Study drug release studies were also conducted without rat caecal contents, in SIF (pH 6.8), by following the same experimental conditions as mentioned above.

***In vivo* X-ray studies**

X-ray imaging technique or Roentgenography was used to monitor tablets throughout the GI system. The inclusion of radio-opaque material into the solid dosage form enables it to be visualized by the use of X-rays. By incorporating barium sulphate into the pharmaceutical dosage forms, it is possible to follow the movement, location and integrity of the dosage form after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time points.

Three healthy human volunteers, male, with an age limit of 22-30 years and 50-70 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 K15M compression coated (F18 formulation) 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 were served with food; 2 h (breakfast) and 4 h (lunch) after the administration of the tablet

Evaluation of release rate kinetics

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Fourier transform infrared spectroscopy (FTIR)

The infrared spectra of FC, physical mixture of drug (fenoprofen calcium) and excipients were recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipients interactions. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (PERKIN ELMER BX-I SYSTEM). The resultant spectra were compared for any possible changes in the peaks of the spectra [33-42].

RESULTS AND DISCUSSION

Physical characterization of FC compression coated Tablets

The compression-coated tablets of different formulations were subjected to various evaluation tests such as uniformity of weight, drug content, hardness, friability, and *in vitro* dissolution. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of more than 250 mg is ± 5%.

The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percent of drug content was in the range of 96.4 to101.2%. All the formulation showed a high hardness value in the range of 5.0 to 5.8 kg/cm^2.Tablet hardness is not an absolute indicator of strength. In the present study, the percentage friability of all the batches formulation was below 1%, indicating that the friability is within the limits.

The physical properties of guar gum/HPMC compression coated tablets are given in Table 3. When HPMC in polymer mixture increased the crushing strength of coated tablets increased. HPMC provides mechanical strength to the tablets.

The thickness of the core tablet was 2mm and their crushing strength was checked at $3kg/cm^2$.

Thickness of the coat of compression-coated FC tablets, which contained 250.300,350,400 and 450 mg coat weights over the core tablets (diameter 9 mm and thickness 3.16±0.011mm), was measured using a digital caliper and results were shown in Table 3. The mean thickness of the compression coated tablets was found to be, 5.01±0.037, 5.11 ±0.032, 5.18 ±0.031, 5.24 ±0.037and 5.37 ±0.032mm for formulations containing 250,300,350,400 and 450 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 250,300,350,400 and 450 mg coat weight were 3.16±0.011, 3.28±0.014, 3.34±0.016, and 3.41±0.019 and 3.53±0.023 mm respectively [32-39].

Table 3: Physical properties of Fenoprofen calcium core and compression coated tablet

Formulation Code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Friability (%)	Thickness of Tablets (mm)	Coat Thickness (mm)	Drug Content (%)
Core	3.2±0.45	249.5±1.28	0.63	2.19±0.028	-	99.8
F1	5.3±0.54	249.2±2.56	0.54	5.01±0.037	3.16±0.011	97.9
F2	5.0±0.45	248.4±2.12	0.43	5.03±0.025	3.20±0.032	96.4
F3	5.1±0.47	249.6±2.54	0.54	5.06±0.051	3.18±0.019	101.2
F4	5.3±0.35	299.8±2.68	0.53	5.11 ±0.039	3.28±0.014	99.6
F5	5.4±0.64	298.3±2.86	0.56	5.14 ±0.034	3.29±0.016	101.2
F6	5.3±0.70	300.2±2.45	0.64	5.13 ±0.032	3.28±0.023	97.6
F7	5.4±0.18	351.5±2.43	0.62	5.18 ±0.031	3.34±0.016	97.2
F8	5.0±0.46	350.7±2.02	0.48	5.21 ±0.042	3.39±0.032	101.9
F9	5.1±0.36	351.1±2.21	0.47	5.20 ±0.056	3.32±0.027	100.6
F10	5.2±0.41	400.7±2.24	0.53	5.24 ±0.037	3.41±0.019	99.0
F11	4.9±0.38	401.3±2.18	0.61	5.27 ±0.039	3.43±0.018	99.2
F12	5.3±0.52	400.0±2.36	0.75	5.24 ±0.030	3.42±0.025	98.0
F13	5.0±0.74	451.0±2.02	0.54	5.37 ±0.032	3.53±0.023	98.6
F14	5.4±0.43	450.5±2.56	0.56	5.41 ±0.037	3.57±0.032	99.0
F15	5.2±0.18	451.3±1.28	0.52	5.45 ±0.036	3.58±0.024	99.1
F16	5.8±0.38	453.1±2.28	0.56	5.42 ±0.042	3.51±0.027	99.0
F17	5.1±0.28	452.3±1.68	0.59	5.39 ±0.091	3.59±0.022	101.1
F18	5.2±0.78	451.6±1.38	0.62	5.45 ±0.032	3.54±0.023	100.1
F19	5.4±0.18	450.3±2.28	0.59	5.37 ±0.047	3.57±0.031	98.0

Disintegration results of FC core tablets

The prepared core tablets were disintegrates rapidly once they reach the colon, digested by the resident microflora of colon. Disintegration time of the core tablets was found to be 53 sec, this may be due to the presence of the sodoium starch glycolate in the core tablet [32].

Dissolution results of compression coated FC tablets

The cumulative mean percent of FC released from tablets coated with 250 mg coat weights of formulations containing varying amounts of guar gum (from F1 to F3) was found to vary from 28.2±1.55 to 35.4±2.03 after 5 h of testing in simulated gastric and intestinal fluids (Figure 2).

The percent of drug released from tablets coated with 300 mg coat weights of formulations contain varying amounts of guar gum (from F4 to F6) was found to vary from 24.7±1.33 to 38.3±2.11 (Figure 2), 350 mg coat weights of formulations contain varying amounts of guar gum (from F7 to F9) was found to vary from15.2±3.14 to 16.3±2.34 (Figure 3). 400 mg coat weights of formulations contain varying amounts of guar gum (from F10 to F12) was found to vary from15.7±0.59 to 20.8±1.57 (Figure 3). 450 mg coat weights of formulations containing varying amounts of guar gum (from F13 to F15) was found to vary from 6.6±1.09 to 11.7±0.78 (Figure 4) after 5 h of testing [34].

Guar gum in the form of coat was capable of protecting the drug from being released completely in the physiological environment of stomach and small intestine. However the tablet with coat formulation F1,F2,F3 and F4,F5,F6 and F7,F8,F9 and F10,F11,F12 was drug released within the 0.1N HCL 2hr and this may be due to lesser gum content (250,300,350,400mg) of the coat, which was unable to remain intact, and failed to protect the drug core from being released. This indicated that gum coat would not permit the release of the bulk of the drug until the coat was broken. The aim of drug delivery system targeted to the colon is not only to protect the drug from being released in the physiological environment of stomach and intestine, but also to release the drug in the colon after enzymatic degradation of colonic bacteria.

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 [37].

To assess the integrity of the coats, the coat weight was further increased for remain intact with the coat weight of 450mg containing formulations F13, F14, F15. Dissolution is continued for 5hr with coat weight of 450mg containing formulations released small amount of drug, drug release was further continued for 19 hr by replacing the dissolution medium with pH 6.8 phosphate buffer. The Optimized formulations are then compressed with different amounts of combination of guar gum and HPMC K15M. Dissolution is continued for 5hr then drug release was further continued for 19 hr containing pH 6.8 phosphate buffer. The cumulative mean percent drug released from F16, F17, F18, F19 formulation containing different amounts of combination of guar gum and HPMC K15M was found to vary from 0.3±0.03 to 1.3±0.17 after 5 hr dissolution testing (Figure 4).Cumulative mean percentage release of the drug after 24hr 6.4±0.30 to 9.4±0.26 (Figure 4) respectively. This indicates that a minimal amount of the drug is released from the guar gum/HPMC K15M 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 [40].

To estimate the integrity of the coats, the drug release studies were further continued for 19 hr 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 F16, F17, F18, and F19 was between 0.3±0.03 to 1.3±0.17 and the coats were intact. This indicates that the guar 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 F1, F2 and F3 was found between 72.3±2.01 to 82.8±3.54 after 24hr study. The percent drug release for the formulations from F4,F5,F6 and F7,F8,F9 and F10,F11,F12 and F13,F14,F15 was found between 51.6±2.58 to 58.0±4.13 and 37.6±4.69 to 41.7±3.95 and 25.8±2.32 to 37.6±2.38 and 26.9±1.46 to 40.2±2.62 after 24h study.

However, the tablets with coat formulation F1 to F12 were found to release 8.2±1.43 to 35.9±2.65 % respectively after 5hr and 24.1±1.98 to 56.4±2.76 % after 24 hr 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 F1 to F12 were not studied further in rat caecal contents. Even though F16, F17, F18, and F19 formulation releasing small amount (6.4±0.30 to 9.4±0.26) of drug after 24 hr, it was further studied in 4% caecal contents to know the effect of coat thickness (450 mg coat weight) compared with 2% caecal contents [40-45].

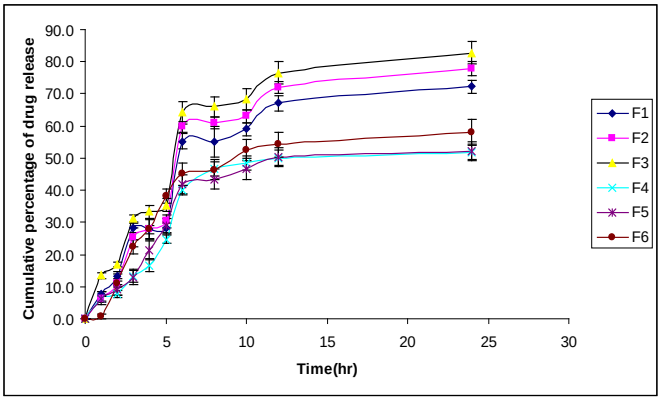


Fig 2: Dissolution profiles of F1-F6 formulations containing different propotions of guar gum (250&300 mg coat weight).

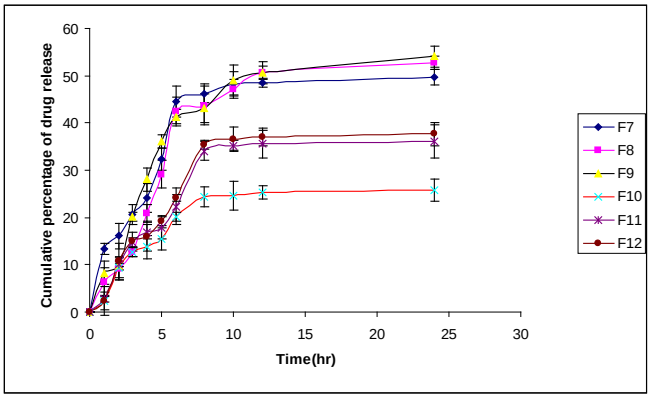


Fig 3: Dissolution profiles of F7-F12 formulations containing different propotions of guar gum (350&400 mg coat weight).

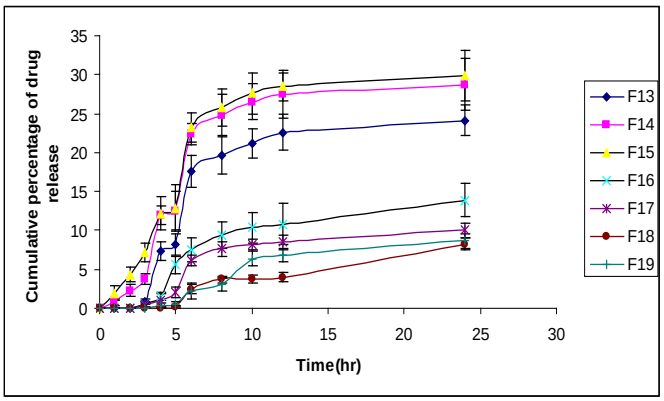


Fig 4: Dissolution profiles of F13-F19 formulations containing guar gum (450mg coat weight).

Dissolution results of compression coated FC 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, the in-vitro drug release studies were carried out in pH 6.8 Phosphate buffer containing 4% w/v and 2% w/v of rat caecal

contents. Optimised F16, F17, F18, F19 formulations were continued Dissolution for 5hr then drug release was further continued for 19 hr by replacing the dissolution medium with pH 6.8 containing 4% w/v and 2% w/v of rat caecal contents. The percent of FC released from the coated tablets. The cumulative mean percent drug released from F16, F17, F18, F19 formulation containing different amounts of combination of guar gum and HPMC K15M with 4% of rat caecal contents was found to vary from 0.1±0.11 to 4.7±1.11 after 5 hr dissolution testing (Table 26).Cumulative mean percentage release of the drug after 24 hr found to vary from 73.3±2.54 to 98.7±2.44 (Figure 6) respectively. The cumulative mean percent drug released from F16, F17, F18, F19 formulation containing different amounts of combination of guar gum and HPMC K15M without rat caecal contents was found to vary from 0.1±0.76 to 0.9±0.78 after 5 hr dissolution testing (Figure 6).Cumulative mean percentage release of the drug after 24 hr found to vary from 54.7±2.98 to 61.5±3.21 (Figure 6) respectively. The cumulative mean percent drug released from the formulations containing the coat weight of 450 mg with different amounts of combination of guar gum and HPMC K15M formulations F16, F17, F18, F19 are released about high amount of drug in 4% of rat caecal contents than with 2% of rat caecal contents and releasing small amount of drug after 24hr without caecal contents The formulation F18 showed increased amount of drug released in 24 hr than F16, F17, F19 and the cumulative mean percentage release of the drug at 24 hr was 98.7 ± 2.44% [24,33,36]

The release rate showed that the coat formulation F18 produced better release of FC. About 98.7% of the drug was released in the colon after protecting drug from the stomach and small intestine. It was also evident from the results of drug release the presence and absence of rat caecal contents that the maximum amount of drug release occurred by the degradation of the coat material by the enzymes present in the caecal content. Even though the in-vitro studies had revealed that the better release was obtained from the coat formulation F18, the in-vivo studies using human volunteers was ultimate requirement to establish their credibility. The pharmacokinetic parameter showed that the drug was released only after 5 hr indicating that the coat formulation (F16, F17, F18 and F19) has a capability of preventing the drug release in the stomach and small intestine [16, 27, 36].

In-vitro drug release studies and in-vivo studies using the formulation F18 clearly indicated that the guar gum as a coat material applied over core tablet was capable of protecting the drug from being released in the physiological environment of stomach, small intestine and susceptible to colonic bacterial enzymatic action with resultant drug release in the colon. Thus, the study clearly indicated that the guar gum was a potential colon specific drug delivery carrier.

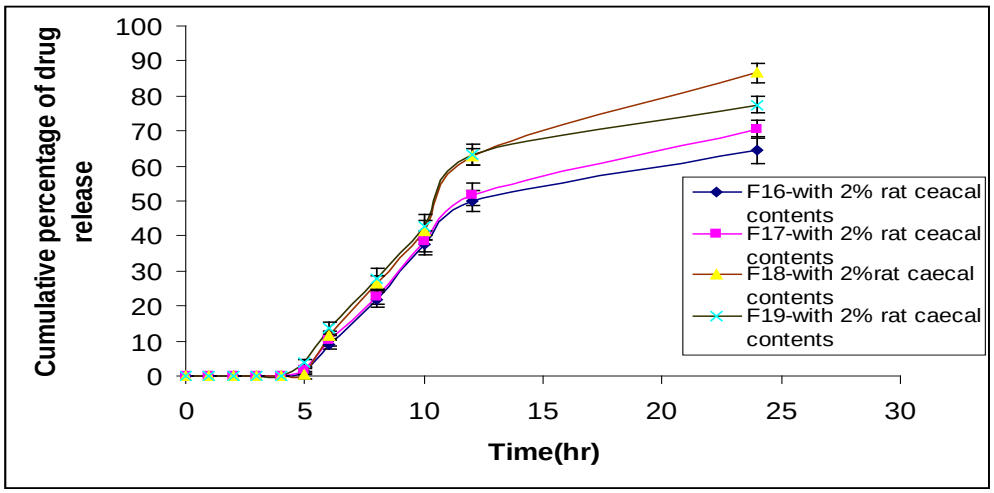


Figure 5: Dissolution profiles of F13-F19 formulations containing guar gum (450mg coat weight) in the 2% rat ceacal contents.

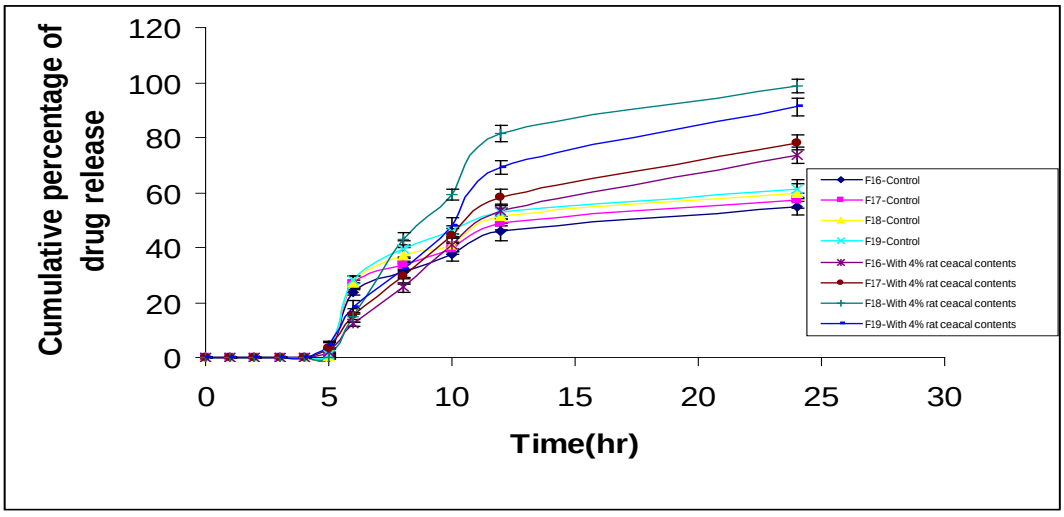


Fig 6: Dissolution profiles of F13-F19 formulations containing guar gum (450mg coat weight) in the 4% rat ceacal contents.

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, tortucity 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 K15M polymer. The percent drug release from F18 formulation at the end of 24 hr study in presence of 4% rat caecal content was found to be 98.7±2.44 (Figure 16). Better controlled release was observed in the system containing Guar gum and HPMC K15M [23, 24, 41].

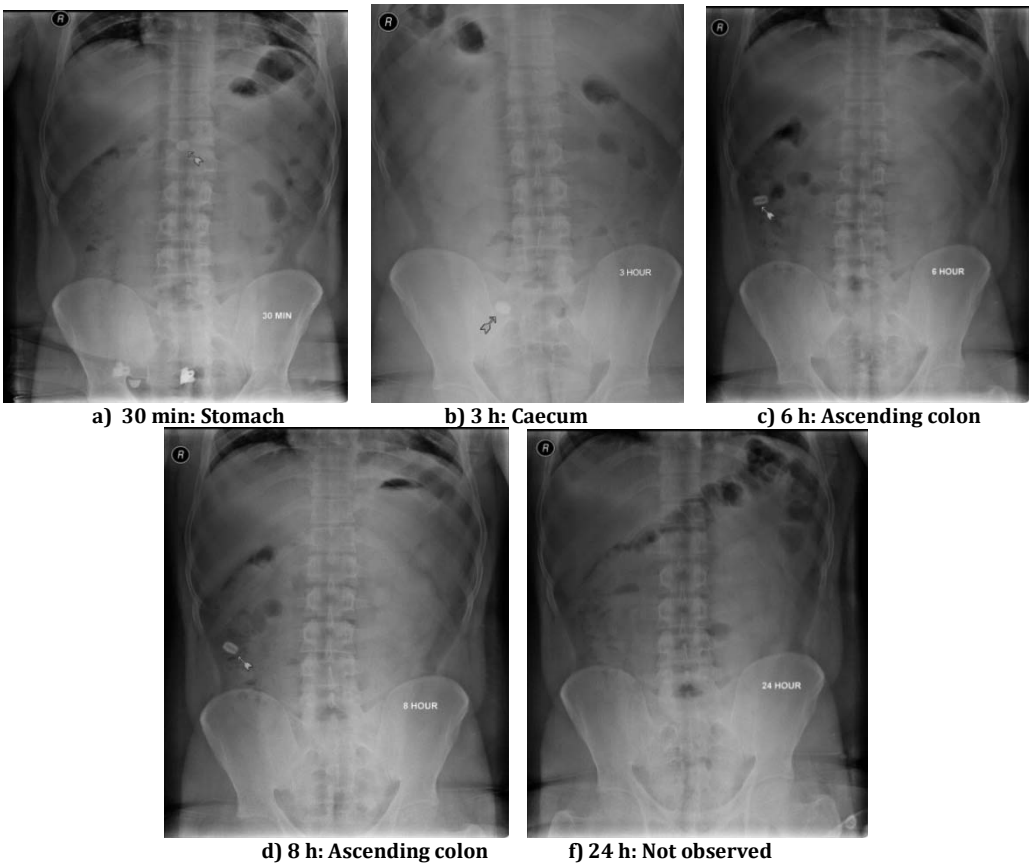
It is evident from the results of the drug release studies in the presence and absence of rat caecal contents that the drug release occurred by the degradation of guar gum coats by the enzymes present in the caecal matter.

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. The F18 formulation was considered better among other formulations to produce colon specific drug delivery of FC and hence these were subjected to in-vivo studies [23].

X-ray studies

X-ray studies were carried out on the F18 formulation 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 24 and the X-ray images of tablet throughout the GI system are shown in Figure 7.

The in-vivo results showed that the tablets (F18 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 hr, small intestinal transit times of 1.8–8.5 hr and colonic arrival time of 3.2–9.8 hr while evaluating pectin as a compression coat for colonic drug delivery, using gamma scintigraphy [23].



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

d) 8 h: Ascending colon **f) 24 h: Not observed**

Fig 7: The localization of the tablet in the gastrointestinal tract in subject.

Kinetic results

The mechanism and kinetics of drug release of FC is determined by the application of korsmeyer-peppas model, higuchi's model, zero order and first order kinetics as shown in Table 29. Most of the tablet formulation follows the zero order release as their r^2 values are between 0.9857 and 0.9946.

The mechanisms of drug release are non-fickian diffusion (super case-II), since they fitted well with Korsmeyer–Peppas models as their r^2 values in the range of 0.9786–0.9876 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: Drug release kinetics of Fenoprofen Colon Specific Drug Delivery Systems

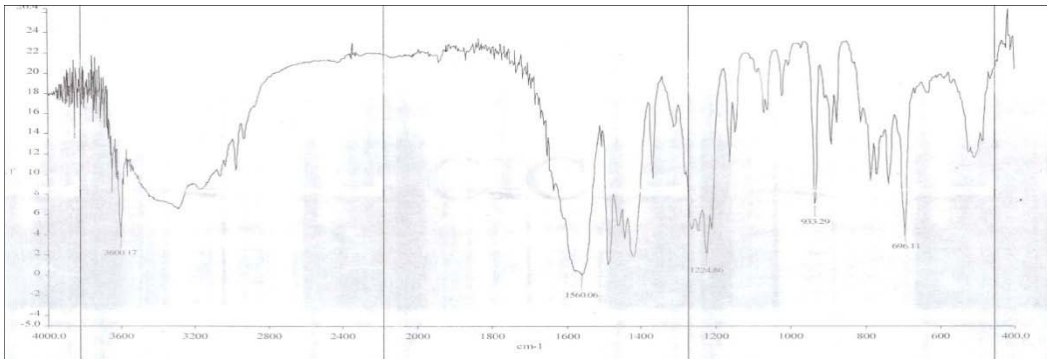
Formulation Code	Zero order	First order	Higuchi	Korsmeyer & Peppas	Peppas (n)
F-16	0.9894	0.9876	0.9754	0.9876	1.2314
F-17	0.9857	0.9768	0.9456	0.9819	1.2302
F-18	0.9876	0.9946	0.9417	0.9786	1.1986
F-19	0.9946	0.9785	0.9456	0.9798	1.1902

Fourier transforms spectroscopy studies

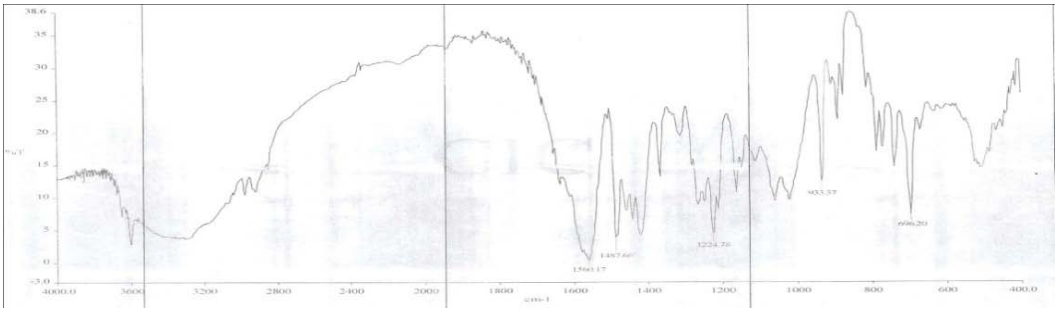
The IR spectra of pure FC drug showed the characteristic absorption bands are as follows: The FTIR spectra have been recorded using Perkin Elmer Spectrum one FTIR over the region 4000-400cm^{-1}The bands exhibited in the region around 3000 cm^{-1}can be immediately assigned to be due to aromatic C-H stretchings. In this view, the vibrational frequencies exhibited at 3600 cm^{-1}.The carbonyl group exhibits a strong absorption band due to C=O stretching vibration and is observed in the region1560 cm^{-1}

A number of C-H in plane deformation bands occur in region 1290-1000 cm^{-1}, the bands being sharp but weak to medium intensity. However, these bands are not normally of importance for interpretation purpose although they can be used. The aromatic C-H out of plane deformation bands occurs below 700 cm^{-1}. The bending vibrations are generally found at lower wave numbers. The frequencies observed at in the FTIR spectra of 1224.86, 933.23 and 696.11 cm^{-1} in Figure 8a.

No drug-polymer interaction was observed in the FT-IR spectra of the powder mixture of optimized formulation (Figure 18b) since the absorption peaks of the drug still could be detected in the mixture [34].



a) FC pure drug



b) Physical mixture of optimized formula

Fig 8: FTIR Spectra's of F18 Formulation. a) FC pure drug, b) Physical mixture of optimized formula

CONCLUSION

It was concluded that Formulation F18 was better formulation as it passed all specifications in limits for angle of repose, hardness test, friability test, content uniformity test as well as weight variation test. The core tablets compression-coated with guar gum and HPMC K15M as a coat material and released less than 1% of drug in the physiological environment of stomach and small intestine and released 98% of the drug in the target area i.e. physiological environment of colon. The in-vitro drug release studies and in-vivo X-ray studies indicated that formulation F18 was a promising system to provide targeting of FC to the colon. The release pattern of the above formulations was best fitted to korsmeyer-peppas model and zero-order model. The presence of guar gum in the coat reduces the initial swelling of HPMC K15M which retards the drug release in physiological environment of upper part of gastrointestinal tract and ensures complete release of drug in the colon due to its microbial degradation.FT-IR spectral studies showed that there is no interaction between the drug and the excipients.

Thus,the tablets containing optimum proportion of guar gum and HPMC K15M is most likely to target FC to the colon without being released significantly in stomach and small intestine.

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