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FORMULATION AND EVALUATION OF COMPRESSION COATED MELOXICAM TABLETS FOR COLON DRUG DELIVERY

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ABSTRACT

A novel dual tablet formulation for oral administration using xanthan gum as the carrier and meloxicam as a model drug has been investigated for colon- specific drug delivery using invitro methods. The tablets were evaluated for hardness, thickness, drug content uniformity, and were subjected to invitro drug release studies under conditions mimicking mouth to colon transit and the results of which shown that xanthan gum protects the drug from being released completely in the physiological environment of stomach and small intestine. Studies in pH7.4 phosphate buffer saline (PBS) containing rat caecal contents have demonstrated the susceptibility of xanthan gum to the colonic bacteria enzyme action with consequent drug release. The pretreatment of rats orally with 1ml of 2%w/v aqueous dispersion of xanthan gum for 3 days induced enzymes specifically acting on xanthan gum thereby increasing drug release. A further increase in drug release were observed with rat caecal contents obtained after 7 days of pretreatment, because of microbial degradation. Combination of xanthan gum and HPMC provided better protection of drug containing core, showing increased release lag time and controlled release rate. Release of drug from compression coated tablets began after a time delay as a result of hydrogel swelling/retarding for most of the formulations studied. The in-vivo X-ray studies showed that, the tablets reached the colon; not being disintegrated in the upper region of the GI system in all subjects. The FTIR data indicated no possible interaction between meloxicam and carriers.

KEYWORDS

Xanthan gum, meloxicam, colon targeting, in-vitro dissolution, compression coating

1. INTRODUCTION

Oral administration of drugs by conventional pharmaceutical formulations is the most convenient and effective delivery system and is preferred over parenteral medication, due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form.[1]

Drug targeting to colon is highly desirable in a variety of colonic disorders such as inflammatory bowel diseases (IBD), infectious diseases and colon cancer. Colon is also found to be a promising site for systemic absorption of peptide and protein drugs because of less hostile environment prevailing in the colon compared with small intestine and stomach[2][3]. The different approaches for targeting orally administered drugs to the colon include coating with pH-dependent polymers, design of timed-release dosage forms and utilization of carriers that are degraded exclusively by colonic bacteria[4][5] .

Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets. As the dissolution medium or biological fluids penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. The widely used polymers for sustaining the drug delivery are HPMC, Na CMC, chitosan, HPC, MC, Eudragits, natural gums, etc. In the present investigation, it is planned to use

Xanthan gum, a naturally occurring and abundantly available polysaccharide, as a release retardant carrier in the design of compression coated tablets for meloxicam (model drug).

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-ve bacterium Xanthomonas campestris. It has a cellulose backbone of D-glucose linked β-D-mannose–(1,4)-β-D-glucuronic acid-(1,2)-α-D-mannose. It has been widely studied and used as tablet excipient to increase the drug rate of delivery. The porous structure, facilitating the diffusion of both the substrate and the product of an enzymatic reaction, appears to be suitable for enzyme immobilization, and also for loading bioactive substances for pharmaceutical formulations.

Meloxicam, an enolic acid- type NSAID, is used in the treatment of rheumatoid arthritis, osteoarthritis, and other joint diseases. The chemotherapy of meloxicam on colorectal polyps and/ or cancer was independent of its cyclooxygenase inhibitory profile, and potential mechanism for its action might be due to the induction of apoptosis and inhibition of proliferation[6]. Goldman et al., showed that the growth of HCA-7 colorectal tumour xenografts in nude mice was significantly inhibited by meloxicam after 4 weeks of treatment. Meloxicam also could significantly suppress experimental colitis induced by trinitrobenzenesulphonic acid or acetic acid in male Sprague-Dauley rats[7]. Therefore, meloxicam has been regarded as a potential drug for the prevention and treatment of colorectal polyps and or cancer [8].

In this investigation, xanthan gum/ HPMC in the form of compression coated tablets has been evaluated for its ability to remain intact in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit using meloxicam as a model drug. The susceptibility of xanthan gum to undergo biodegradation in colon is assessed by conducting in-vitro drug release studies in the presence of rat caecal contents in pH 7.4 (PBS). This research paper also illustrates the effect of concentration of caecal matter induction in dissolution fluids and on the degradation of xanthum gum consequent drug release [9].

2 MATERIALS AND METHODS

2.1 Materials

Meloxicam was a kind gift sample from Apex Health Care Pvt. Ltd, Ankaleshwar Xanthum gum was purchased from Zeal chemicals , MCC(Avicel,typep105) was a kind gift sample from Dr. Reddy's laboratories, Hyderabad., Magnesium stearate and talc was purchased from S.D Fine chemical Pvt.Ltd, Mumbai. Crosscarmellose sodium was purchased from Amishi Drugs and chemicals Ahmedabad, HPMCK4M was a kind gift sample from Dr. Reddy's laboratories, Hyderabad.

2.2 Preparation of Compression Coated tablets

2.2.1 Preparation of Core tablets

Meloxicam, a poor water soluble drug, was chosen as a model drug to evaluate xanthum gum for its colon specific drug delivery and to differentiate the drug release by disintegration of coat. Each core tablet (average weight 100mg) for invitro drug release studies consisted of meloxicam (15mg), microcrystalline cellulose (MCC, 78mg) dried cross carmellose sodium (4mg), talc (2mg) and Magnesium Stearate (1mg). Cross carmellose sodium was incorporated to obtain fast disintegration of tablets (disintegration time <1min) of meloxicam (**Table 1**).

Table 1. Composition of core tablet

Ingredients	Quantity (mg)
Meloxicam	15
Microcrystalline cellulose	78
Crosscarmellose sodium	4
Talc	2
Magnesium stearate	1
Total Weight	100

All the materials were accurately weighed, mixed and passed through a mesh (250µm/sieve no.60) to ensure complete mixing. The tablets were prepared by compressing the through mixed materials using 7mm round, flat and plain punches on a 16-station tablet machine (Cadmach, India). The core tablets were tested for hardness content, uniformity, friablility and disintegration. The thickness of the core tablet was 2.08±0.008mm and their crushing strength was 2.5kg/cm$^{2.}$

Table 2. Composition of different quantities of Xanthan gum and HPMC coats used to cover meloxicam core tablets

Ingredients (mg)	Xanthan gum	HPMC	MCC	Talc	Magnesium stearate	Total weight
F1	30	-	65	3	2	100
F2	40	-	55	3	2	100
F3	50	-	45	3	2	100
F4	60	-	35	3	2	100
F5	70	-	25	3	2	100
F6	45	-	100	3	2	150
F7	60	-	85	3	2	150
F8	75	-	70	3	2	150
F9	90	-	55	3	2	150
F10	105	-	40	3	2	150
F11	120	-	25	3	2	150
F12	60	-	135	3	2	200
F13	80	-	115	3	2	200
F14	100	-	95	3	2	200
F15	120	-	75	3	2	200
F16	140	-	55	3	2	200
F17	95	10	40	3	2	150
F18	85	20	40	3	2	150
F19	75	30	40	3	2	150
F20	65	40	40	3	2	150

HPMC= hydroxy propyl methyl cellulose; MCC=microcrystalline cellulose

2.2.2 Preparation of Compression Coated tablets

The above meloxicam core tablets were compression coated with different quantities (**Table 2**) of coating material containing 100,150,200mg of xanthum gum. MCC was included in the coat formulations to impart enough hardness. Half the quantity of the

coating material was placed in the die cavity the core tablet was carefully positioned in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed around the core using 9mm round, flat and plain punches. The crushing strength of the compression coated tablets was found to be in the range of 4.5-5.5kg/cm2. The compression coated tablets were tested for hardness, drug content and in-vitro drug release characteristics with a suitable number of tablets for each test. The hardness of the compression coated tablets was determined by using Monsanto hardness tester. HPMC was incorporated in the coat formulations in order to increase the mechanical strength of the tablet.

2.3 Physical characterization of tablets

The tablets were characterized immediately after preparation. 20 tablets were tested for weight variation, thickness, and friability. The mean values were calculated. The disintegration time of the tablets was determined using the compendial USP method with the disintegrates apparatus.in which 6 tablets were evaluated from each formulation for disintegration test. The dissolution apparatus was operated using simulated gastric fluid (SGF) without enzyme for 1h. Then the dissolution medium was replaced with simulated intestinal fluid (SIF) without enzyme.

2.3.1 Determination of drug content

Meloxicam core and compression coated tablets both were tested for their drug content. The tablets were finely powdered, 100mg of powder was accurately weighed and transferred to 100ml of volumetric flasks containing approximately 50ml of methanol and the volume was made up with pH7.4 phosphate buffer and allowed to stand for 24h with intermittent sonication to ensure complete solubility of drug. Then the samples were allowed to centrifuge, and the supernatant was collected and determined for drug content at 362nm.

2.4 Drug release studies in presence of rat caecal contents

To assess the susceptibility of xanthan gum being acted upon by the colonic bacteria, drug release studies were carried out in the presence of rat caecal contents because of the similarity with human intestinal micro flora [10]. In order to induce enzymes specifically acting on xanthan gum in the caecum, male albino rats (supplied by Mahavir Enterprise, Hyderabad, India) weighing 150-200g and maintained on normal diet were incubated with Teflon tubing and 1ml of 2% w/v dispersion of xanthumgum in H_20 was administered directly into the stomach.

The tubing was removed and this treatment was continued for 7 days in one set of rats and one set of rats were kept without induction of Gum. Forty – five minutes before the commencement of drug release studies 5 rats were killed by spinal traction the abdomen were opened the caecai were isolated, ligated at both ends cut loose and immediately transferred into pH 7.4 PBS, previously bubbled with CO_2. The caecal bags were opened their contents were individually weighed pooled and then suspended in PBS to give a final caecal dilution of 2% w/v and 4%w/v respectively. As the caecum is naturally anaerobic all these operations were carried out under $C0_2$. Initially the drug release studies were carried out using USP dissolution rate test apparatus (USPI, 100rpm, 37˚C). The tablets were tested for drug release for 2h in SGF without enzyme (pH1.2) followed by mixture of SGF and SIF (pH 4.5) and tested for drug release for 3h as the average small intestinal transit time is about 3h. At the end of time periods, samples each of 5ml were taken and were measured at 362nm using a double beam UV spectrophotometer (Systronic) to find the amount of meloxicam released from the tablets. Then the drug release studies were

carried out in USP dissolution test apparatus (apparatus 1, 100 rpm, 37±0.5 °C) with slight modification. A beaker (capacity 250 mL) 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 tablets were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal contents.

The experiment was carried out with continuous $C0_2$ supply into the beakers to simulate anaerobic environment of the caecum. The drug release studies were continued for 24h (usual colonic transit time is 20–30 h).At different time intervals, 1ml sample was withdrawn and replaced with 1ml of fresh PBS bubbled and CO_2 and the experiment was continued upto 24h. One milliliter of methanol was added to the samples to ensure solubility of finely suspended drug particles released due to the erosion of xanthum gum by caecal enzymes and the volume was made up to 10ml with PBS and the samples was analyzed for meloxicam content at 362nm using a double beam UV spectrophotometer. The drug release studies was also carried out with 2% w/v of caecal contents obtained without pre-treatment of xanthum gum for 7 days. The study protocol involving the use of rat caecal contents was approved by the Ethics Committee, faculty of SPIPS, Warangal, A.P, and India.

2.5 In-vivo studies

X-ray imaging technique or Roentgenography was used to monitor the transit of 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.

One healthy human volunteer, male, with an age limit of 22 years and 60 kg body weight, was participated in vivo studies. He was non-alcoholic, non-smoker and has not taken any drugs. The purpose of the investigation was fully explained and volunteer had given his written consent. The subject ingested barium sulphate containing xanthan gum/HPMC K4M compression coated (F19 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 the subject. The volunteer was served with food; 2 h (breakfast) and 4 h (lunch) after the administration of the tablet [11].

2.6 Kinetics of drug release

The cumulative amount of meloxicam released form compression coated tablets at different time intervals was fitted to zero-order kinetics using the least squares method of analysis to find out whether the drug release from the formulations is providing a constant drug release. The correlation coefficient between the time and the cumulative amount of drug release was also calculated to find out the fit of the data to zero-order kinetics.

The fit of the data to first-order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug release from the formulations.

The data were fitted to the model developed by [12] in order to determine the drug release mechanism from the formulations. The cumulative percent of drug released from the formulations was plotted against time on log scale and analyzed for linearity using the least squares method.

2.7 Statistical analysis

The cumulative percent of meloxicam released from xanthan gum compression coated tablets

(n=3) in the dissolution medium at 24h, with and without rat caecal contents was compared and the statistical significance was tested using the student's t-test. A value of P<0.01 was considered statistically significant.

2.8 Fourier transforms infrared spectroscopy (FTIR)

The infrared spectra of meloxicam, physical mixture of drug (meloxicam) 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.

3. RESULTS AND DISCUSSION

3.1 Physical characterization of tablets

The tablets were characterized immediately after preparation. 20 tablets were tested for weight (247.3±0.08), thickness (2.08±0.008), and friability (0.6%). The mean values were calculated. The disintegration time of the tablets was determined using the compendial USP method with the disintegrates apparatus (35Sec).6 tablets were evaluated from each formulation and the results was shown in **Table 3**. The apparatus was operated using simulated gastric fluid (SGF) without enzyme for 1h. Then the dissolution medium was replaced with simulated intestinal fluid (SIF) without enzyme.

Table 3. Physical properties of meloxicam core and compression coated tablets

Formulation code	Hardness (kg/cm^2)	Deviation in weight variation (mg)	Friability (%)	Drugcontent (%)
Core	2.5±0.64	95.6±0.05	0.34	99.2.±1.76
F1	6.0±0.76	199.5±0.06	0.52	103.2±0.35
F2	4.6±0.70	252.9±0.06	0.64	100.6±1.74
F3	5.5±0.79	296.3±0.06	0.60	99.5±0.71
F4	5.5±0.86	255.4±0.09	0.69	103.2±0.86

All the tablet formulations were evaluated from the point of the view of the physical properties and their in-vitro release.

Drug content: The mean percent drug content of the meloxicam core tablets was found to be 99.2±1.76 of the labeled amount indicating uniformity of drug content in the formulation.

Core tablets: The core tablets of meloxicam were prepared by direct compression of the core mixture prepared. Cross carmellose sodium was added to the tablet core in order to ensure the core disintegrates rapidly. This would allow the core tablets to disintegrate rapidly once the coat material is digested by the resident microflora of the colon. The hardness of the core tablets was found to be in the range of 2.5-0.64kg/cm^2. These tablets were found to comply with friability test since the weight loss found to be less than 0.6%. The tablet thickness was found to be 2.08±0.008mm. The disintegration time of the core tablets was found to be 35sec.This may be due to the presence of Cross carmellose sodium in these core tablets.

Compression coated tablets: The tablets were compression coated using different coat materials of varying polymer ratios. The hardness of the tablets was found to be in the range of 4.5-5kg/cm2.The thickness of compression coat varied from (4.54±0.008) mm. it was found that crushing strength of compression coated tablets was dependent on xanthan gum/HPMC polymer ratio. As the HPMC ratio in polymer mixture was increased,

the crushing strength of coated tablets was also found to be increased. It appears that HPMC provides mechanical strength of xanthan gum tablets.[13]

3.2 In-vitro drug release studies

For drug delivery systems designed for colon targeting, it is desirable that the system remains intact and shows minimal drug release in the physiological environment of the stomach and the small intestine and triggers drug release in the tracts of the colon. All the formulations were found swollen and retained their physical integrity till the end of the 5-h dissolution study except that the edges of the swollen formulations were rounded off due to slight erosion of swollen gum.

In the drug release studies in PBS without rat caecal contents at pH7.4, only 25.0±1.65%of drug release after 24h (usual colonic transit time is 20-30h) of testing was found. At the end of the experiment, the tablet retained its shape indicating that the drug release is by matrix diffusion controlled mechanism and not by erosion. The presence of rat caecal contents in the dissolution medium resulted in improved drug release at different time periods when compared to control. The percent drug released after 24h of testing was 82.6±(2.59) with 2%w/v caecal matter whereas it was only 25.0±(1.65)in the absence of caecal matter indicating that polysaccharide are present in the caecal matter that metabolise xanthan gum was shown in **Figure I**. As complete drug release was not achieved with 2%w/v, hence the level of caecal matter in the dissolution medium was increased to 4%w/v and the percent drug released after 24h of testing was found to be 95.0±2.99.

The amount of drug released in the study was found to increase with an increase in the quantity of rat caecal contents in the disslolution medium.

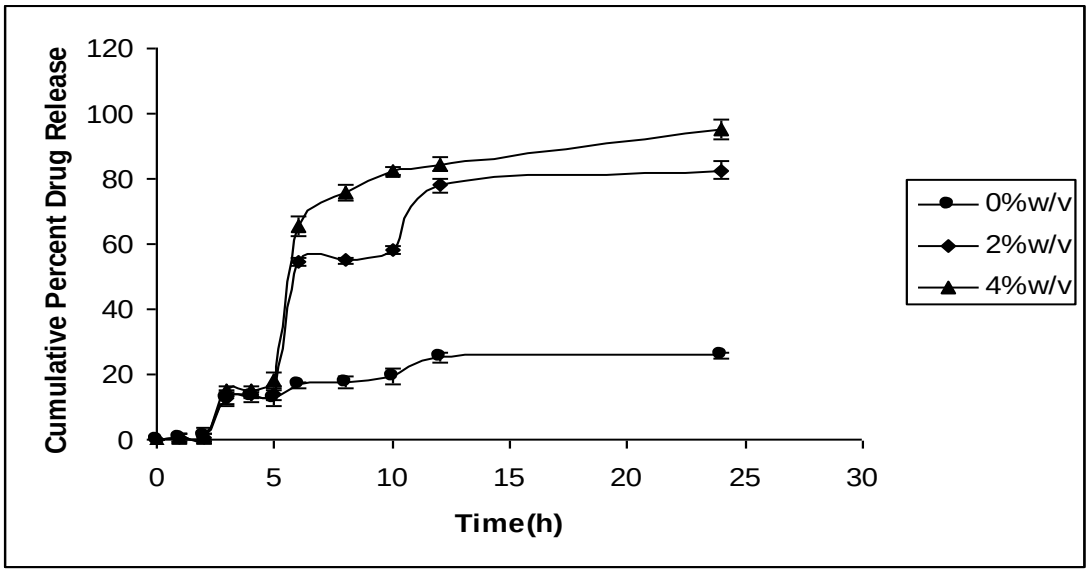


Figure I. Percent drug released of optimized formulation with and without rat caecal contents

Drug release studies were also conducted in 2%w/v rat caecal contents without xanthan gum pre-treatment and were compared with 2%w/v caecal contents which followed pre-treatment of xanthan gum for 7 days. The percent drug released after 24h testing was 65.5±(1.52) without pre-treatment and was 82.6±(1.59)with pre-treatment of xanthan gum was shown in **FigureII**. This is because of

absence of gum for metabolism with the caecal enzymes of colonic bacteria.

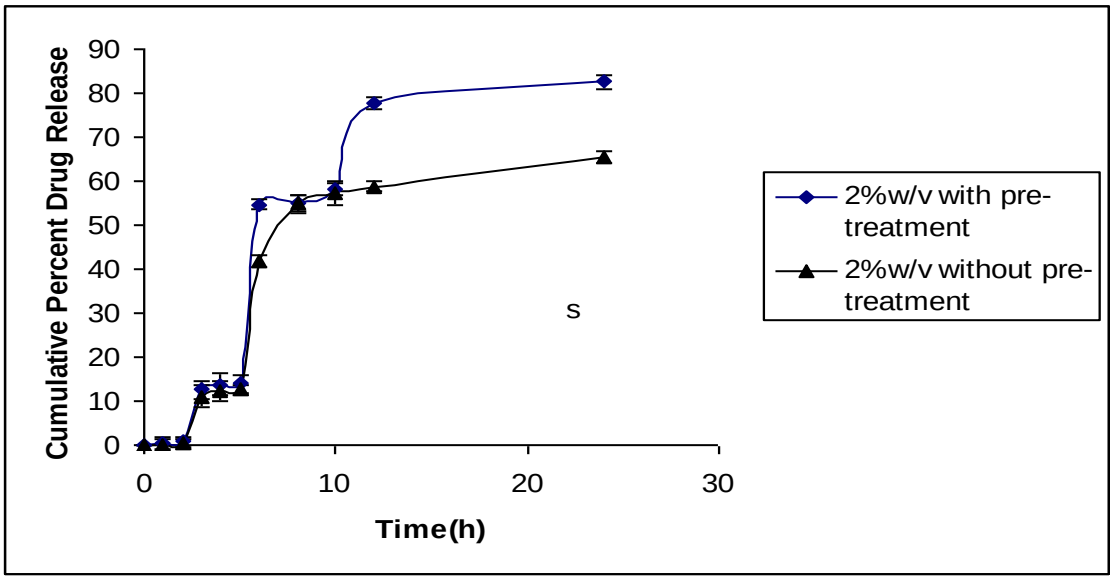


Figure II. Percent drug released of optimized formulation with and without pre-treatment of xanthan gum dispersion

3.3 X-ray studies

X-ray studies were carried out on the optimised formulation tablets, in order to observe the transit of compression coated tablets through 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 the subject. The transit time of the tablets throughout the GI system was found to be variable. The position of tablets at different time points and the X-ray images of tablet throughout the GI system are shown in **Figure III**.

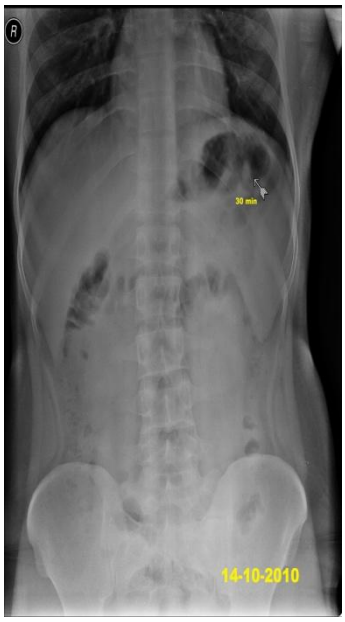
The in vivo results indicate that the tablet (optimized formulation) reached the colon without disintegrating in the upper region of the GI system in the subject. From the abdominal radiographs, taken at different time points, it is evident that the tablets entered the colon; at different times varying between 3-6h for all volunteers after tablet administration. The X-ray images showed that the tablets disintegrated slowly in the colon after reaching it. These results are in agreement with the results of Ashford et al., (1993) [14], 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 xanthan gum as a compression coat for colonic drug delivery, using gamma scintigraphy.

3.4 FTIR Studies

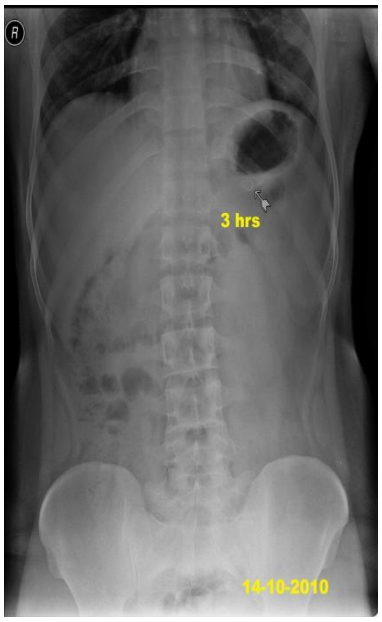
FTIR spectra of meloxicam showed a distinct peak of teritiary amine at 3291 cm^{-1}, 1620 cm^{-1} and amidic keto group at 1580 cm^{-1}.

FTIR spectra of xanthan gum showed distinct peaks of C=O stretching at 1599 cm^{-1}, and C-H stetching at 2883.4 cm^{-1}, 2847cm^{-1} , and 2942cm^{-1}.

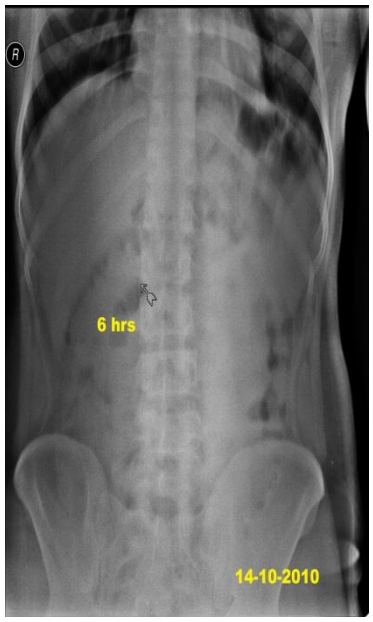
No drug polymer interaction was observed in the FTIR spectra of the powder mixture of optimized formulation (**Figure IV**) since the absorption peaks of the drug still could be detected in the mixture.



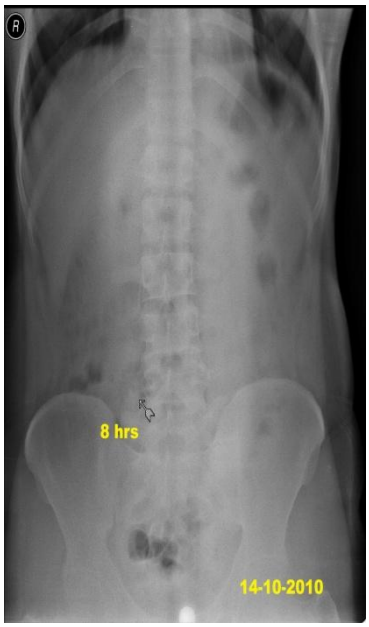
a) 30 min: Stomach



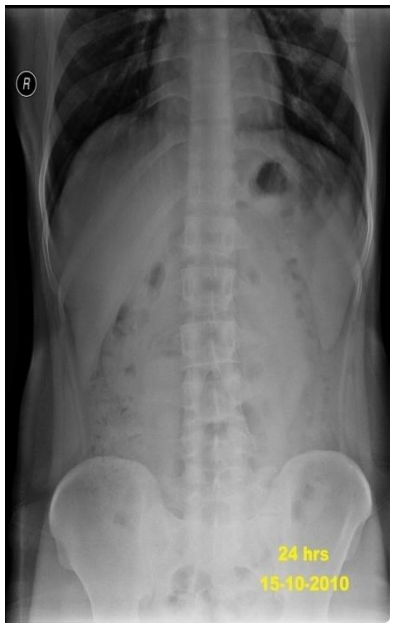
b) 3 h: Ileo-caecal junction



c) 6 h : Ascending colon



d) 8 h: Ascending colon



f) 24 h: Not observed

Figure III. The localization of the tablet in the gastrointestinal tract in subject 1.

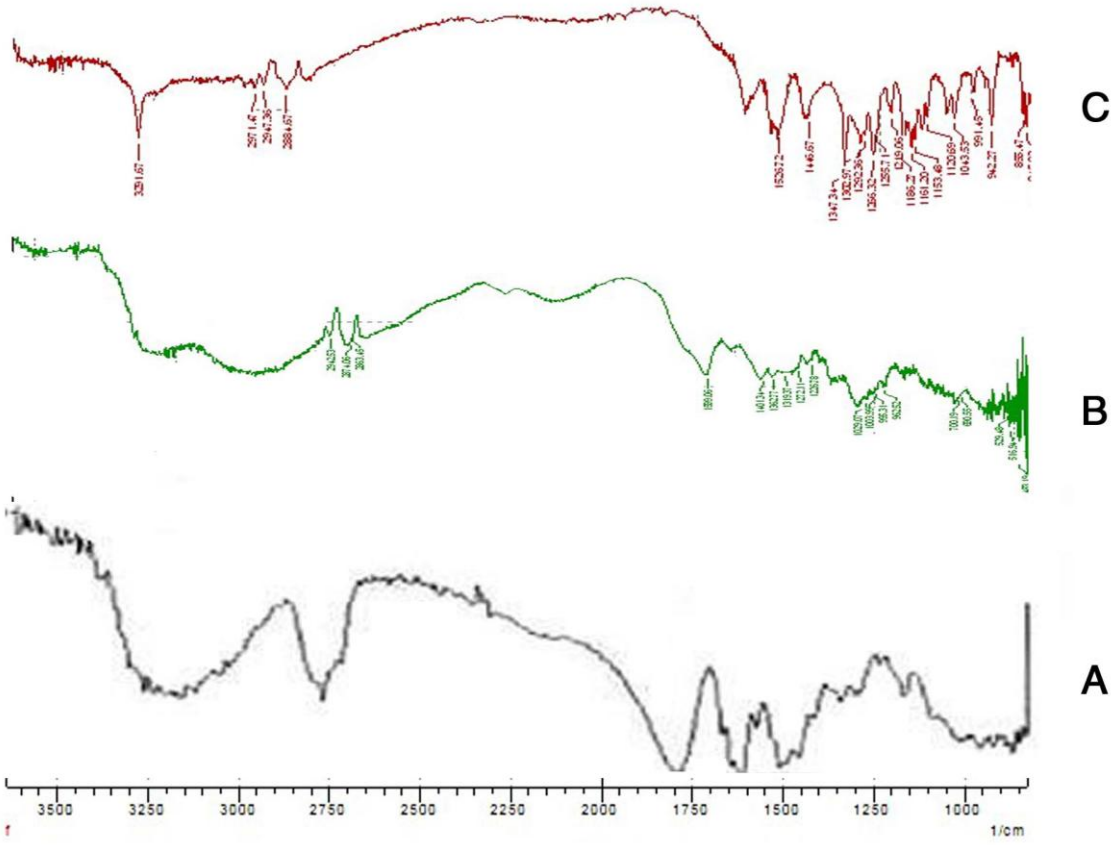


Figure IV. FTIR Spectra of F19 Formulation A) Meloxicam pure drug, B) Xanthan gum and C) physical mixture of optimized formula

3.6 Kinetics of drug release

Table shows data analysis of release profile of optimized and selected formulation according to different kinetic models. The kinetic treatment reflected that release data of r^2 value of 0.9911 which is close to 1, indicating that release of drug follows zero order kinetics, indicating that the concentration was nearly independent of drug release. Further Korsmeyer and Peppas equation resulted into the value of n=1.1715, appears to indicate super case II transport.

DISCUSSION

A colon –targeted drug delivery system should not only protect its load from being released in the physiological environment of the stomach and small intestine but also deliver its load to the colon. Conventional dissolution testing is less likely to accurately predict in-vivo performance of colon delivery systems triggered by bacteria residing in the colon. Hence, release studies were performed in an alternate release medium called rat caecal content release medium [15].

The ability of xanthan gum to retain the integrity of tablets in the physiological environment of stomach and small intestine was assessed by conducting drug release studies in 0.1MHcl for 2h and in pH4.5 phosphate buffer for 3h conditions mimicking mouth to colon transit).

Since, the hydrophilic polymer used is not soluble in acidic pH and started to dissolve

above pH 7; no significant amount of drug was released from tablets in pH1.2 and 4.5. The tablets released some amount of drug in pH4.5, which may be due to diffusion process but release in pH 7.4 could follow both diffusion and erosion mechanisms. Only 0%to 10% of the drug was released in the upper gastro intestinal tract environment. Thus, xanthan gum compression coated tablets can prevent the drug from being released in the physiological environment of the stomach and small intestine [16].

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 of the tablets. The hydration of xanthan gum seems not to be affected by the pH of the dissolution medium. The initial drug release may be attributed to the dissolution of the drug present on the surface of the tablet and the lag time required for complete hydration of xanthan gum to form viscous gel layer around the tablet.[4][5] (vanden mooter et al.,1995; Ramaprasad et al.,1996).

In the first 6h of drug release studies in the presence of 4%w/v of rat caecal matter, the release of drug was found to be faster which may be because of the combined effect of enzyme activity and release of drug present on the surface of the tablets. The amount of drug released during the next 8h of study may be due to slow erosion of the hydrated gum by enzymatic action. A further rise in the amount of drug released during 10-12h may be because of complete erosion of the hydrated gum thereby exposing a fresh surface containing drug particles. At 8h, the tablets were found to be broken into 2-3 pieces thereby increasing the specific surface area available to the dissolution fluid and enzymatic action. Hence, a steep rise in the percent drug release was observed between 8-10h. The increase in surface area also could have resulted in increased drug release between 12 and 24h. Thus the 2nd phase of drug release was observed between 8-24h may be the result of the breaking of the tablets and the erosion of the hydrated gum. Since, the level of enzymes in 2%w/v caecal matter is low, the tablets didn't break and hence such a biphasic curve was not observed.

As xanthan gum and HPMC are hydrophilic in nature and the system made from a mixture of these polymers swells and forms a hydrogel layer when they come in contact with aqueous medium. With the diffusion of medium into the polymer a hydrogel layer forms. When there is an enzyme in the environment, it breaks out the polymer chains and as a result dissolution of tablet increases with the increase of diffusion of dissolution medium. As the ratio of HPMC increased in the polymer mixture, release of meloxicam and dissolution rate of tablets decrease. Hence, (75:30) combination has appropriate mechanical strength and is optimized for dissolution in caecal contents. [13]

Hence, the pretreatment of rats with 1 ml of 2%w/v of xanthan gum dispersion was carried out for 7 days and the above experiments were repeated with 2%w/v and 4%w/v of caecal matter to find its influence on drug release from tablets. The percent drug released after 24h of testing was 82.6±(2.59) with 2%w/v of caecal matter and

95.0±(2.99)with 4 % w/v of caecal matter. Thus there was a marked improvement in total percent drug released with caecal matter obtained after 7 days of induction when compared with those without induction.

The results clearly demonstrate that xanthan gum is susceptible to enzymatic action of rat caecal contents as the percent drug released in the presence of different levels of caecal matter is better than without caecal matter. Pre-treatment with xanthan gum for 7 days further improved the enzyme induction with the drug

release raised to about 95%at 4 %w/v level of caecal matter. Hence, it appears that the presence of 4%w/v of caecal matter in the dissolution medium obtained after 7 days of induction is ideal for in-vitro evaluation of xanthan gum tablets meant for colon targeting.

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 xanthan gum coats by the enzymes present in the caecal matter. Tablets containing two polymeric systems show much more promising release than the single polymeric system. From this we conclude that the retarding effect could be achieved more effectively by the use of a combination of polymers rather than a single one.

When the dissolution study was conducted in the physiological environment of stomach, small intestine and colon as described above no significant difference ($P<0.01$) was observed in the cumulative percent of meloxicam.

The occurrence of any drug –xanthan gum /other excipient interaction in the formulation was predicted by conducting Fourier Transform infrared spectra. The spectra of xanthan gum, pure drug (meloxicam), powdered sample of compression coated tablet is shown in figure IV. Based on the FTIR spectra, there appears to be no possibility of interaction between meloxicam and xanthan gum/other excipients used in the preparation of meloxicam compression coated tablets in present study.

CONCLUSION

Xanthan gum and HPMC K4M in combination, in the form of compression coated tablets is capable of protecting meloxicam from being released in the upper regions of GI system, i.e. stomach and small intestine. The in-vitro drug release studies suggested the ability of xanthan gum to release the drug in the colon in the presence of rat caecal contents. The rat caecal contents at 4% w/v level in the dissolution medium after 7 days of enzyme induction provide the best conditions for assessing the susceptibility of xanthan gum to colonic bacterial degradation. 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. In-vivo studies indicated that optimsed formulation was a promising system to provide targeting of meloxicam to the colon. FT-IR spectral studies showed that there was no interaction between the drug and excipients. It is concluded that the release lag time and release rate could be tailored through adjusting the formulation variables to achieve colon specific drug delivery of meloxicam.

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