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Research Article

Optimization of Colon Specific Drug Delivery System for Ornidazole using Modified Gum

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ABSTRACT

The present study aimed to optimize a colon-specific formulation of ornidazole for the treatment of Crohn's disease and intestinal amoebiasis. Firstly carboxymethyl xanthan gum was prepared from xanthan gum reacting with monochloroacetic acid in alkaline conditions using the Williamson synthesis method. Fourier transform infrared spectrophotometer (FTIR) spectroscopy confirmed the formation of carboxymethyl xanthan gum. The differential scanning calorimetry (DSC) revealed the crystalline nature of carboxymethyl xanthan gum. A 3^2 full factorial design was used for optimization. The independent variables employed were the amount of Carboxymethyl Xanthan gum and the amount of hydroxy propyl methyl cellulose (HPMC), each at three levels. Drug release studies were carried out in various media [pH 1.2, 7.4, and 6.8]. The optimized formulation consisting of Carboxymethyl Xanthan gum (66 %) and HPMC (22%) released a small fraction of drug at pH 1.2 and pH 7.4, whereas significant drug release was observed at pH 6.8. The results of the study established Carboxymethyl Xanthan gum compression coated tablet to be a promising system for the colon-specific delivery of ornidazole to treat active Crohn's disease and intestinal amoebiasis.

INTRODUCTION

Colon-specific drug delivery systems utilized in treating colon-related diseases like Crohn's disease, colitis, inflammatory bowel syndrome, colorectal cancer, amoebiasis, etc., have become one of the thrust areas in pharmaceutical research; for colon targeted systems, two aspects need to be considered.^[1] First, the delivery device should be able to avoid drug release within the upper parts of the alimentary tract, including the stomach and small intestine, and secondly, the dosage form should be able to supply the drug in optimum therapeutic concentrations within the colonic lumen for the intended duration of some time. The retention time of dosage forms within the stomach usually averages to 2 hours and within the intestine 3–4 hours. Therefore, 5–6 hours lag time of drug release should be needed.^[2]

Natural gums are used extensively in food and pharmaceutical applications due to their easy availability,

low cost, biocompatibility, and biodegradability, but their applications are limited due to uncontrolled hydration, microbial contamination, pH-dependent solubility and viscosity changes during storage. Xanthan gum could also be a high relative molecular mass extracellular heteropolysaccharide natural gum produced by fermentation of gram-negative bacterium *Xanthomonas campestris*, which has been used widely in the cosmetic and pharmaceutical industry as suspending, stabilizing, thickening, and emulsifying agent. Xanthan gum is soluble in hot and cold water, but its dissolution is extremely slow and requires intense agitation to stop the formation of lumps on dispersing in water.^[3] Xanthan gum particles hydrate and swell with the formation of a partially hydrated gelatinous layer on the surface of the gum. This gelatinous layer prevents penetration and complete hydration of the particle and slows down the gum's dissolution. Chemical modifications of natural gums are

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employed to enhance their properties as a biopolymer. Carboxymethylation is among one the various strategies used for the functionalization of natural polymers. It is a widely employed modification approach; thanks to its simple processing, lower cost of chemicals, and adaptability of the merchandise, carboxymethyl derivatives usually have better aqueous solubility.^[4]

In the present investigation, xanthan gum (XG) was derivatized to carboxymethyl xanthan gum (CMXG) and characterized by various instrumental analyses. Colon-specific drug delivery can be accomplished either by film coating or compression coating processes. Among these, compression coating has higher stability is a solvent-free process, which is safe and inexpensive that does not require special coating equipment, but it required highly skilled persons and more care during compression to avoid compression-related problems.^[5]

Ornidazole is employed in the treatment of susceptible protozoal infections, anaerobic bacterial infections, intestinal amoebiasis, amoebic liver abscesses, duodenal ulcers, giardiasis, and vaginitis. Ornidazole has recently been used successfully in patients with active Crohn's disease. Ornidazole is a 5-nitroimidazole derivative that has a plasma elimination half-life of 11 to 14 hours. Oral absorption of the drug is almost complete, with the bioavailability of 90% and T_{max} ranging between 2 and 4 hours Crohn's disease may be a chronic disorder that causes inflammation of the digestive or alimentary canal. It most commonly affects the end of the small intestine (ileum) and the beginning of the large intestine (colon). This inflammation causes pain and makes the intestine empty frequently, resulting in diarrhea. Ornidazole is an efficient and safe drug for the treatment of active regional enteritis. It has also been used as a maintenance treatment with promising results.^[6,7]

We have prepared the carboxymethyl derivative of xanthan gum in the present approach to modify its release behavior. The compression coated tablets of ornidazole were prepared using carboxymethyl xanthan gum and HPMC. Prepared tablets could prevent or minimize premature release in the upper gastrointestinal tract and provide release of a significant amount of the drug in 12 hours during which the tablets might reach the colon.

MATERIALS AND METHODS

Materials

Ornidazole was obtained as a gift sample from Torrent Pharmaceuticals, Ahmedabad, India. Xanthan gum (Loba Chemie Pvt. Ltd. Mumbai, India), monochloro acetic acid (Thomas Baker Chemicals Pvt. Ltd Mumbai, India). Each reagent and solvent used was of analytical grade.

Preparation of Carboxymethyl Xanthan gum

Xanthan gum was chemically derivatized into Carboxymethyl Xanthan gum by Williamson's ether

synthesis method. A 2 g of Xanthan gum was slowly sprinkled in ice-cold deionized water containing 3.024 g of sodium hydroxide with stirring for 30 minutes at 0–8°C. Monochloroacetic acid (1.5 g) dissolved in 3.3 mL of deionized water was added slowly with constant stirring while maintaining the temperature at 15–18°C. The temperature of the reaction vessel was slowly raised to 75°C and kept for 1-hour The wetted mass was washed with three successive amounts of 20 mL 80% (v/v methanol) for 15 minutes each. During the last washing, the pH of the mixture was adjusted to neutrality with glacial acetic acid. Finally, it was washed with pure methanol and kept for drying at 45–50°C until a constant weight was obtained.^[5]

Characterization of carboxymethylated gum

Fourier Transform Infrared Spectroscopy

FTIR spectra of xanthan gum and carboxymethyl xanthan gum was recorded using FTIR spectrophotometer (Bruker India Scientific Pvt. Ltd.) in range of (4000–500 cm^{-1}).

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermogram of xanthan gum, and CMXG was recorded using DSC (PerkinElmer India Pvt. Ltd.) in the temperature range of (30–300°C) at a heating rate of 40°C per minutes in a nitrogen atmosphere.

Viscosity

The viscosity of xanthan gum and carboxymethyl xanthan gum solutions was determined using Brookfield viscometer (Model RVDVE 230, Brookfield Engineering Laboratories, Middleboro, USA) using spindle number 3 at different revolutions per minute (rpm).

Preparation of Core Tablets

The core tablets of the drug were prepared by direct compression technique. The drug, sodium starch glycollate, lactose, magnesium stearate, and talc were thoroughly mixed and passed through a sieve (no 60). The mixture was compressed into tablets using round, flat, and plain punches on a single station tablet machine (Modern Engineering New Delhi, India).^[8] Composition of fast disintegrating core tablets are presented in Table 1.

Evaluation of Powder Mixture

The powder blend for each formulation was evaluated for the following flow properties.^[7]

Table 1: Composition of fast disintegrating core tablets of drug

Ingredients	Quantity (mg)
Ornidazole	250
Anhydrous lactose	16
Sodium starch glycollate	25
Talc	6
Magnesium stearate	3

Angle of Repose

The angle of repose of powder mixture was determined by the fixed funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The funnel height was so adjusted that the tip of the funnel just touches the apex of the heap. The diameter of the powder cone so formed was measured, and the angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where,

- θ = Angle of repose
- h = Height of powder heap
- r = Radius of powder heap in cm

Tapped Bulk Density (TBD) and Loose Bulk Density (LBD)

For this sufficient quantity of powder blend from each formulation was taken and then was introduced into a 10 mL measuring cylinder. It was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula

$$\text{TBD} = \text{Weight of powder blend} / \text{Tapped volume of packing}$$

$$\text{LBD} = \text{Weight of powder blend} / \text{Volume of packing}$$

Carr's Compressibility Index

The compressibility index of the powder blends was determined by using following formula.

$$\text{Carr's Index \%} = \text{TBD} - \text{LBD} \times 100 / \text{TBD}$$

Hausner Ratio

Hausner ratio was determined for characterization of the flow of powder blend. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability. The formula used was as follows

$$\text{Hausner Ratio} = \text{TBD} / \text{LBD}$$

Evaluation of Core Tablets

Weight Variation

All prepared core tablets were evaluated for weight variation as per the (USP XXIV 2005) monograph. Twenty tablets of core tablets were used to evaluate weight variation among tablets, and the standard deviation was calculated.

Friability

Ten core tablets were used to evaluate friability as per the (USP XXIV 2005) monograph. Friability test was performed for 4 minutes at a speed of 25 rpm, with the tablet dropping from a height of 6 inches. After the test, tablets were de-dusted and reweighed. The test was done using the Friability test apparatus (Electro lab, India) with triplicate readings.

Hardness

The hardness of core tablets was determined using Pfizer hardness tester India. Tablet was placed vertically between the hardness tester's jaws, which was pressed until the tablet breaks. Reading was noted from the display.

Disintegration Test

The disintegration time of the core tablets was determined by using the disintegration test apparatus (Electro lab, India). The endpoint of the test is indicated when the tablets pass through the screen. A disintegration test was carried out in pH 6.8 phosphate buffer.

Diameter and Thickness

Diameter and thickness were measured using a Vernier caliper as per (USP XXIV 2005) monograph. The readings were carried out in triplicate, and the average values were recorded.

Drug Content

The 20 tablets were powdered, and 250 mg equivalent weight of ornidazole in tablet powder was accurately weighed and transferred into a 100 mL volumetric flask. Initially, 20 mL of phosphate buffer (pH 6.8) was added and shaken for 10 minutes. Then, the volume was made up to 100 mL with the buffer. Subsequently, the solution in the volumetric flask was filtered, and 1 mL of the filtrate was diluted sufficiently and analyzed at 317 nm using a UV-visible spectrophotometer (Shimadzu UV-1800, Japan). The drug content of the samples was estimated from their standard curve.^[9]

Preparation of the Compression Coated Tablets

Granules containing different ratios of CMXG and HPMC were prepared by a wet granulation method with the help of a required amount of calcium chloride (CaCl_2) solution compression-coating material. To prepare compression-coated tablets, 40% of the granules are placed in the die, the core tablet was placed centrally in the die cavity, and the remaining 60% of granules are poured into the die cavity and finally compressed using a punch.^[4]

Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors are evaluated, each at three levels, and experimental trials are performed at all nine possible combinations. The concentration of Carboxymethyl Xanthan gum and concentration of HPMC in compression coating were selected as two independent variables.^[10,11] Factorial Experimental design presented in Table 2.

Evaluation of the Compressed Coated Tablets

Weight Variation Test

Twenty compressed coated tablets were weighed individually. The weight of each tablet was compared with the respective average weight of the tablets.



Hardness

Tablet was placed vertically between the hardness tester's jaws, which are pressed until the tablet breaks. Reading was noted from the display

Friability Test

Ten (10) compression coated tablets were weighed and placed in a plastic drum of a Friability test apparatus (Electro lab, India). The tablets were rotated for 4 minutes at 25 rpm, then the tablets were dedusted with a soft brush and reweighed. The percentage of weight loss was calculated

In vitro Drug Release

These studies were carried out using the USP XXIII dissolution test apparatus Type II, paddle speed (100 rpm/min and temperature, $37 \pm 0.5^\circ\text{C}$). The ornidazole compressed coated tablets of each formulation were immersed 900 mL 0.1 N HCl (simulated gastric fluid, SGF) for 2 hr, which was then replaced with 900 mL phosphate buffer (pH 7.4) solution (simulated intestinal fluid, SIF) wherein it was kept for 3 hours. Lastly, SIF was replaced with 900 mL of pH 6.8 phosphate buffer solution (simulated colonic fluid, SCF), and tested for release for the rest of the dissolution test. An aliquot of 5 mL sample was withdrawn and replaced with another 5 mL of fresh dissolution fluid warmed at $37 \pm 0.5^\circ\text{C}$ at various time intervals. The aliquots were filtered through a Whatman (no. 1) filter paper. The absorbance was measured spectrophotometrically for both acid solution of pH 1.2 and buffer solutions of pH 7.4 and 6.8. The amount of drug released from the tablet was determined using calibration curves drawn within the respective medium.^[4]

RESULTS AND DISCUSSION

FTIR Spectroscopy

The results of the FTIR analysis revealed a successful etherification of Xanthan gum. In the pure Xanthan gum spectra (Fig. 1), typical absorption bands were observed at 1017.03, 1399.65, 1597.85, and 1732.34 cm^{-1} which correspond, respectively, to C-O-C stretching of ether, C-H banding of methyl groups, and asymmetric vibration of COO^- and CO stretching of alkyl esters. The characteristic peak at 3262.12 cm^{-1} is attributed to OH group stretching.

In the Carboxymethyl xanthan gum spectra (Fig. 2), new peaks appeared at 1023.19 cm^{-1} for Carboxymethyl xanthan gum. These peaks may be attributed to additional C-O-C ether stretching due to carboxymethylation. Peaks at 1242.88 cm^{-1} also appeared and are attributed to CO stretching of O-carboxymethyl groups or CH_2 scissoring in the carboxymethyl group. These results confirmed the successful etherification of native Xanthan gum. The peaks at 1407.85 cm^{-1} may be attributed to OH in the plane band of carboxymethyl groups. A particular observation was

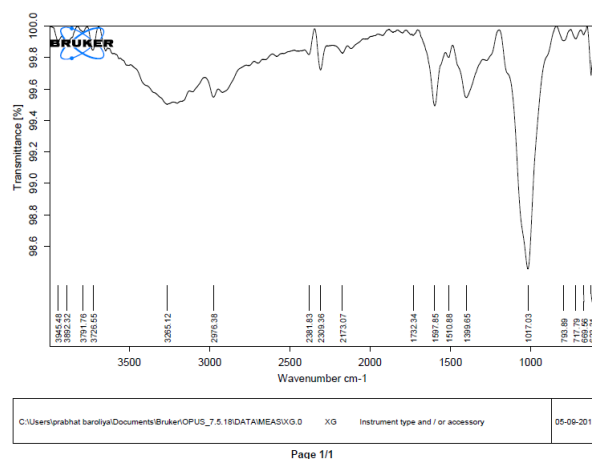


Fig. 1: FTIR spectra of pure Xanthan Gum

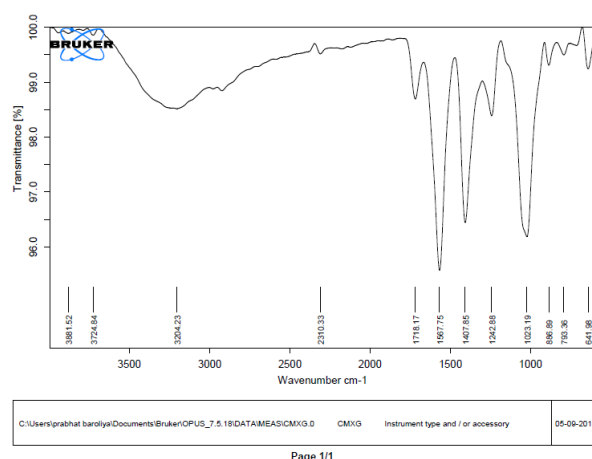


Fig. 2: FTIR spectra of Carboxymethyl xanthan gum

Table 2: Experimental design using two independent variables with three levels

Formulations	Independent variables	
	Concentration of Carboxymethyl Xanthan gum (X1)	Concentration of HPMC (X2)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

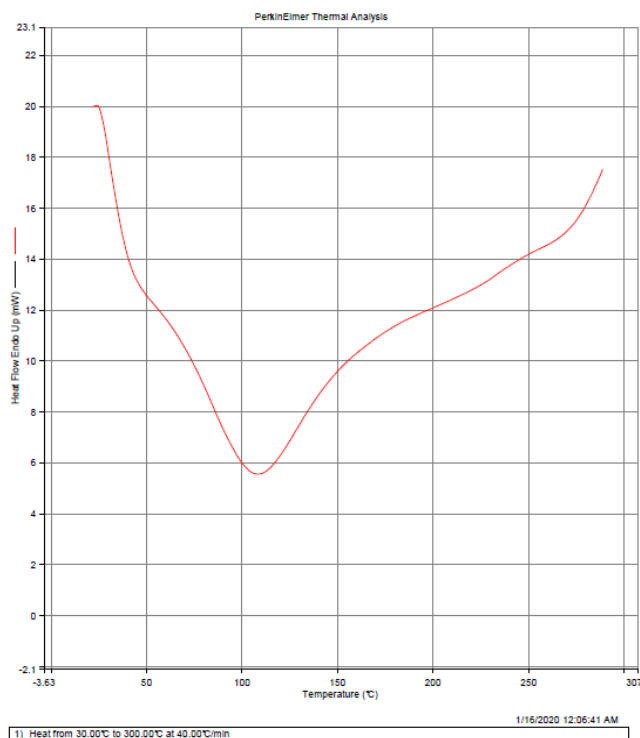
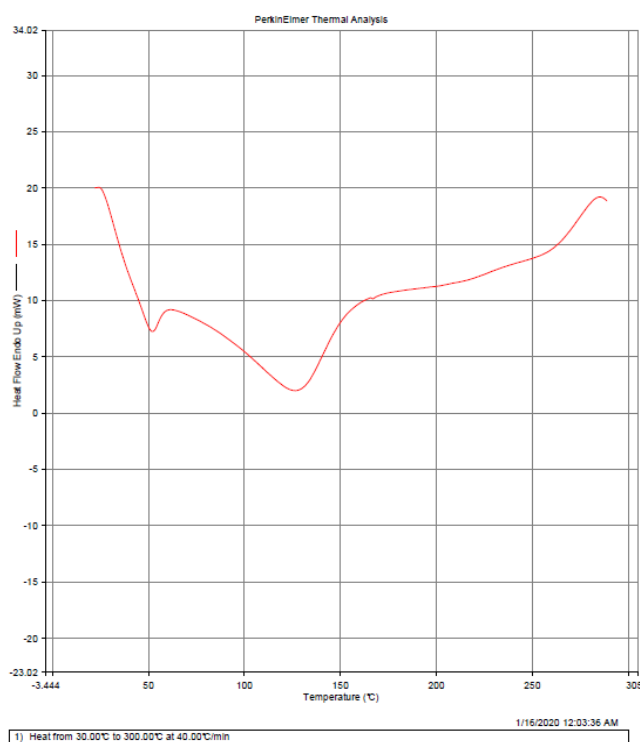
X1: Concentration of Carboxymethyl Xanthan gum in compression coating (%), level: -1 (22), 0 (44), +1 (66)

X2: Concentration of HPMC in compression coating (%), Level: -1 (11), 0 (22), +1 (33)

Table 3: Evaluation parameter of Core tablets powder mixture

Evaluation parameter	Angle of repose (θ)	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Carr's index (%)	Hausner ratio
Core tablets powder mixture	31 ± 0.5	0.430 ± 0.13	0.505 ± 0.32	14.85 ± 0.52	1.17 ± 0.25

Value with " $\pm$ " showed standard deviation, n=3

**Fig. 3:** DSC thermogram of the pure Xanthan gum**Fig. 4:** DSC thermogram of the Carboxymethyl xanthan gum**Table 4:** Evaluation parameter of core tablets

Sr. No.	Evaluation parameters	Core tablets batch
1	Average weight (mg)	301.1 ± 0.90
2	Friability (%)	0.703 ± 0.16
3	Hardness (kg/cm ²)	3.23 ± 0.27
4	Diameter (mm) average	8.05 ± 0.05
5	Thickness (mm) average	3.12 ± 0.10
6	Disintegration time (min.) average	2.46 ± 0.14
7	Drug content	99.9 ± 0.10

Value with " $\pm$ " showed standard deviation, n=3

concerning the intensity of OH⁻ groups of the glycosidic chain, which decreased due to the substitution of these OH groups, and the peaks at 1567.75 cm^{-1} characteristic of COO⁻ stretching, which increased due to the gradual increase of the COOH groups. The intensity of the peaks at 1407.85 and 1567.75 cm^{-1} increased with R, which may be explained by the increased degree of substitution. The peak at 1732.13 cm^{-1} disappeared in the spectra of CMXG due to the alkaline reaction conditions that caused deacetylation of native Xanthan gum.

Differential scanning calorimetry

The DSC curve of xanthan gum (Fig. 3) shows a broad endotherm at 108°C . The thermal curve of Carbomethyl xanthan gum (Fig. 4) shows two endothermic peaks at 58°C and 140°C . The DSC curve of CMXG is typical of crystalline substance type, while that of Xanthan gum is like that of amorphous material.

Evaluation of Core Tablets Powder Mixture

The flow characteristics of the physical mixtures of drug ornidazole with sodium starch glycollate, lactose, magnesium stearate, and talc are presented in Table 3.

The angle of repose of the powder mixtures predicts good flow characteristics, The value of Carr's Index and Hausner Ratio exhibit good flowability.

Evaluation of Core Tablets

The developed core tablets were evaluated for their various physical properties like thickness, diameter, weight variation, hardness, friability, disintegration time, and drug content

The results of the physical characterization of the Ornidazole core tablets are presented in Table 4. The physical appearance of the prepared core tablets was uniform. The tablets had adequate hardness, uniform average weight, drug content and passed the friability test.



Table 5: Evaluation of compression coated tablets

Batch	Weight variation (mg) average	Friability (%)	Hardness (kg/cm ²)
F1	697 ± 0.04	0.53 ± 0.02	4.45 ± 0.05
F2	700 ± 0.07	0.54 ± 0.05	4.51 ± 0.03
F3	695 ± 0.05	0.52 ± 0.01	4.35 ± 0.03
F4	698 ± 0.10	0.56 ± 0.04	4.47 ± 0.04
F5	699 ± 0.08	0.55 ± 0.03	4.53 ± 0.02
F6	700 ± 0.04	0.52 ± 0.02	4.65 ± 0.05
F7	703 ± 0.06	0.53 ± 0.05	4.53 ± 0.02
F8	695 ± 0.02	0.51 ± 0.01	4.35 ± 0.01
F9	705 ± 0.05	0.50 ± 0.03	4.20 ± 0.05

Value with " ± " showed standard deviation, n=3

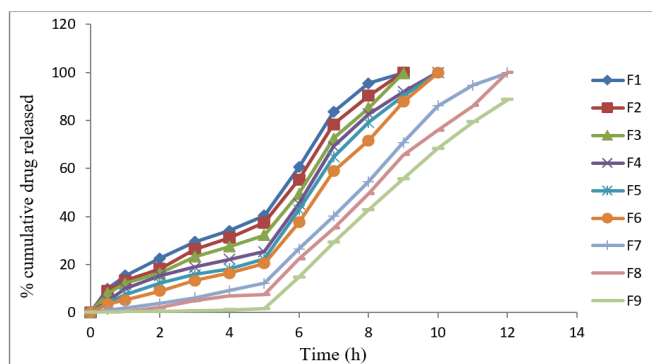


Fig. 5: Percent cumulative drug release of ornidazole tablet formulations (F1 to F9)

Evaluation of the Compression Coated Tablets

In weight variation test, the average weight of prepared tablets (F1 to F9) was given in Table 5. The hardness and friability of tablets were found to be 4–5 kg/cm² and below 0.6%, respectively, signifying the integrity and strength of tablets. In a word, all the tablets showed acceptable results in the sense of physical characteristics along with good mechanical integrity. Table 5 showed all the physical parameters evaluated for compression coated tablets.

In vitro Drug Release

In vitro drug release assess the significance of the coat in preventing the drug release in the stomach as well as the role of CMXG and HPMC in compression coating in modulating the drug release in the small intestine and colon, a preliminary investigation involving the comparative evaluation of the release profile of ornidazole from compressed coated tablets.

The comparative release profile of ornidazole from the nine experimental formulations (F1-F9) in media mimicking mouth to colonic transit is shown in Fig. 5 on analyzing % cumulative drug release in 0.1N HCl medium of pH 1.2 (gastric pH), the study was carried out for 2 hours. It was found that the formulation F1, F2, and F3 containing 22% Carboxymethyl Xanthan gum demonstrated a percent cumulative drug release of 22.66,

18.31, and 16.42%, respectively. This shows that 22% CMXG was not sufficient to minimize drug release in the gastric environment. As the amount of CMXG increased from 22% to 44% in formulation F4, F5, and F6, the percent cumulative drug release at the end of 2nd hour decreased 15.40, 12.35, and 9.01%, respectively. This demonstrates that even 44 % of Carboxymethyl Xanthan gum is not sufficient to minimize the release of ornidazole in the gastric environment. On further increasing the amount of Carboxymethyl Xanthan gum to 66% in formulation F7, F8, and F9, a reduction in the amount of %cumulative drug release at the gastric environment was observed. Formulations F7, F8, and F9 were found to release 3.78, 2.07, and 0.58% of the drug. So a further increase in the amount of CMXG in these formulations is not needed.

On analyzing the percent cumulative drug release of formulation F1–F9 in intestinal fluid (phosphate buffer, pH 7.4, 3 hours), it was found that formulation F1, F2, and F3 containing 22% Carboxymethyl Xanthan gum demonstrated a percent cumulative drug release of 40.37, 37.43, and 32.27% respectively. This shows 22% Carboxymethyl Xanthan gum was not sufficient to minimize drug release in the small intestine. As the amount of Carboxymethyl Xanthan gum was increased from 22 to 44% in formulation F4, F5, and F6, the percent cumulative drug release at 5th hour decreased to 25.46, 22.33, and 20.49%, respectively. This demonstrates that even 44% of Carboxymethyl Xanthan gum is not sufficient to minimize the release of ornidazole in the small intestine milieu. On further increasing the amount of CMXG to 66% in formulation F7, F8, and F9, a reduction in the amount of % cumulative drug release at intestinal pH was observed. Formulations F7, F8, and F9 were found to release 12.21, 7.51, and 1.53% of the drug, respectively. This could be due to the reason that further increase in the amount of Carboxymethyl Xanthan gum in these formulations led to the formation of a stringent barrier owing to absorption of water leading to the development of a highly viscous diffusion control layer

Eventually, the release of the drug from the nine experimental formulations was analyzed in the colonic environment [phosphate buffer pH 6.8] to precisely describe the release behavior of these formulations in the colonic environment. Amongst the formulations F1–F9, F8 was found to exhibit the maximum amount of percent cumulative drug release of 92.49% in the colonic environment. This could be attributed to the presence of the highest amount of CMXG in F8. Hence maximum drug release was observed in F8 within 12 h of study in the colonic environment. The beauty of the present system is that CMXG is behaving as a bifunctional release controlling excipient since it is responsible for retarding the drug release in the gastric and small intestinal environment but has the potential to maximize the drug release in the colonic milieu.

CONCLUSION

In the present work, modified xanthan gum (CMXG) was successfully synthesized via an etherification process with monochloroacetic acid. The successful carboxymethylation of these products was confirmed by FTIR spectroscopy. The DSC studies revealed the crystalline nature of carboxymethyl xanthan gum. Ornidazole compressed coated tablet with Carboxymethyl Xanthan gum and HPMC were successfully optimized using 3² full factorial designs. The optimized tablets contained 66% CMXG and 22% HPMC had proper physical properties and could prevent drug release in the gastric environment. The optimized tablets released only 7.51% of their drug content in the small intestine environment and exhibit the maximum amount of % cumulative drug release of 92.49% in the colonic environment. This proves the ability of the optimized tablets to minimize drug release in the upper gastrointestinal tract and sense the arrival of the tablets to the colon where it gave the highest release. Thus, F8 could be a novel formula for ornidazole colon-specific delivery.

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