RESEARCHARTICLE

Preparation and Characterization of Hydroxypropyl methylcellulose Gastroretentive Film using Metoclopramide HCl

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ABSTRACT

This study aimed to formulate a gastro retentive slow release dosage form based on oral film for metoclopramide hydrochloric acid (HCl), a medication with a narrow absorption window. The gastroretentive film was made using a solvent casting method with varying ratios of primary polymers (HPMC 15000 cps and HPMC K4M), secondary polymer (carbopol 934), and PEG-400 as a plasticizer. The film of hydroxypropyl methylcellulose (HPMC) K4M-3 (50:50) (HPMC K4M: carbopol) was buoyant for 20 minutes. The 52 wt % of metoclopramide HCl (metclo) was released from the HPMC K4M-3 film after 24 hours, and its swelling index was (46.5%). The mucoadhesive strength of the HPMC K4M-3 was 18 gm, and the film showed no effect on the rat's stomach tissue compared to normal rat tissue histologically. The HPMC K4M-3 produced modest values of percent elongation of 77.6%. To conclude, the optimized film appeared to be a promising mucoadhesive gastro retentive oral film with the ease of administration and controlled release.

Keywords: Carbopol, Gastroretentive film, Hydroxypropyl methylcellulose, Metoclopramide HCl, Mucoadhesive property.

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INTRODUCTION

Gastroretentive dosage forms got highly researched due to the ability of these dosage forms to retain and slow their dissolution in the favorable absorption sites in the upper part of the gastrointestinal tract, which are the stomach and/or the duodenum. Hence, the chosen drugs that are retained in the stomach and highly matched with gastro retentive dosage forms are weak basic drugs as their absorption is highly restricted to the duodenum or their local pharmacological effect. These systems to deliver drugs in the upper part of the gastrointestinal tract include high-density (sinking) systems, low-density (floating) systems, expandable systems, ultra porous hydrogel systems, mucoadhesive systems, and magnetic systems. These could be formulated as tablets, capsules, gel, and films as the last one is the focus of the current work. Gastroretentive films were prepared by Matharu *et al.* to retain the release of captopril.[1] Also, Abubakr O. *et al.* combined hydroxypropyl methylcellulose (HPMC) 4000 and HPMC 15000 cps with carbopol to make floating tablets in another investigation.[2] In a different study, Amit *et al.* prepared bilayer film of atorvastatin calcium and amlodipine besylate from eudragit, HPMC 3K, HPMC 5 cps, and carbopol 934P.[3] Also, Md. Bashir *et al.* used enalapril maleate to prepare film using HPMC (methocel K15) and eudragit RLPO.[4]

This work aimed to prepare gastro retentive films from the HPMC 15000cps and HPMC K4M as primary polymers and carbopol 934 polymers as a secondary polymer using the metoclopramide HCl as a model drug (metclo) to be loaded in a hard gelatin capsule for film delivery. As previously, no research prepared metclo film for gastro retentive purposes. However, metclo was formulated as films for a different goal, like as Iman *et al.* used metclo in fast-dissolving film from HPMC 15 cps and sodium carboxymethylcellulose in different concentrations.[5] Another metclo film was formulated as a mucoadhesive buccal film using these polymers PVP, sodium carboxymethylcellulose, HPMC K4M, and ethylcellulose.[6]

MATERIALS AND METHODS

Materials

Metclo (a gift from SDI Samarra pharmaceutical company), HPMC 15000cps and HPMC K4M were purchased from alpha chemical, India and Nanjing Duly Biotec. Company. Ltd., China, respectively. Carbopol®934P NF and PEG-400 were brought from Xi'an Prius bioengineering, China, and HiMedia Laboratories Pvt. Ltd., India, respectively.

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Table 1: Formulation ingredients of metoclopramide HCl loaded polymeric film

Formulations	*HPMC 15000 cps (mg)*	*HPMC K4M (mg)*	*Carbopol® 934 NF (mg)*
HPMC 15000-1	100	-	-
HPMC 15000-2	75	-	25
HPMC 15000-3	50	-	50
HPMC 15000-4	-	-	100
HPMC 15000-5	25	-	75
HPMC K4M-1	-	100	-
HPMC K4M-2	-	75	25
HPMC K4M-3	-	50	50
HPMC K4M-4	-	25	75

*Ten mg of metclo was added to all formulations.
* Half mL of PEG-400 was added to different ratios of HPMC films.

Table 2: The physical properties of film formulations include the average weight, thickness, and folding endurance.

Formulation	*Average weight (gm)*	*Thickness (mm)*	*Folding endurance*
HPMC 15000-1	0.477 ± 0.056	0.209 ± 0.057	>300
HPMC 15000-2	0.483 ± 0.001	0.193 ± 0.057	>300
HPMC 15000-3	0.473 ± 0.009	0.366 ± 0.108	>100
HPMC K4M-1	0.476 ± 0.001	0.345 ± 0.262	>300
HPMC K4M-2	0.475 ± 0.161	0.446 ± 0.209	>300
HPMC K4M-3	0.467 ± 0.001	0.304 ± 0.121	>300

Table 3: floating lag time and floating duration of the film.

Formula	*Floating duration (min)*
HPMC 15000-1	10 ± 2.64
HPMC 15000-2	5 ± 2.08
HPMC 15000-3	10 ± 0.00
HPMC K4M-1	20 ± 5.77
HPMC K4M-2	60 ± 26.45
HPMC K4M-3	20 ± 5.77

Methods

Film Preparation

As shown in Table 1, each film in this study was prepared by solvent casting technique.[7] Starting with dissolving the primary polymers (HPMC 15000 cps and HPMC K4M) and the second polymer (Carbopol® 934 NF) in a different ratio in the distilled water and metclo then added with the plasticize (PEG-400) to the mixer, which needs vigorous mixing. This step was followed by placing molds in the oven at 40ºC for 24 hours, after pouring the mixture into the mold (the diameter of mold was 4.2 cm). There are some differences in the dissolving technique of the polymers. The HPMC polymers must be dissolved in hot water, representing 30 wt% of the total water, then added to cold water immediately (Figure 1).

Weight Uniformity

Three films from each batch were randomly selected and weighed individually using a digital balance. The results were analyzed for mean weight and standard deviation.[8]

Average Thickness

Digital micrometer screw gauge (Aerospace, China) was used to measure film thickness at different film locations, which are essential to ascertain film thickness uniformity.[9,10]

Folding Endurance

Evaluation of folding endurance is the study to check the folding capacity of the film when subjected to frequent extreme folding conditions. This study was carried out manually by folding and opening the dried film at the same place several times until a break developed at the folding site. Folding endurance is expressed as the number of folds required to break or to develop visible cracks on the film.[11]

Buoyancy/Floating Study

Three floating films from each formulation were put in a flask containing 250 mL of 0.1N HCl (pH 1.2). The time taken by the film to come from bottom to top was named as floating lag time, and the duration of time for which the film constantly floated on the surface was noted as total floating time.[8]

In-vitro Drug Release Study

Each successful film was rolled and placed in a hard gelatin capsule separately. Then, the USP type II apparatus was used to set the metclo release from different formulations. The dissolution vessels were filled with the dissolution medium 0.1 N HCl solution pH 1.2, and the temperature was maintained at 37 ± 0.5°C with stirring at 75 rpm. Aliquots of 10 mL were withdrawn in the first hour every 10 minutes, then till 4 hours of the study every hour, this followed to withdrawal samples at the 8th, 12th, 16th, 20th, and 24th hours. Last, samples were

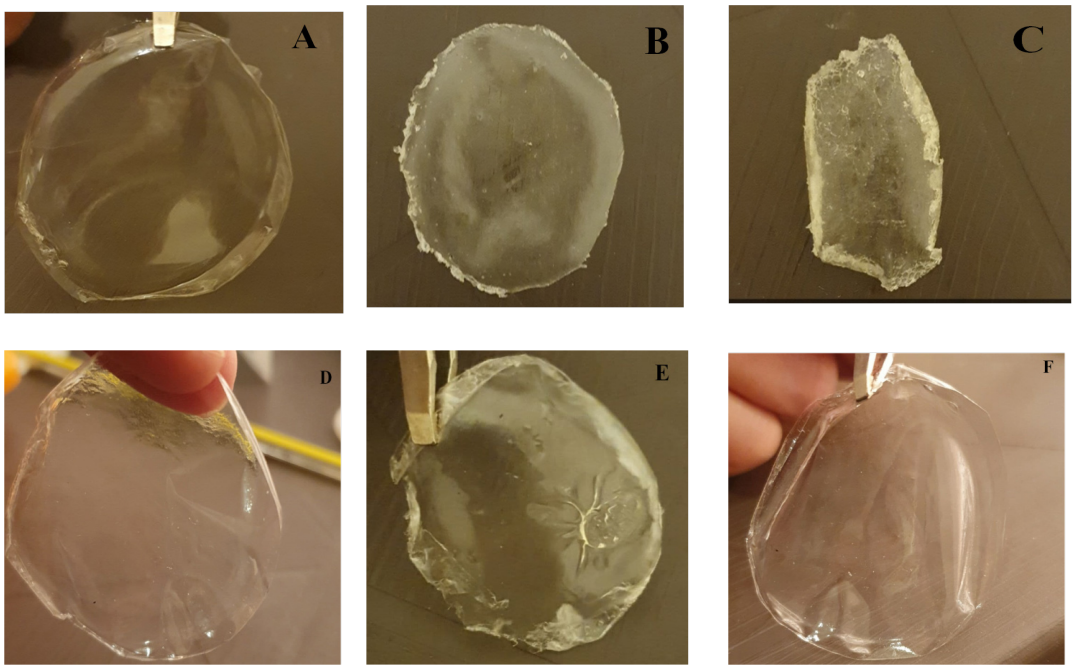

Figure 1: Images of the films (A) HPMC 15000-1. (B) HPMC 15000-2. (C) HPMC 15000-3. (D) HPMC K4M-1. (E) HPMC K4M-2. (F) HPMC K4M-3.

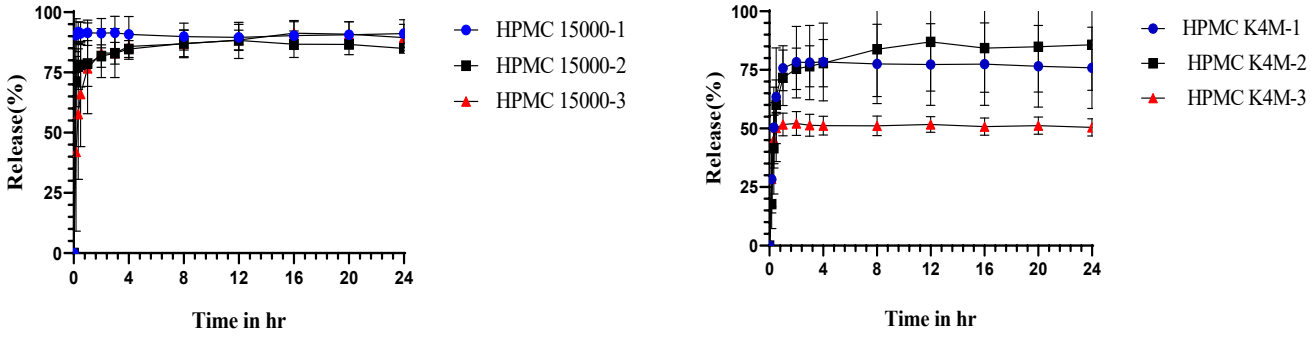

Figure 2: *In-vitro* release of metclo for all films in 900 mL of 0.1N HCl pH 1.2 as a replicate of each release study.

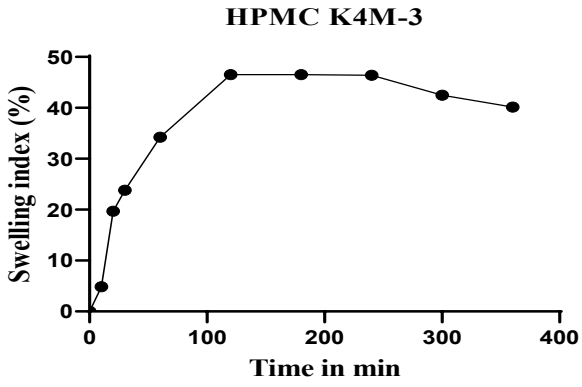

Figure 3: Swelling index percentage (S%).

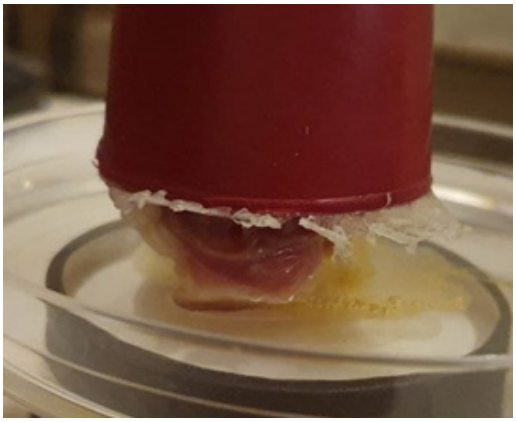

Figure 4: The adhesion of film with mucus covering the stomach tissue.

analyzed by a UV-spectrophotometer at their maximum wavelength (273 nm). The concentrations were obtained using the following equation (y=30.935x + 0.0172) that showed R^2= 0.9919 and resulted from different prepared concentrations versus their absorbance. The study was conducted in triplicate.

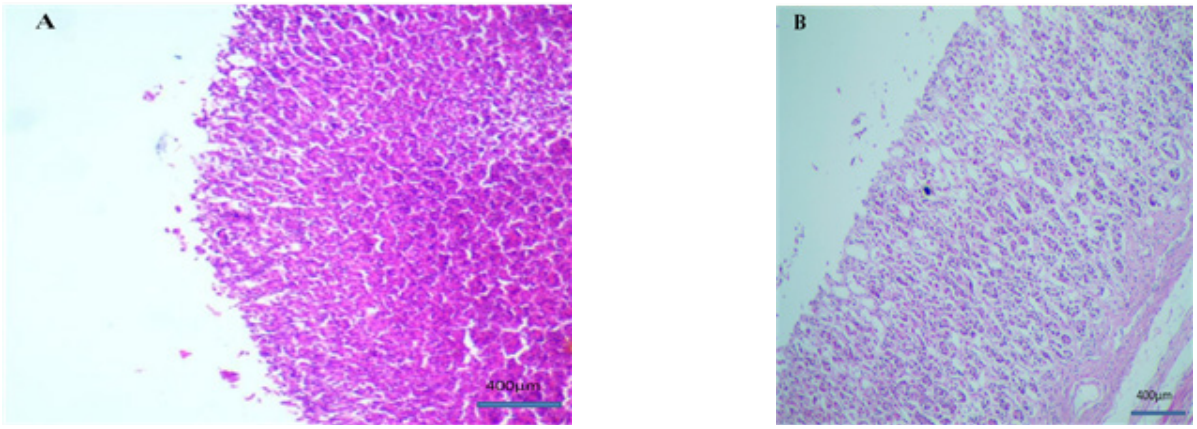

Figure 5: Histological photographs of rat gastric mucosal membrane film administration. A) Normal tissue. (B) The tissue treated with film HPMC K4M-3 as the objective was X40 .

Swelling Index

The swelling index of the prepared metclo films was determined in simulated gastric fluid (pH 1.2). The film was taken and weighed. Then, it was placed in 0.1N HCl in a petri dish and was allowed to swell. After 10 minutes, the water was removed from the petri dish, and the film was appropriately cleaned with tissue paper and weighed again. This procedure was repeated until the weight of the sample began to decrease or become stable. The swelling index of the films was determined using equation (1):

$$Swelling\ index = \frac{Ws - Wd}{Wd} \text{----------equation (1)}$$

The Ws and Wd represent the weights of the swollen and dried films, respectively. The swelling index of each film was calculated three times for 360 minutes, and the average was taken to note the final reading.[12,13]

Ex-Vivo Mucoadhesive Strength

A modified physical balance was used for determining *ex-vivo* mucoadhesive strength. Fresh tissue of the rat's stomach was gotten from the animal house and used as a model mucosal membrane.[13]

The tissue was used within 2 hours of slaughter, washed with distilled water, and stuck on the bottom of the petri dish by cyanoacrylate glue to keep the mucosal surface facing upwards. Then, HCl solution was added until it reached the mucosal membrane's surface and kept moist. This experiment started with the two sides of physical balance equal with placing 5 gm weight on the right-hand pan, whereas a modification to the left side pan held the rubber stopper. The modified left pan arrangement was by submitting the film to stick to the rubber stopper's lower side with cyanoacrylate glue as the rubber stopper was connected to the non-pan left balance arm by threads. Then, once the 5 gm weight was removed in the right pan, the rubber stopper was laid down and adhered over the mucosa in the petri dish. This set was left for 10 minutes, followed by adding drop by drop of water to gain complete detachment from the tissue.[6] The mucoadhesive strength (bioadhesive strength) represents the added amount of water to be subtracted from the weight of the experiment data. Further, the adhesion force and bond strength calculation was done by applying the following equations.[14]

$$Force\ of\ adhesion\ (N) = Bioadhesive\ strength\ x \frac{9.8}{1000} \text{ ------equation (2)}$$

$$Bond\ strength\ \left(\frac{N}{m^2}\right) = Force\ of\ adhesion(N)/surface\ area \text{---equation(3)}$$

Histopathological Study

After the mucoadhesive study, the used and unprocessed stomach tissues were subjected to histological examination. Then, this was followed by parting films from the mucosa of the stomach retained incubating for 12 hours in the refrigerator. For 24 hours, a fixation process was established using neutral buffered formalin followed by paraffin, and later, the tissues were sectioned into 4 µm thick sections using a microtome. The mucosal membrane was examined under light microscopy after staining the tissue sample with hematoxylin and eosin.[15]

Tensile Strength

The film's mechanical properties represented by the tensile strength and percent elongation at break were measured with a texture analyzer (TA-XT2, TA Instruments, UK) according to the American Society for Testing Materials (ASTM) standard method D882 as the tensile strength and % elongation at break was assessed. Sample films were made in a rectangle form with dimensions (20×2) cm. The film was held by the analyser's two clumps.[16] The software calculated the tensile strength values and the percent of elongation at break after applying the pulling force toward the clumps on the film.

RESULTS AND DISCUSSION

Film Preparation

According to Table 1, after taking the 9 formulations out of the oven, not all formulations successfully formed a film: HPMC 15000-5 in which this formulation is composed of 100 mg carbopol. As the intention of the addition carbopol to the films was to increase the gastric retention property of the film.[13] Previous studies are in common with our results of having no film containing carbopol as Tae *et al.* reported of failure

making the film from carbopol in 50: 50 v/v ethanol: water. Furthermore, Skulason S. *et al.* result was sticky and liquidly film in carbopol formulation free of HPMC.[17,18]

Also, no film was formed in formulations HPMC 15000-4, and HPMC K4M-4 contained 75 mg carbopol with 25 mg of the primary polymers. Evidently, the formulations containing a high percentage of carbopol did not produce films. D. Rai *et al.* in his study showed that increasing temperature on solubility of polymer resulted in a shorter polymer dissolution rate but this was also dependent on the concentration and type of HPMC, lots of air and the air bubbles of HPMC solutions were not removed after overnight incubation. On the other hand at a medium speed, fewer air bubbles were observed with HPMC. Also, D. Rai *et al.* showed that drying temperature affected the final appearance of the films. High drying temperatures produced films that were brittle and usually cracked.[19]

Weight Uniformity

The assessment of weight variation was for the successful film formulations, which indicates the homogeneity of the film's formulation composed of primary, secondary polymers, and the active constituent. As shown in Table 2, each film was uniform based on its weight.

Average Thickness

The film thickness uniformity is an essential parameter for finding out the film's drug release characteristics. The release rate varies if the thickness varies from one point to another. Normally, with an increase in film thickness, the rate of drug diffusion decreases. So, uniform thickness is ideal for constant and consistent drug diffusion from the films. The thickness of the floating films also affects the buoyancy behavior of a film. The thickness of the film was increased with an increase in polymer concentration. This might be due to the increased viscosity at higher polymer concentrations.[20] The present study found the thickness of floating films in Table 2.

Folding Endurance

Evaluation of folding endurance is to check the folding capacity of the film when subjected to frequent extreme folding conditions.[8] The folding of the film for each formula was shown in Table 2 and was more than 300 times.

Buoyancy/Floating Study

As clarified in Table 3, the floating lag time for drug-loaded floating films was zero, which might be referring to the gelatin capsule that the film was already folded within, helping to achieve zero lag time and instant floating.

During the first 10 minutes , all the developed films showed good buoyancy during the buoyancy test. As time passed, water gradually entered into the films and subsequently increased the density; hence, films sunk to the bottom. But in this study, the films that rapidly sunk to the bottom from 5 to 10 minutes due to HPMC films during the floating period were fragmented into small pieces after the capsule opened and this might be related to the films fragmentation in the HCl solution or the incompatibility of polymer crosslinking in the formulated film. Indeed, HPMC films floating durations were inversely associated with the increasing HPMC grade, which disagrees with the general notion of the HPMC grade relation with the floating duration.[21] In conclusion, HPMC K4M-2 showed the longest floating period.

***In-vitro* Drug Release Study**

The drug release behavior of the films was carried in 0.1 N HCl (pH 1.2) for 24 hours. The release of metclo from the HPMC 15000 cps films with and without carbopol 934 was shown in Figure 2A.

All gave a similar rapid burst release of metclo. The films within the first hour released 95% w/w metclo, and there was no significant difference between films ($p > 0.05$). But another study did not give slow release.[22] While metclo release from the second group HPMC K4M polymer is shown in Figure 2B, which revealed the HPMC K4M-1, and HPMC K4M-2 released around 70% w/w of metclo within the first hour of the study. Also, these two films showed a very close pattern of metclo release (non-significant difference ($p > 0.05$)), and after 24 hours, the release of metclo was around 80% w/w. Whereas the HPMC K4M-3 slowed the release of metclo to 50 % w/w and did not release metclo more than 52% w/w after 24 hours, as this was a significant release difference ($p \leq 0.05$) in comparison with the two other films. Hence, the HPMC K4M-3 was chosen for further investigation due to its slowing metclo release, representing part of the current work aim.

Swelling Index

The application of the swelling study was to ensure the film swelling once being in touch with the acidic media. This is because swelling initiates the release of drugs. As illustrated in Figure 3, the swelling index for HPMC K4M-3 generated an augmentation in swelling values then stabilization. This was harmonized with the film's metclo percentage release, as shown in the *in-vitro* release study. The direct trend relationship of metclo release with the swelling index values was similar to the combination of hydroxyl ethyl cellulose and HPMC K4M films.[16]

Many studies showed that film with low swelling index had low % of drug release and that was similar our results. Similarly, the HPMC film resulted in low % of drug release that showed low swelling index. Mona *et al.* studied HPMC buccal film showed low swelling and drug release of glipizide.[23]

***Ex-vivo* Mucoadhesive Strength**

In order to comprehend the gastro retentive approach of the selected film, mucoadhesion is an important factor to consider.

Mucoadhesion aids in maintaining a high drug concentration at the administration site while keeping the formulation intact for a longer period. The mucus layer that covers the stomach tissue must remain in close contact with the gastro retentive film for it to be effective.

Also, the force of adhesion refers to the strength of adhesion between two surfaces as a function of the force required to separate the two surfaces. The needed mucus detachment force

also refers to the strength of the adhesive bond. The amount of fracture work is determined by the length of the polymer chain and the degree of cross-linking in the polymer network.

The HPMC K4M-3 film result as shown in Figure 4, the mucoadhesive strength and force of adhesion were 18 gm and 0.1764 N, respectively. This result was close to the carbopol 981: HPMC film of previous work that showed mucoadhesion property.[17]

Histopathological Study

The effects of film mucoadhesive administration on the rat stomach mucosal membrane were assessed histopathologically and compared to normal tissue. The stomach mucous membrane of the rats treated with the film showed no alteration when compared to the normal rats, as shown in Figure 5. There was no evidence of inflammation or changes in histological architecture.[15] Figure 5A presents rat stomach as control or normal untreated mucous tissue. Figure 5B shows the mucosa after applications of HPMC K4M-3 films and had no observed changes.

Tensile Strength

Mechanical properties are measured by tensile strength and percent elongation at break. Several factors influence mechanical properties, including interactions between film constituents, temperature, microstructural features, and chemical conditions.[24] The tensile strength is defined as the maximum stress (force per unit area) applied to the point where the film is torn. In addition, % elongation at break represents the strain magnitude responsible for the film elongation.[19] Remarkably, polymeric films manifest an opposite relationship between tensile strength and % elongation. Hence, applying the tensile strength test to evaluate the film's elasticity is important in the integrity of the film that is favorable to be intact one piece. The HPMC K4M-3 presented moderate values 77.6% and 1.78 MPa its tensile strength as the common secondary polymer was the carbopol that might aid in exhibiting this kind of elasticity. The same outcome in a different study prepared a buccal film composed of sodium carboxymethylcellulose, and the carbopol increased quantity led to increasing %elongation values.[25]

CONCLUSION

The development and characterization of a gastro retentive dosage form for the slow release of metoclopramide HCl showed the best film was HPMC K4M-3 which demonstrated slow release. This was supported by both the swelling index and the tensile strength tests. The results also indicated that the gastro-retentive property was achieved by mucoadhesive that was shown by HPMC K4M-3 rather than floating.

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