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Original article

Formulation of metoclopramide HCl gastroretentive film and *in vitro- in silico* prediction using Gastroplus® PBPK software

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ABSTRACT

The new trends in pharmaceutical studies focus on targeting drug delivery and computer software that help in the body environment simulation, such as Gastroplus® software. The interest of this study is to prepare a gastroretentive film of metoclopramide HCl (MTC) that was followed by applying the *in silico* approach to estimate the *in vivo* prepared formulations. The films were prepared from HPMC E5 and sodium alginate polymers as primary polymers with the aid of secondary polymers. The sodium alginate high proportions films showed instant and long floating duration reaching 24 h but with variable folding endurance. Moreover, sodium alginate films with their secondary polymers carbopol and HPMC E5 slowed the release of MTC. The floating and slow-release patterns assessed the gastroretentive properties of sodium alginate films and were further examined by a mucoadhesive study that guaranteed mucosal adhesion, and the film's FESEM images showed similar top morphology, but different side view structures. Last, the pharmacokinetic profile of selected films that approached the gastroretentive properties was *in silico* predicted depending on *in vitro* release study and floating duration employing the physiological-based pharmacokinetic model in Gastroplus® software. The model determines this prediction found successfully of intravenous and immediate oral release tablets (10 and 30 mg) of MTC. The simulation showed a high amount of MTC retained for long periods in the stomach to Sod.Alginate-3, Sod.Alginate-8, and Sod.Alginate-10 films (films of secondary polymers carbopol and HPMC E5) aid in reaching the optimum site of absorption jejunum 1 due to the slow MTC release.

1. Introduction

The oral route is the most accessible and practical way to deliver drugs to patients, and many progressive approaches were practised and studied to serve specific goals (Jagdale et al. 2009). A case in point is the gastroretentive delivery system which establishes an extended drug delivery with increased residence time in the stomach (Kakumanu et al. 2008, Darandale,Vavia 2012, Bhardwaj et al. 2014, Tripathi et al. 2019). This system sets about for drug's action locally (Klausner et al. 2003, Kumar et al. 2008) or the drugs that are unstable in the intestinal or colonic environment (Meka et al. 2008). Moreover, medicines exhibit low solubility at high pH values (Streubel et al. 2006) or drugs with a short half-life (Vrettos et al. 2021). Also, drugs demonstrate absorption from only a particular portion of the gastrointestinal (GI) tract or show a regional variability in intestinal absorption. Such drugs showed an absorption window, which signified the region of the GI tract from where absorption primarily occurs (Rapolu et al. 2013). As an example, the oral provision of cyclosporine emulsion displayed the jejunum as the main absorption site by comparing the areas under the curve and the maximum absorption concentration in each gastrointestinal segment (Pancholi 2011). Also, levodopa, metformin, gabapentin, ciprofloxacin, and ofloxacin are highly absorbed from the upper small intestine. Indeed, the narrow absorption window drugs usually reveal low bioavailability due to limited absorption after these absorption sites in the gastrointestinal tract; thus, it is hard to formulate sustained release dosage forms (Davis 2005). Many dosage forms serve the gastroretentive goal, including tablets, gels, and last films, the approach of the current study (Arza et al. 2009, Farshforoush et al. 2017).

Several studies have recently used physiologically based pharmacokinetic software (PBPK) to produce a validated model

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depending on factors such as formulation factors, physicochemical drug properties, and human or animal physiology. The models that come from PBPK software with the integration of *in vitro* data lead to the prediction of *in vivo* data that assist in overcoming all the difficulties of formulation progress and the *in vivo* complexity work (Zhang et al. 2017). Herein, this work focuses on metoclopramide HCl (MTC), a drug that exerts its prokinetic influence on the smooth gastrointestinal muscle leading to increase gastric emptying into the intestine (Davis 2005, Singh et al. 2007). Essentially, MTC is classified as class III according to BCS. Remarkably, MTC established variable bioavailabilities due to different individual first-pass effects (Stosik et al. 2008).

The current work aimed firstly to formulate a gastroretentive film with (MTC) delivered in a hard gelatin capsule using HPMC E5 and sodium alginate polymers, as no previous study developed MTC as a gastroretentive film. However, MTC was previously prepared in a floating matrix tablet (Singh et al. 2007). Retention of MTC in the stomach guarantees the prolonged effect and improves systemic availability, which is considered to overcome nausea or vomiting due to chemotherapy treatment or migraine disease (Friedman et al. 2008, Sharif et al. 2019, Farooqi et al. 2020). Also, the MTC's prolonged effect formulations overcome the rapid systemic or plasma concentration dropping due to MTC's short half-life of 5 to 6 h (Zabirowicz,Gan 2019). The second aim was application MTC physiologically based pharmacokinetic model on the *in vitro* MTC release profiles of gastroretentive prepared films to predict the *in vivo* of the MTC films and pharmacokinetic parameters using Gastroplus® software (version 9.8, SimulationPlus Inc., Lancaster, CA, USA). Previously, MTC was modelled using PK-sim® software (PK-Sim® 7.4, Bayer AG, Wuppertal, Germany) by relying on clinical trials for Korean people with different CYP2D6 genotypes who received 10 mg MTC orally (SHIN 2020).

2. Material and methods

2.1. Materials

MTC was a gift from Samarra pharmaceutical company, and HPMC K4M with HPMC E5 were purchased from Nanjing Duly Biotec. Company. ltd./China. Carbopol 934 and PEG-400 were brought from Xi'an Prius bioengineering, China, and HiMedia Laboratories Pvt. ltd./India, respectively. Last, sodium alginate was purchased from Sino pharm Chemical Reagent, China.

2.2. Methods

2.2.1. Formulation of the film

According to Table-1, the casting method was used to prepare films by first dissolving the primary polymers (sodium alginate and HPMC E5) with the secondary polymers (Carbopol® 934 NF and HPMC K4M) in water with the required amount of PEG 400 to be mixed vigorously then poured and placed in a glass mold (diameter 4.2 cm) into the oven at 40 °C for 24 h. HPMC film needed to be dissolved in 30 % w/v portion of hot water, then add the remaining water as cold while sodium alginate dissolving required no heating to the water.

2.2.2. Physical properties (Folding endurance, and buoyancy / floating test)

Films were subjected to physical tests starting with folding endurance, an examination of counting the number of folds applied manually by folding and opening the films until developing a crack or break at the folding site. Second, the floating test was done in triplicate by placing the film in 250 ml 0.1 N HCl (pH 1.2) and monitoring the time for films to buoyant from the bottom to the top of the container, representing the lag time. The film's time to stay float is the floating duration.

Table 1
Films formulation content (wt %).

Formulations	Sodium alginate (mg)	HPMC E5 (mg)	Carbopol® 934 NF (mg)	HPMC K4M (mg)
HPMC E5-1	–	100	–	–
HPMC E5-2	–	75	25	–
HPMC E5-3	–	50	50	–
HPMC E5-4	–	25	75	–
Sod. Alginate-1	100	–	–	–
Sod. Alginate-2	75	–	25	–
Sod. Alginate-3	50	–	50	–
Sod. Alginate-4	25	–	75	–
Sod. Alginate-5	75	–	–	25
Sod. Alginate-6	50	–	–	50
Sod. Alginate-7	25	–	–	75
Sod. Alginate-8	75	25	–	–
Sod. Alginate-9	25	75	–	–
Sod. Alginate-10	50	50	–	–

*Ten mg of MTC was added to all formulations.

2.2.3. In vitro release study

A hard gelatin capsule contained an enrolled film placed in a filled jar with 900 ml of USP type II apparatus of 0.1 N HCl pH 1.2. This experiment was set at a temperature of 37 ± 0.5 °C and stirred at 75 rpm. The samples were taken according to the study's time frame and replaced with fresh media. All withdrawn samples were analysed using a UV spectrometer at 273 nm the MTC λ^{max} and applied the equation of the MTC calibration curve (y = 30.93 5x + 0.0172) to find the concentrations. The *in vitro* release study was in triplicate, and the standard deviation between release profiles was evaluated by the statistical test One-way ANOVA using SPSS software.

2.2.4. Ex-vivo mucoadhesive strength

This test needs fresh rat stomach tissue from the animal house to be used within 2 h of slaughter after washing with distilled water to be stuck to the bottom of a petri dish by glue, making the stomach mucosa facing upwards and moistening it with HCl solution. To apply this test, a modified physical balance was used as 5 gm weight on the right-hand pan to equal the 2 sides and adjusted the left pan by holding a rubber stopper. The film was placed and stuck to the rubber stopper connected by threads to the non-pan left arm. The rubber stopper was laid down and cohered over the stomach mucosa (in a petri dish) on the left side of the balance after removing the 5 gm weight from the right side. Keep this step for 10 min, then drop water on the right side of the pan until gaining complete film detachment from stomach tissue. The mucoadhesive strength represents the subtracted value of water weight addition from the 5 g (Pendekal,Tegginamat 2012).

2.2.5. Field emission scanning electron microscopy (FESEM)

The top and side of prepared films were subjected to FESEM to probe their morphology using TESCAN MIRA3, Czech Republic, as the film processing was done by fixing the film on stubs to be then coated with a thin gold layer.

2.2.6. In silico modelling for absorption

Gastroplus® software (version 9.8, SimulationPlus Inc., Lancaster, CA, USA) assisted in building a model of MTC to predict *in vivo* for *in vitro* release data. As shown in Table 2, the input data were predicted *in silico* using ADMET Predictor and PKPlus modules. In addition, the *in vitro* release data of MTC films were

Table 2
The inputs summary of MTC absorption model was taken from ADMET Predictor and PKPlus in Gastroplus® software (version 9.8, Simulation Plus, Inc., Lancaster, CA, USA).

Parameter	Values
Log P	2.32
Molecular weight (g/mol)	299.8
Solubility (mg/ ml) at pH 10	1.95
Diffusion coefficient (cm^2/ $sec \times 10^{-5}$)	0.73
Jejunal Effective Permeability (Peff) (X 10^{-4} cm/s)	1.46
Unbound Percent in Human Plasma (Fup %)	43.2
Mean precipitation time (*sec*)	900
Drug particle density (gm/ml)	1.2
Body weight (kg)	70
Blood/plasma conc. Ratio	1.01
Clearance (Cl) (L/hr/ kg)	0.368
Volume of distribution V2 (L/kg)	0.645
Distribution constant k12 (1/h)	0.517
Distribution constanr k21 (1/h)	0.99
fup.GFR (systemic renal clearance L/hr)	3.118

inputted into the gastroplus® software. This predicting model assigned the MTC specific absorption site from the gastrointestinal tract by Advanced Compartmental Absorption and Transient (ACAT) model, where this model itself relied on the PBPK model. ACAT comprises 9 segments: stomach, duodenum, jejunum 1 and 2, ileum 1–3, caecum and ascending colon. All these segments were controlled by dissolution, absorption, and drug transport equations. The building model depended on intravenous and oral 10 mg of MTC, the dose assigned and incorporated in the prepared films. These intravenous and oral MTC data were extracted using GetData Digitizer version 2.26.0.2 software (Ross-Lee et al. 1981). The Km and Vmax were 1.2 μm and 6.1 pmol/min/pmol, belonging to the P2D6 enzyme that mainly metabolises MTC (Livezey et al. 2014). The PKPlus software module application determined the MTC,s clearance and metabolism values depending on intravenous 10 mg that exhibited two compartmental models as shown in Table 2. The error percentage (%PE) of prediction was applied between the observed and simulated data using the following equation (Cvijic et al. 2018):

$$\%PE = \frac{(Observed - predicted) * 100}{Observed}$$

The created model for 10 mg immediate-release tablet was for fasted American female, 30 years old, 59.5 kg weight, was used to predict the *in vivo* absorption of the MTC after release from films (Ross-Lee et al. 1981). The gastroretentive time corresponded to the floating duration as the mucoadhesive strength is hard to relate with physiological parameters. The physiology of males 26 years old and 77 kg was the base of building the model for 30 mg immediate-release tablet (Hasan et al. 2003). Both models were set as limited perfusion models. The input of *in vitro* MTC release from the film data were used to predict their concentration plasma time curve by selecting CR gastric as the dosage form.

3. Results

3.1. Formulation of the film

Eleven formulations showed films of smooth surfaces and no uneven or clumps within the films, whereas 3 formulations did not formulate films which were HPMC E4, Sod.Alginate-4 and Sod.Alginate-7 as they composed of 75 mg of the secondary polymers (carbopol and HPMC K4M). This outcome was comparable to Skulason S. *et al*, who found fragile and lousy handling films composed of carbopol (Skulason et al. 2009). Also, 75 mg of HPMC K4M could be a small amount to assist in film fabrication as a glibenclamide film formed by adding 300 mg of HPMC K4M (Bahri-Najafi et al. 2014).

3.2. Physical properties (Folding endurance and buoyancy / floating test)

Starting with the folding endurance study to assess the film's ability to be packaged in capsules, the results are demonstrated in Table 3. The folding endurance values were different as some films showed low values of the folding capacity of > 10; in others, their folding degree was higher,>100 and > 300. The good folding value is > 300, as this was documented in bilayer film of rabeprazole sodium and famotidine (Lenson,Marina 2016). Secondly, all films presented prompt floating; however, they showed different floating duration, as clarified in Table 3. The floating lag time for drug-loaded floating films was zero, referring to the gelatin capsule that the film was already folded within, helping achieve zero lag time and instant floating. Clearly, Sod. Alginate films floated for more extended periods compared with HPMC E5 films. Likewise, Suvana *et al* prepared sodium alginate film with gelatin and carboxymethylcellulose that was buoyant for 10 h (Chittam,Bhosale 2020). HPMC films during the floating period turn into small pieces, whereas Sod. Alginate films stayed intact during their floating duration.

3.3. In vitro release

The films were investigated for their MTC release pattern after hard gelatin capsule rapid dissolution in gastric media; as shown in Fig. 1, the HPMC E5-1, and HPMC E5-3 films did not slow the MTC release, but HPMC E5-2 slowed the MTC release to 39.8 wt% as shown in Fig. 1A. The HPMC E5-2 had a significantly slower release than the other films in the same group ($p \leq 0.05$), which might be due to the lower 25 mg carbopol 934 film components.

Fig. 1B illustrated the sodium alginate films that contained Carbopol® 934 NF as a secondary polymer (Sod. Alginate-1, Sod. Alginate-2 and, Sod. Alginate-3), and their MTC release was an analogous non-significant different ($p>0.05$) in which the effect of different concentrations of carbopol® 934 NF addition was not pronounced. However, these films slowed the release of MTC to 40, 50, 60, and 75 (wt%) after 1, 2, 4 and 24 h, respectively. Likely, the films in Fig. 1C related to sodium alginate films that its secondary polymer HPMC K4M also exhibited no difference in the release profiles and released all its content fastly. Last, in Fig. 1D, the Sod. Alginate-8, Sod. Alginate-9, and Sod. Alginate-10 films clarified the effect of HPMC E5 addition in the film formulations, and it was found that the proportion 75:25, as well as 50:50, had the same release pattern (non-significant $p>0.05$). Strangely, these two films slowed the MTC release to 30 wt% after one hour of the release study and then sustained the MTC release of not > 40 wt% till the end of the study. The release of drugs from the polymeric matrix is directly related to the polymer swelling (Özçelik et al. 2021); hence, the difference and the MTC rapid release from HPMC films compared with slow MTC released from sodium alginate films could be attributed to the HPMC swelling (Kaunisto et al. 2011). This is consistent with a previous study for the buccal film that found slight sodium alginate swelling and a swelling augmentation upon HPMC increased concentration (Skulason et al. 2009).

The release study helped discriminate the films that slowed the release of MTC as this was the aim of the gastroretentive film, and these films HPMC E5-2, Sod. Alginate-3, Sod. Alginate-8, Sod. Alginate-9, and Sod. Alginate-10 were subjected to further analysis. These films slowed MTC release more than the hydrodynamical balance tablet that released 100 wt% of MTC after 8 h (Wamorkar et al. 2010) and MTC in situ gel (Wamorkar et al. 2011). In conclusion, the films HPMC E5-2, Sod. Alginate-3, Sod. Alginate-8, Sod.

Table 3
Physical properties of films folding endurance and floating test.

Film formulation	HPMC E5-1	HPMC E5-2	HPMC E5-3	Sod. Alginate-1	Sod. Alginate-2	Sod. Alginate-3	Sod. Alginate-5	Sod. Alginate-6	Sod. Alginate-8	Sod. Alginate-9	Sod. Alginate-10
Folding endurance	>10	>300	>300	>100	>100	>100	>300	>300	>50	>300	>100
Floating duration (min) ± SD	60 ± 23.09	20 ± 0.00	120 ± 57.73	720 ± 364.96	720 ± 396.27	1440 ± 727.75	25 ± 0.00	960 ± 277.12	960 ± 138.56	20 ± 5.77	1440 ± 480

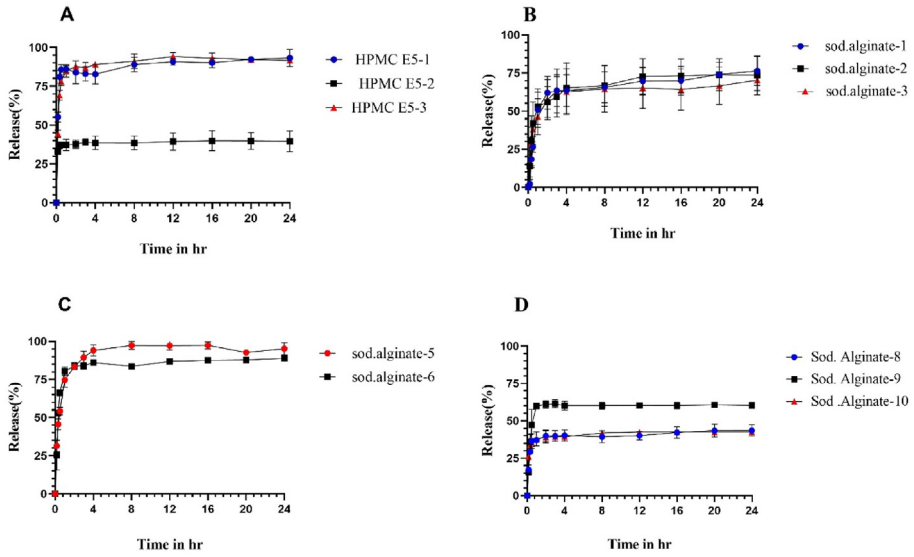

Fig. 1. *In vitro* MTC release for different films where Figure A represents HPMC E5 films with Carbopol® 934 NF, Figure B represents sodium alginate with Carbopol® 934 NF films, Figure C shows the sodium alginate with HPMC K4M films, and Figure D exhibits sodium alginate with HPMC E5 film as this study was done in triplicate in 900 ml acidic media 0.1 N HCl pH 1.2.

Alginate-9, and Sod. Alginate-10 slowed the drug's release at a different rate as this represents the core of gastroretentive film property; however, these films showed different floating durations.

3.4. Ex-vivo mucoadhesive strength

Mucoadhesion is essential in this study to understand the gastroretentive approach of films as there is a chance these films adhere to the stomach mucosa upon hard gelatin capsule rapid dissolution. The mucoadhesive strength results in gm were 8, 57, 22, 49.5, and 52.5 for the films HPMC E5-2, Sod.Algenate-8, Sod. Alginate-9, Sod. Alginate-10 and Sod. Alginate-3, respectively. The high strength values in this study (57, 49.5 gm, 52.5 gm) of Sod. Alginate-8, Sod. Alginate-10 and Sod. Alginate-3 were close to the mucoadhesive strength value of the captopril films that contained carbople® 934 NF (Anupam et al. 2013). Cetirizine buccal film of sodium alginate and HPMC showed fair mucoadhesion, broadly comparable to the films in the current work (Pamlényi et al. 2021). Mucoadhesion could be due to the bond of the film's component with a mucosal surface which might be kept for prolonged periods (Boddupalli et al. 2010). Interstengely, the films Sod.Alginate-3, Sod. Alginate-8 and Sod.Alginate-10 exhibit good gastroretentive properties by showing extended floating periods and suitable adhesion to the gastric mucosa. In contrast, the other films in our work were buoyant for a short period, and their adherence to the gastric mucosa was lower.

3.5. Field emission scanning electron microscopy (FESEM)

The film's top and underlying morphology were essential to probe and might help to understand the film's different polymers proportions on the medicament release or other physical properties, as illustrated in Fig. 2. Images A, C, E, G and I showed smooth surfaces and similar structures comparable to the previous work that used FESEM to study the surfaces or tops of the PVA films (Nur,Nasir 2008).

The cross-sectioned morphology in images D, F, H and J showed a compact sponge-like structure which this kind of structure might be the reason for the slow release of MTC from the film. At the same time, image B showed a very different structure of beads in clusters arranged in such uniformity. These non-similar constructions of underlying films might have a role in the drug release. To conclude, the cross or side view of the film showed dissimilar underlying structures, while the surfaces of the films showed no difference in morphology.

3.6. In silico MTC model for absorption

The physicochemical and pharmacokinetics inputs that were used to generate the physiological model for the *in silico* simulation are shown in Table 2 and the pharmacokinetic parameters of the constructed model are screened in Table 4. The model constructed for 10 mg intravenous (IV), as shown in Fig. 3A, was validated depending on the error percentage of comparison data: Cmax, Tmax, AUC $_{0\text{-inf}}$, and AUC $_{0\text{-t}}$. Many studies accepted higher values of the error percentage as long as the predicted (calculated value) is not double the observed value or a non-doubled fold error value (The fold error = calculated value/ observed value)(Park et al. 2017). Fig. 3A presents the two-compartment model that was 10 mg IV followed. The outcome of this process (Cmax, Tmax, AUC $_{0\text{-inf}}$, and AUC $_{0\text{-t}}$) is shown in Table 4, with a very acceptable difference.

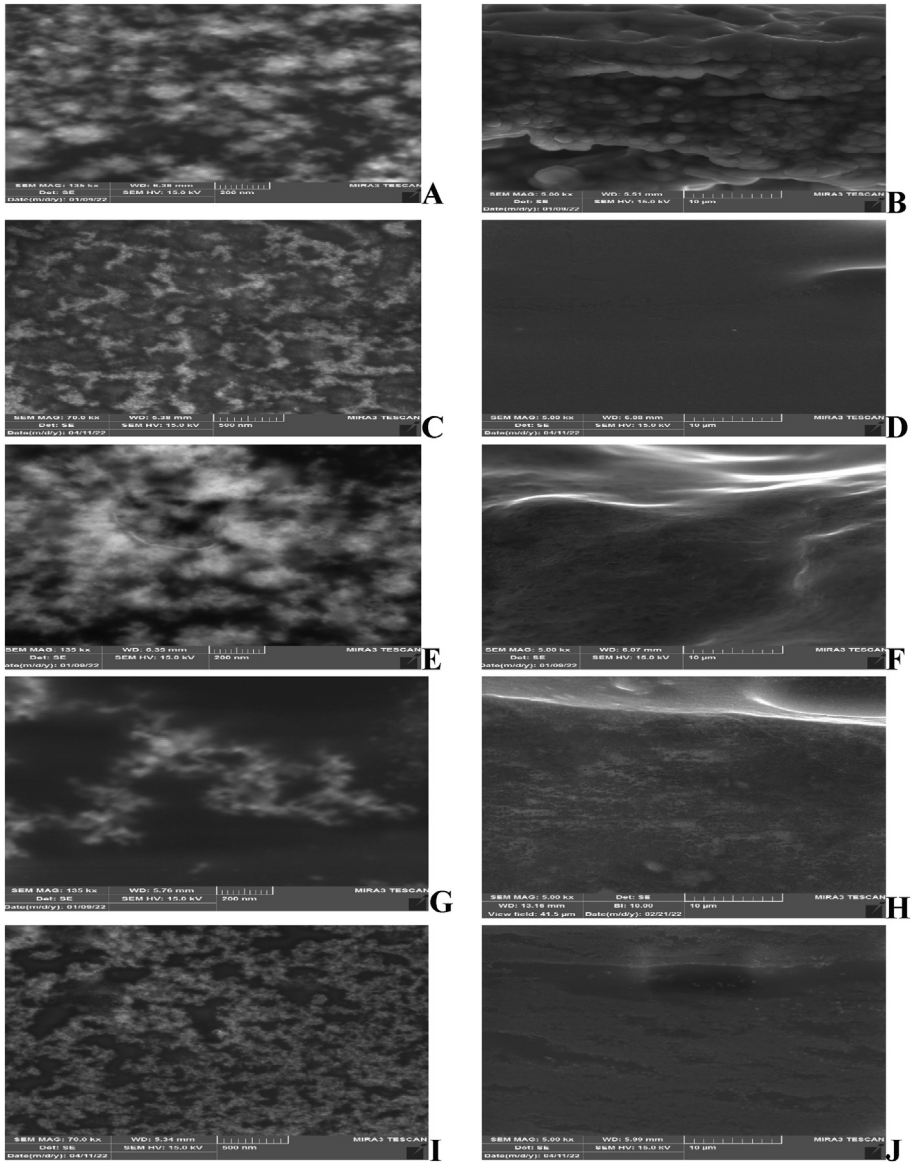

Fig. 2. FESEM picture of the films. (A and B) top and cross-section of HPMC E5-2. (C and D) top and cross-section of Sod. Alginate-9. (E and F) top and cross-section of Sod. Alginate-3. (G and H) top and cross-section of Sod. Alginate-8. (I and J) top and cross-section of Sod. Alginate-10. Images (A, E, and G) in the left column were scaled against 200 nm, and images (C and I) in the left column were scaled against 500 nm, whereas images in the right column were scaled against 10 μm.

Additionally, building the oral model 10 mg immediate-release tablet, as shown in Fig. 3B, the error percentage for the comparison data was also within acceptable values. Only Tmax showed a high %PE but the fold error is 1.3. This may be referred to the lack of accuracy of blood sampling to specify the time at the maximum concentration in blood. Similarly, the values near the 2-fold error were also found and verified in the pharmacokinetic parameters of lorazepam, oxazepam and zidovudine (Docci et al. 2020). Also, the predicting model for 30 mg MTC immediate-release tablets, as illustrated in Fig. 3C, showed acceptable error limits, except the Tmax and AUC $_{0\text{-inf}}$ presented a little higher value but were kept within the adequate 1.27 and 1.2 of fold error. The 30 mg immediate-release model was different by adding the same values of km and Vmax to the liver and were already included in the gut and PBPK. This addition helped obtain this model and established that the liver enzyme has an essential role in the MTC metabolism with the dose increased or to the differences of individuals. Additionally, as mentioned in the experiment section, the obtained models were subjected to perfusion limited model despite the conservative classification of MTC to class III. The proceeding with the non-permeability limited model can be related to the MTC good permeability value (1.46 $X10^{-4}$ cm/s) that was predicted using ADMET software. As the permeability theory relied on previous findings that concluded the drugs with 1.5 $X10^{-4}$ cm/s permeability and higher values showed complete absorption, whatever the absorption mechanism (Lennernäs 2007).

Consequently, the generated models were used to simulate the MTC absorption and disposition from gastrointestinal segments and demonstrate the pharmacokinetic parameters of selected gastroretentive film depending on their *in vitro* release data and floating duration, as shown in Fig. 4, Fig. 5 and Table 5. For comparison purposes, the Sod.Alginate-5 that showed rapid MTC release was simulated as an immediate release system, and its pharmacokinetic parameters were close to the predicted values of a 10 mg immediate-release tablet model. The simulating curves of plasma concentration–time as in Fig. 4 and Table-5 revealed the films

Table 4
Gastroplus® pharmacokinetic MTC parameters of oral tablets 10 mg and 30 mg for observed and predicted values.

Pharmacokinetic parameters	Observed	Calculated	% PE	Observed	Calculated	% PE
	Oral			**IV**		
Cmax (ng/ml) (10 mg)	47.336	45.72	3.4	105.59	115.45	9.33
Cmax (ng/ml) (30 mg)	89.305	92.156	−3.19			
Tmax (hr) (10 mg)	0.975	1.3	−33.3			
Tmax (hr) (30 mg)	1.064	1.36	−27.81			
AUC $_{0\text{-inf}}$ (ng-h/ml) (10 mg)	286.74	262.14	8.57	351.08	387.11	10.26
AUC $_{0\text{-inf}}$ (ng-h/ml) (30 mg)		592.45	−28.65			
AUC $_{0\text{-t}}$ (ng-h/ml) (10 mg)	186.37	208.43	−11.83	331.73	326.53	1.56
AUC $_{0\text{-t}}$ (ng-h/ml) (30 mg)	434.98	475.13	−9.23			

The negative sign indicates the observed values are > than predicted values.

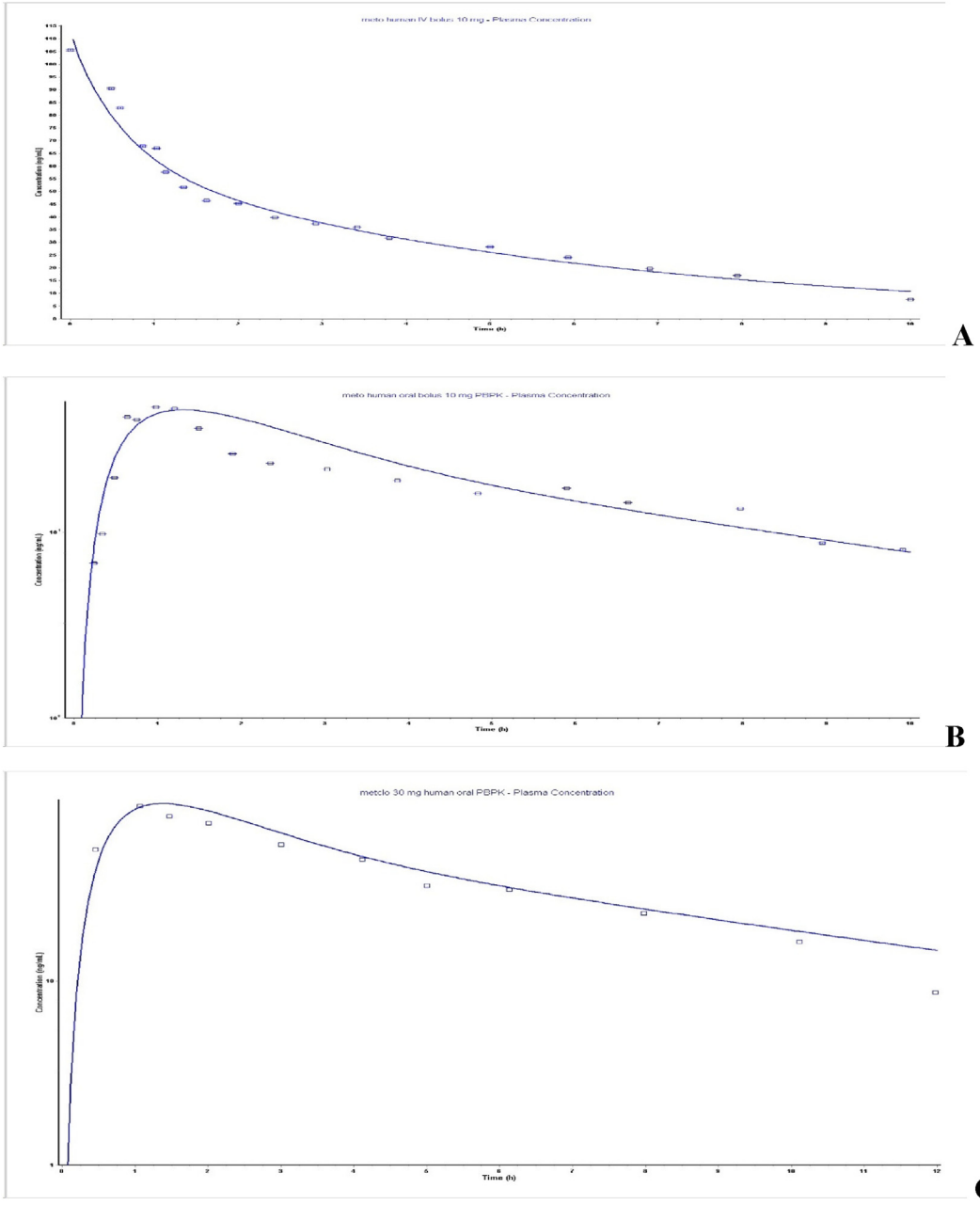

Fig. 3. A and B are Gastroplus® figures as the dotted line represents the observed data while the solid represents the MTC predicted values after IV and oral immediate-release tablet administration of 10 mg, respectively. Figure C represents the predicted model for oral immediate-release 30 mg.

Sod. Alginate-3 and Sod.Alginate-8 with very low Cmax and non-steeply declining curves confirm the *in vitro* gastroreteintive properties of the slow release of MTC.

In contrast, Sod.Alginate-5 rapid release, Sod.Alginate-9, and to some extent HPMC E5-2 showed significant peaks of Cmax, as, after this point, a declining curve was evidence of these films not sustaining the MTC released in the stomach due to floating in short periods in the stomach. These results indicated a direct relationship between predicted bioavailabilities and *in vitro* MTC released amount within simulation time. As this relationship is comparable to furosemide prolonged-release formulation, which revealed lower predicted furosemide bioavailability (Markovic et al. 2020).

Furthermore, Fig. 5A signifies no absorption in the stomach region, whereas the maximum MTC absorption was in the jejeunum 1 followed by the duodenum since the absorption hardly occurs after these two segments. Similarly, carvedilol gastroretentive beads predicting results presented no absorption in the stomach region; however, the main absorption site was the duodenum (Praveen et al. 2017). The floating or the gastroretentive time in the stomach had a role in the pharmacokinetic parameters that were screened in Table 5 and shown in Fig. 5B and 5C. These figures demonstrate the films Sod.Alginate-3, Sod.Alginate-8, and Sod. Alginate-10 with a site high amount in the stomach that floating for 16 to 24 h long by showing a straight curve within the first 2 h of time simulation. Whereas the HPMC E5-2 and Sod. Alginate-9 curves demonstrate (Fig. 5C) a gradual rapid decrease in the gastric MTC amount within the 20 min of simulation time, representing the floating duration. Last, the Sod.Alginate-5 revealed a rapid decline in the gastric amount of MTC within 25 min of the simulation time, as this time represents the average gastric retention time for a fasted human. Thus, this amount in the stomach reflected its impact on the AUC $_{0\text{-}t}$ as films Sod.Alginate-9 and HPMC E5-2 showed double the AUC $_{0\text{-}t}$ of MTC compared with the Sod.Alginate-10 and Sod.Alginate-8. These prediction outcomes helped to conclude that the gatroretentive floating properties of the film assist in the persistent residence of MTC in the film, and the slow MTC release in the stomach aid in guaranteeing the MTC transfer rate to the appropriate absorption site to increase bioavailability. However, a better MTC plasm level might be

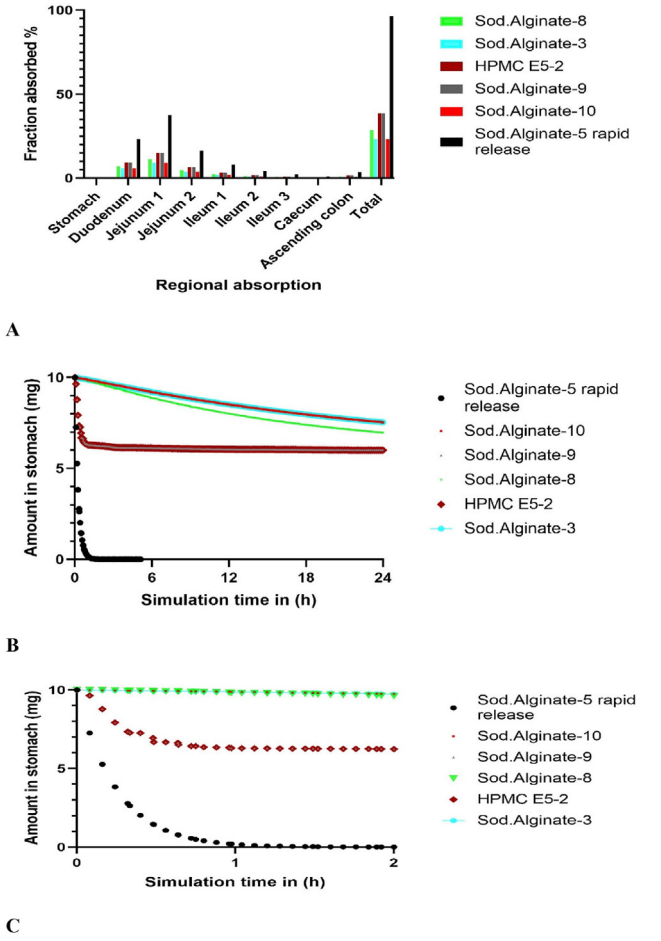

Fig. 5. Predicting data A- The regional absorption of the 10 mg MTC selected gastroretentive films. B- The MTC amount retained in the stomach for 24 h of each MTC gstroretentive film. C- The MTC amount retained in the stomach for each MTC gstroretentive film in the first 2 h of simulated time. These data were obtained from Gastroplus® software (version 9.8, SimulationPlus Inc., Lancaster, CA, USA).

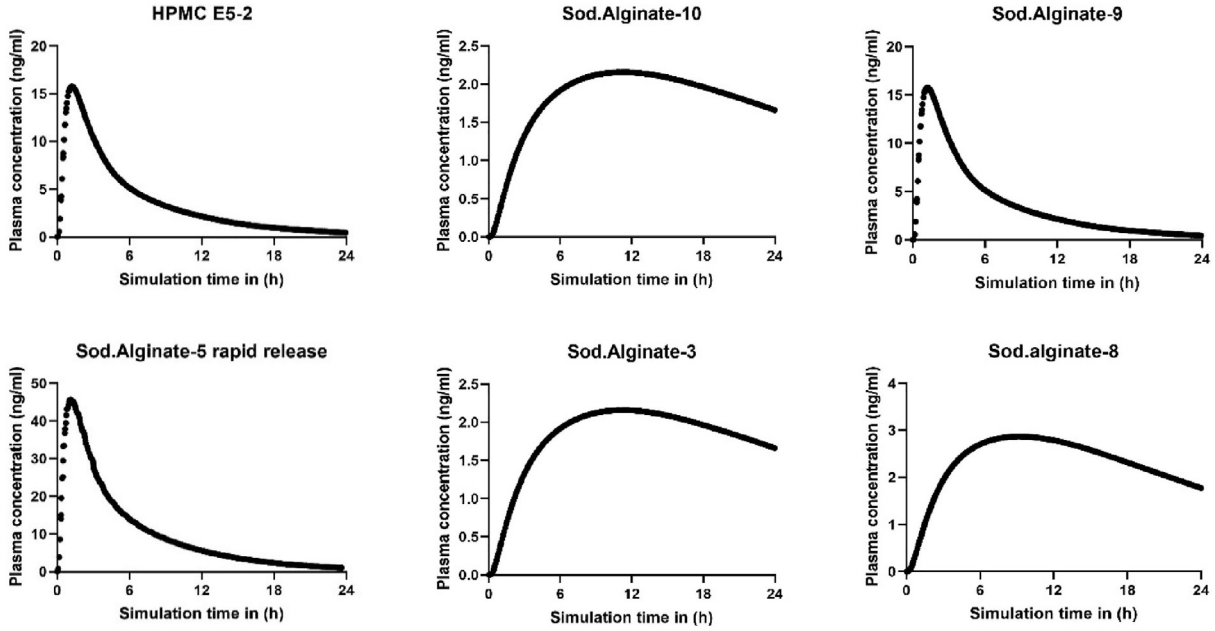

Fig. 4. Predected plasma concentration–time curves of selected films.

Table 5
Pharmacokinetics parameters of selected films.

Formulation film	Cmax (ng/ml)	AUC $_{0\text{-inf}}$ (ng-h/ml)	AUC $_{0\text{-t}}$ (ng-h/ml)
Sod.Alginate-10	2.1583	95.171	42.948
Sod.Alginate-9	15.78	93.374	89.998
Sod.Alginate-8	2.8704	91.264	54.826
Sod.Alginate-3	2.1583	95.171	42.948
Sod.Alginate-5 rapid release	45.713	263.03	256.06
HPMC E5-2	15.78	93.374	89.998

achieved if the Sod.Alginate-5 rapid release film as an initial dose followed simultaneously by Sod.Alginate-3 film to sustain the MTC plasma level as a maintenance dose.

4. Conclusion

This work aimed to formulate films for gastroretentive purposes using MTC as a model drug suitable for this dosage form. This aim was established by developing several gastroretentive films using primary and secondary polymers and evaluating them via many studies such as floating test, mucoadhesive strength, and the *in vitro* release study, in addition to the folding endurance. Gastroretentive properties were served by the films Sod. Alginate-8 and Sod. Alginate-10 were buoyant for > 16 h, and at the same time, their mucoadhesive strength was 57 g and 49.5 g, respectively. Prosperous-generated models of MTC were acquired by using Gastroplus® software that assisted *in vivo* simulation. Also, the *in silico* outcomes that depend on *in vitro* release study showed the highest amount of MTC in the films (Sod. Alginate-8 and Sod. Alginate-10) retained for an extended period was parallel to the film's floating duration at the stomach site as evidence of the gastroretentive approach and the slow MTC release. Also, the Gastroplus® software simulation revealed that jejunum 1 has the highest MTC absorption site.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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