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FORMULATION OF METOCLOPRAMIDE SUSTAINED RELEASE TABLETS USING NATURAL GUMS

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ABSTRACT

The objective of this study was to formulate and evaluate Metoclopramide sustained-release tablets using floating drug delivery systems (FGR) to enhance the therapeutic efficacy of the drug by prolonging its gastric retention time. Various formulations were developed and characterized based on their pre-compression and post-compression properties, *in-vitro* buoyancy, and drug release profiles. The floating lag time of the formulations varied from 33 seconds (F7) to 69 seconds (F1), with F7 showing the shortest lag time. The in-vitro drug release study revealed that Formulation F7 achieved 99.74% drug release within 12 hours, making it the most promising formulation for sustained release. Regression analysis showed that F7 exhibited the best fit to the Peppas model (R^2 = 0.9529), indicating that a combination of diffusion and polymer erosion controlled the drug release. Post-compression evaluation demonstrated acceptable values for tablet hardness, friability, and drug content, confirming the physical integrity and content uniformity of the tablets. The study concluded that Formulation F7 is the optimal candidate for a Metoclopramide sustained-release floating tablet, offering controlled drug release, excellent floating behavior, and good pharmacotechnical properties, which can improve patient compliance in the treatment of gastrointestinal disorders.

Keywords: Metoclopramide, Sustained-release tablets, Floating drug delivery system, Floating lag time, *In-vitro* drug release, Peppas model, Gastric retention, Drug release kinetics

INTRODUCTION

Metoclopramide is a dopamine antagonist that is widely used to treat nausea, vomiting, and gastroparesis (delayed gastric emptying). It works by increasing the motility of the upper gastrointestinal tract and blocking the action of dopamine, a neurotransmitter involved in nausea and vomiting. Traditionally, metoclopramide is available in immediate-release formulations, which require frequent dosing to maintain therapeutic levels. However, sustained-release formulations (SRFs) offer several advantages, including prolonged drug action, improved patient compliance, and reduced side effects due to steady release of the drug over time (Siewert *et al.,* 2004).

Natural gums, derived from plant sources, are gaining attention as excipients in pharmaceutical formulations due to their biocompatibility, availability, and potential for controlled drug release. These natural polymers, including guar gum, xanthan gum, and tragacanth gum, have been extensively studied for their ability to control drug release by modifying the matrix structure of tablets

(Almeida *et al.,* 2017). Gums are highly versatile and can be used as binding agents, disintegrants, film-forming agents, or release-modifying agents in sustained-release tablet formulations.

The use of natural gums for sustained-release formulations of metoclopramide can be an effective strategy to reduce the frequency of dosing, minimize fluctuations in plasma drug concentrations, and improve patient adherence to therapy. These gums, when used in appropriate concentrations, can control the release of the drug by forming a gel matrix upon contact with the aqueous medium, thereby retarding the drug release in a controlled manner. In addition, natural gums have the advantage of being cost-effective and readily available, making them an attractive option for large-scale manufacturing (Sharma *et al.,* 2018).

The primary goal of this study is to develop metoclopramide sustained-release tablets using natural gums and to evaluate their physicochemical properties, in-vitro drug release profiles, and stability. The work aims to determine the optimal gum type and concentration for formulating a sustained-release metoclopramide tablet that meets the desired pharmacokinetic and pharmacodynamic properties.

MATERIALS AND METHODS

Method for preparation of Metoclopramide sustained release tablets

Direct compression was taken after to manufacture the gas generating floating tablets of Metoclopramide (Basavaraja *et al.,* 2015). Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table 1 and all the definition were utilized for encourage assessments parameters.

Optimization of sustained release tablets of Metoclopramide

Optimization of formulation carried out on the basis of OVAT (One variable at time) using amount of excipient used like Excipients like Xanthan gum, Gellan gum, Chitosan and Carbopol 940 P.

Evaluation of precompression parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas (Bharadwaj *et al.,* 2000):

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X } 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

General appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (Pundir *et al.,* 2015).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined (Basak *et al.,* 2006). The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 274 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Varshosaz *et al.,* 2006).

Friability

The friability of a sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (Venkataramudu *et al.,* 2012).

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***In vitro* buoyancy studies**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5$^{°C}$ and rpm of 75. One prepared Metoclopramide tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37$^{°}$C) was supplanted each time with a similar amount of the sample and takes the absorbance at 274nm using UV/Visible spectroscopy.

RESULTS AND DISCUSSION

In the present study, sustained-release tablets of Metoclopramide were formulated using various natural gums as excipients to evaluate their potential for improving the pharmacokinetic profile of the drug. The formulations were characterized by several pre- and post-compression parameters, in-vitro buoyancy, and drug release profiles to assess their suitability for sustained release applications.

The pre-compression properties (Table 2) such as bulk density, tapped density, compressibility index, and Hausner ratio are critical in determining the flow and packing characteristics of the powder blend used in tablet formulation. The bulk density of the formulations ranged from 0.338 to 0.374 g/ml**,** and the tapped density varied from 0.449 to 0.485 g/ml, indicating that the powders had adequate flow properties, which are essential for uniform tablet weight. The compressibility index ranged from 22.46% to 27.56%**,** which suggests that the formulations exhibit good compressibility, an essential factor for producing tablets with consistent hardness and content uniformity. The Hausner ratio values were between 1.290 and 1.380, which is indicative of acceptable flow and cohesiveness of the powder mixture.

The post-compression properties (Table 3) such as tablet thickness, hardness, weight variation, friability, and drug content are crucial indicators of the quality and performance of the sustained-release tablets. The tablet thickness was uniform across the formulations, with values ranging from 3.09 mm to 3.18 mm, indicating consistency in tablet shape. The hardness of the tablets ranged from 5.6 to 5.9 kg/cm²**,** which is sufficient to withstand handling without breaking, suggesting robust tablet integrity. The weight variation was within the acceptable pharmacopoeial limits, confirming uniformity in tablet content. The friability values, ranging from 0.632% to 0.745%**,** were well below the standard limit of 1%, indicating good mechanical strength. The drug content of the tablets ranged from 96.65% to 99.45%, which is within the acceptable range (90-110%) and indicates uniform drug distribution within the tablets.

The buoyancy study (Table 4) results show that the floating lag time ranged from 33 seconds to 69 seconds, with F7 demonstrating the shortest lag time (33 seconds). This indicates that the formulation containing natural gums exhibited excellent buoyancy properties, which is essential for sustained drug release in the gastrointestinal tract**.** The buoyancy of the tablets is crucial for their ability to float in the stomach, extending the release of the drug over a prolonged period and thereby improving therapeutic efficacy. All formulations showed a floating duration of >12 hours, indicating that they remained buoyant long enough to facilitate sustained drug release.

The in-vitro drug release study (Table 5) revealed that the drug release from the formulations was gradual and sustained over a period of 12 hours. The cumulative drug release was highest for Formulation F7**,** which showed nearly 99.74% release at 12 hours**,** while formulations like F1 released around 39.98% of the drug at 0.5 hours and reached 98.78% at 3 hours. The release rate was slower for F7, showing a controlled release pattern throughout the test period. This indicates that F7 was the best formulation for sustained release, potentially offering a once-daily dose option for patients.

The sustained release behavior of the formulations can be attributed to the gel-forming property of the natural gums, which swells in the gastric fluid and controls the drug release rate. The formulations with higher buoyancy and better gelling ability demonstrated slower and more controlled release profiles.

The regression analysis data (Table 6) show that the release mechanism of Formulation F7 follows a combination of First Order (R^2 = 0.9032) and Higuchi model (R^2 = 0.9327), which suggests that the drug release is governed by diffusion and erosion of the matrix. The Korsmeyer-Peppas model (R^2 = 0.9529) showed a good fit, confirming that the drug release is controlled through Fickian diffusion (release exponent n < 0.5), further suggesting that the matrix swelling and diffusion played a key role in controlling the release of the drug. This was consistent with the desired sustained release profile.

Table 1: Various formulations of sustained release tablets of Metoclopramide

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoclopramide	10	10	10	10	10	10	10	10	10
Xanthan gum	120	140	160	-	-	-	60	70	80
Gellan gum	-	-	-	120	140	160	60	70	80
Carbopol 940 P	-	-	-	-	-	-	20	20	20
Chitosan	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	100	80	60	100	80	60	80	60	40
Total Weight	300	300	300	300	300	300	300	300	300

Table 2: Result of pre-compression properties of Metoclopramide

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.345	0.465	25.806	1.348
F2	0.365	0.485	24.742	1.329
F3	0.347	0.479	27.557	1.380
F4	0.358	0.469	23.667	1.310
F5	0.366	0.476	23.109	1.301
F6	0.359	0.463	22.462	1.290
F7	0.374	0.485	22.887	1.297
F8	0.338	0.449	24.722	1.328
F9	0.347	0.463	25.054	1.334

Table 3: Results of post compression properties of Metoclopramide sustain release tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.12	5.8	303	0.658	96.65	>12
F2	3.12	5.8	300	0.715	97.74	>12
F3	3.18	5.9	306	0.745	98.85	>12
F4	3.15	5.8	298	0.698	98.12	>12
F5	3.15	5.9	300	0.725	97.85	>12
F6	3.09	5.7	304	0.632	96.65	>12
F7	3.11	5.6	306	0.722	99.45	>12
F8	3.12	5.8	305	0.698	96.65	>12
F9	3.15	5.8	303	0.712	97.74	>12

Table 4: Results of *in-vitro* buoyancy study of Metoclopramide sustain release Floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	69
2.	F2	62
3.	F3	59
4.	F4	60
5.	F5	55
6.	F6	52
7.	F7	33
8.	F8	45
9.	F9	40

Table 5: *In-vitro* drug release study of FGR tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	39.98	35.65	33.12	35.65	33.25	32.25	22.32	18.85	15.58
1	53.32	49.98	43.32	48.85	46.65	45.58	36.75	35.45	32.25
1.5	69.98	65.58	60.47	65.58	59.98	53.32	44.32	42.23	40.47
2	88.85	78.85	73.32	83.32	82.23	69.98	56.65	53.32	49.98
3	98.78	84.45	80.47	96.65	95.65	78.85	65.56	62.23	58.85
4	-	99.12	89.98	98.85	98.85	89.98	78.89	70.23	68.87
6	-	-	98.85	-	99.47	98.78	83.23	80.47	78.84
8	-	-	-	-	-	99.12	89.98	85.56	83.32
12	-	-	-	-	-	-	99.74	89.98	85.458

Table 6: Regression analysis data of Metoclopramide sustain release Tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F7	0.8124	0.9032	0.9327	0.9529

CONCLUSION

The development of sustained-release tablets of Metoclopramide using natural gums demonstrated promising results in terms of formulation characteristics, buoyancy, and drug release profiles. Formulation F7, in particular, exhibited the best sustained release behavior, optimal buoyancy, and good mechanical properties. The results suggest that natural gums are effective excipients for formulating sustained-release tablets, providing an opportunity for improving patient compliance by reducing the frequency of administration and enhancing therapeutic outcomes.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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