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Development and Evaluation of Novel Floating Drug Delivery Systems of Metoclopramide Hydrochloride

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ABSTRACT

Several distinct novel drug delivery systems are being employed for effective delivery of medications to patients. Oral delivery is by far the most preferable route of drug delivery and oral sustained-release gastroretentive drug delivery systems offer several advantages. These drug delivery systems are beneficial for drugs with absorption from the upper parts of the gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of these drugs. Floating drug delivery systems (FDDS) are one of the gastroretentive drug delivery systems used to achieve prolonged gastric residence time. Multiple unit FDDS avoid the "all-or-none" gastric emptying nature of single unit systems. In the present research study, floating formulation as solid (capsule) or liquid (*in situ* gel) drug delivery systems were developed for improving the gastric residence time of the anti-emetic agent metoclopramide hydrochloride. Floating capsules were prepared using combinations of various natural and synthetic polymers. Simultaneously, *in situ* gel was prepared using completely bio-degradable natural polymers. Both systems were able to sustain drug release for up to 8 hours. These formulations were compared with marketed forms and found to be more convenient from a patient as well as a biopharmaceutical standpoint. To assess the stability of these formulations, accelerated stability testing was conducted as per ICH guidelines. Both formulations were found to be stable upon completion of the accelerated stability period.

KEYWORDS: Oral delivery; floating capsule; *in situ* gel; metoclopramide; ICH guidelines.

Introduction

The purpose of design and development of floating drug delivery systems is to create a principal mechanism of floatation to achieve gastric retention. Gastric emptying of dosage forms is an extremely variable process with the ability to prolong and control the emptying time, which is a valuable asset for dosage forms which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs (Ali et al, 2008). Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility in a high pH environment. It also has applications for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better bioavailability of new products with new therapeutic possibilities and sustained benefits for patients (Jain et al., 2008; Saxena et al., 2009).

Vomiting is a forceful action accomplished by a fierce, downward contraction of the diaphragm. At the same time, abdominal muscles tighten against a relaxed stomach with an open sphincter. Nausea and vomiting can sometimes be symptoms of more serious diseases such as heart attack, kidney or liver disorders, central nervous system disorders, brain tumors or some forms of cancer. In addition to this, nausea and vomiting are prominent in many cytotoxic drugs due to direct stimulation of chemoreceptor trigger zone (CTZ) by drug as well as by generation of emetic impulses/mediators from the upper gastrointestinal tract (GIT) and other areas (Peppas et al., 1994; Zhidong et al., 2006; Al-Tahami et al., 2007).

Metoclopramide hydrochloride (MCP) is used as a dopamine receptor antagonist and effective antiemetic agent. Chemically, metoclopramide is a 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy-benzamide hydrochloride. It is available in white or almost white crystalline powder or crystals, and is very soluble in water, freely soluble in alcohol, and sparingly soluble in methylene chloride (BP, 2009). This antiemetic agent is chemically related to the procainamide and acts predominantly as a dopamine antagonist (Satoskar et al., 2007).

The objective of this present study was to develop floating capsules (FC) and floating stomach specific *in situ* gel (FG) of metoclopramide hydrochloride using natural and/or synthetic polymers and release retardant to optimally releases the drug in a sustained manner over a period of 8 hours.

Materials and Methods

Drugs and chemicals

Metoclopramide hydrochloride was supplied by Ajanta Pharma (Mumbai, India). Hydroxypropyl methyl cellulose K-4-M (HPMC, Colorcon, India), methyl cellulose (Qualichem Fine chemical Pvt. Ltd. India), carbopol 934 P and carboxy methyl cellulose sodium salt (Qualichem Fine Chemical Pvt. Ltd. India), hard gelatin capsules Number 3, mannitol, stearic acid (Nice chemical Pvt. Ltd. India) and ethyl cellulose, sodium alginate, guar gum, calcium carbonate and magnesium stearate (SD Fine Chemical Ltd. Mumbai, India) were procured from the local vendor.

Instrumentation

In vitro dissolution was performed using the USP-XXIV Type I (basket) dissolution test apparatus (Electrolab Dissolution Tester, India). Drug concentrations in various tests were determined spectrophotometrically (SL-164 Double beam UV spectrophotometer, Elico, India) at 272 nm. Pre- and post-lubrication blending was done in a double-cone glass blender (Lab Scale Kalweka Apparatus, Gujarat, India).

Formulation of gastro-retentive capsule formulation

Preparation of physical mixtures. Before the conception of the actual formulation, set of studies were carried out to find out the optimum combination of drug and polymer. Polymers such as hydrocolloids of natural as well as synthetic origins were selected. Hydroxyl propyl methyl cellulose (HPMC), methyl cellulose (MC), sodium carboxy methyl cellulose (CMC) and carbopol 940 were selected as the hydrocolloid polymers. In addition to this, stearic acid and ethyl cellulose were selected as the rate controlling polymers.

The physical mixture of the polymers was prepared by a gentle and smooth mixing of the selected hydrocolloids using mortar and pestle. This polymer blend was transferred to the double coned glass blender. The drug was added in it by the geometric blending method. The blender was operated at the optimum speed for 15–20 minutes. On completion of this step, the lubricants were added. The mixing was continued for 5 minutes. The efficiency of mixing was verified by determination of the drug content.

The powdered blend was filled in a hard gelatin capsule, manually. The composition of each of the prepared capsule formulations is shown in Table 1. Each 159 mg of blend per capsule contains 20 mg of metoclopramide hydrochloride.

Preparation of *in situ* gel of MCP. The drug was passed through sieve no. 60 to break lumps. Other polymers such as sodium alginate (SA), guar gum (GG) and calcium carbonate were passed through sieve no. 40 to form free–flowing powder. In order to protect solutions from microbial contamination and degradation, distilled water was boiled for a sufficient period. At ~80°C, methyl paraben and propyl paraben (in a ratio of 9:1) were added (as antimicrobial agents) and allowed to cool at room temperature.

To determine the most suitable combination of GG and SA polymers, initial trials were conducted on individual polymers, followed by combinations of polymers. The combinations of the formulation were started with 0.5% w/v amount of both polymers. These amounts were increased until thick, viscous solution was obtained. This set of experiments was used to find the most suitable viscosity of formulation for handling the formulation.

Guar gum was weighed and dispersed in distilled water containing antimicrobial agents at 50°C. The dispersion was then stirred for 15-20 minutes at the same temperature and allowed to cool at room temperature. Accurately weighed quantity of the drug was added to this polymer solution and stirred thoroughly for 10–15 minutes. Pre-weighed quantity of calcium carbonate was added slowly with continuous stirring, and mixing continued for 15–20 minutes. The dispersion so formed was sonicated for 10 minutes. Table 2 provides the composition of all formulations. Formulations were packed in 10 ml amber colored glass vials, capped with rubber closures, and sealed with aluminum caps. In their final pack, the formulations were terminally sterilized by autoclaving at 121°C and 15 Pa for 20 min. Sterilized formulations were stored at 25-30°C.

TABLE 1

Composition of floating capsule formulations.

Sr. No.	Ingredients (in mg)	F-1	F-2	F-3	F-4	HP-1	MC-2	CM-3	CP-4
1	Metoclopramide hydrochloride	20	20	20	20	20	20	20	20
2	HPMC K-4 M	43.17	43.17	43.17	43.17	**43.17**	21.58	8.88	6.35
3	Methyl cellulose	21.58	21.58	21.58	21.58	21.58	**43.17**	21.58	21.58
4	Caroxymethyl cellulose sodium	8.88	8.88	8.88	8.88	8.88	8.88	**43.17**	8.88
5	Carbopol 940	6.35	6.35	6.35	6.35	6.35	6.35	6.35	**43.17**
6	Ethyl cellulose	**10**	**15**	**20**	**25**	25	25	25	25
7	Stearic acid	25	25	25	25	25	25	25	25
8	Mannitol	14	14	14	14	14	14	14	14
9	Magnesium stearate	15	15	15	15	15	15	15	15
	Total Weight	**159**	**159**	**159**	**159**	**159**	**159**	**159**	**159**

TABLE 2

Composition of floating *in situ* gel formulations (FG-1 to FG-9).

Sr. No.	Ingredients (in mg)	FG-1	FG-2	FG-3	FG-4	FG-5	FG-6	FG-7	FG-8	FG-9
1	Metoclopramide hydrochloride	200	200	200	200	200	200	200	200	200
2	Guar gum	500	500	1500	1000	1500	500	1000	1000	1500
3	Sodium alginate	1500	2500	2500	2500	2000	2000	2000	1500	1500
4	Calcium carbonate	2000	2000	2000	2000	2000	2000	2000	2000	2000
5	Methyl paraben	180	180	180	180	180	180	180	180	180
6	Propyl paraben	20	20	20	20	20	20	20	20	20
7	Purified water	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml	q. s. to 100 ml

Evaluation of formulations

Development of MCP calibration curve. To generate the calibration curve, 20 mg of MCP was weighed accurately on an electronic balance. It was transferred to a 100 ml calibrated volumetric flask and a volume was made with 0.1 N HCl. From this stock solution, further dilutions were made to obtain the solutions of 2-20 µg/ml. Solutions were analyzed using double beam UV-visible spectrophotometer at 272 nm using 0.1 N HCl as blank.

***In vitro* buoyancy studies.** The capsules were immersed in 900 ml of citrate phosphate buffer pH 3 (simulating the pH of the gastric contents in the fed state) contained in a US Pharmacopoeia (USP) paddle type apparatus where the speed of rotation maintained at 50 rpm. The duration of time during which the capsules remained buoyant was the floating time. The polymer that showed the best floating behavior was used for *in vitro* release studies (Bhise et al., 2008; Korsmeyer et al., 1996).

For the *in situ* gel, *in vitro* floating study was carried out using 0.1 N HCl, (pH 1.2). Medium temperature was maintained at 37°C ± 0.5°C. A ten ml formulation was introduced into the dissolution vessel containing medium without much disturbance. Time formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on surface of the dissolution medium (duration of floating) were noted (Patel et al., 2010).

Determination of drug content. Formulations equivalent to 20 mg of MCP were measured and transferred to a 100 ml volumetric flask. To this, 100 ml of 0.1 N HCl was added and shaken on a mechanical shaker for 30 min, followed by sonication for 15 minutes. Complete dispersion of contents was ensured, visually and filtered using a 0.45 µm membrane filter. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1 N HCl. The contents of MCP were determined spectrophotmeterically at 272 nm using a double beam UV-visible spectrophotometer.

***In vitro* release studies.** *In vitro* release studies of formulations (n = 6) were performed in a USP basket (Type I) apparatus at 50 rpm using 900 ml of 0.1 N HCl. 2 ml samples were withdrawn at pre-determined intervals of 0.5, 1, 2, 3, 4, 6, 7, 8 hours and replaced with 0.1 N HCl pre-warmed at 37°C ± 0.5°C. The samples withdrawn were filtered and drug content in each sample was analyzed after a suitable dilution. The samples were evaluated spectrophotometrically at 272 nm.

Stability studies

To assess the drug and formulation suitability, accelerated stability studies were performed according to I CH Q1A guidelines. For floating capsules, the optimized formulation was wrapped in aluminum packaging coated inside with polyethylene, and *in situ* gel formulations were packed in 10 ml amber colored glass vials, capped with rubber closures, and sealed with aluminum caps. Various replicates were kept in the humidity chamber and maintained at 45°C and 75% RH for 6 months. At the end of pre-determined intervals, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters (ICH, 1999).

Results and Discussion

The *in situ* formulation contained Ca^{++} ions in complex form and the release of which, in acidic conditions of stomach content, ensures reproducible gelation, complexation and flotation of the gel. The presence of acidic environment containing hydrochloric acid ensures that the process of complexation and gelation (by interaction of $CaCO_3$ and HCl) takes place *in situ*, followed by the generation of gas (carbon dioxide) leading to floatation of formed complexes.

An optimum amount of polymer ensures that the gel has sufficient strength to control the release. From the Table 1-2 it is evident that the gel must has a minimum 0.5% w/v concentration of GG and minimum 1.0% w/v concentration of SA, to produce good *in situ* gel. Lower concentrations either failed to undergo sol to gel transformation or formed poor gel with low viscosity. The use of sodium alginate in the *in situ* gel forming system was substantiated by the property of its aqueous solution to transformed into stiff gel when comes in contact with exchangeable Ca^{++} ions. An optimum level of CaCO3 was selected so that it should form sufficient gas and $CaCl_2$ *in situ* solution.

The floating capsule is known for its “zero” density nature. The purpose of these formulations was to study the effect of various concentrations of hydrocolloids on release as well as the nature of floating tendency. To study impact of release retardant ethyl cellulose and

stearic acid used, ethyl cellulose concentration was varied to study the effect on the release from formulation.

Linearity and range

The linearity and range was studied using various concentrations and plotting against absorbance. The solutions were found to obey Lambert-Beer's law with R^2 values of 0.999 in the range of 2-20 µg/ml (Figure 1).

In vitro buoyancy studies

The capsules containing lower proportions of polymers than that of drug were dispersed within 1 hour. Hence, the amount of hydrocolloids polymers was important to maintain not only matrix integrity but also buoyancy of the formulation. Formulations containing high concentrations of HPMC (HP-1) were found to continue longer than other hydrocolloids (MC-2, CM-3, CP-4) (Table 3).

The time taken by the formulation to emerge on the medium surface (floating lag time) and time for which the formulation continuously floated (duration of floating) are shown in Table 4. The released CO_2 was entrapped in a gel network-producing buoyant formulation, and then calcium ion reacted with SA produced a cross-linked 3D-gel network and a swelled structure that with further diffusion of CO_2 and drug molecules resulted in an extended period of floating and drug release respectively. All formulations showed floating lag time ranging from 21-35 second depending on composition. Less viscous formulations reached surface early, and also dispersed in less time (> 1.5 hours) than more viscous formulations (12 hours).

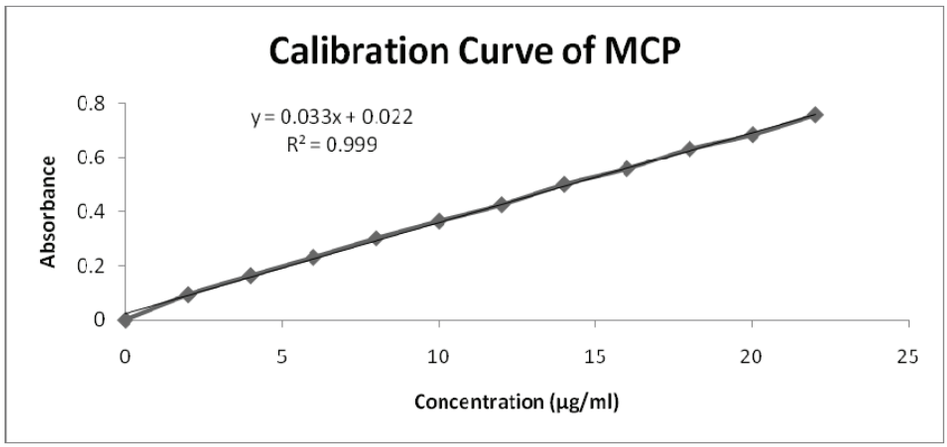

Fig. 1. Calibration curve of metoclopramide hydrochloride in 0.1 N HCl.

TABLE 3

Buoyancy, matrix integrity and total floating time of floating capsule.

Formulation	Buoyancy	Matrix integrity	Floating duration	Drug content uniformity	Average weight(in mg)	Floating lag time
F-1	+	+	>12	99 ± 2.13	159 ± 1.63	0 sec
F-2	+	+	>12	97 ± 1.69	159 ± 1.27	0 sec
F-3	+	+	>12	98 ± 2.13	159 ± 1.72	0 sec
F-4	+	+	>12	99 ± 1.29	159 ± 0.97	0 sec
HP-1	+	+	>12	100 ± 1.45	159 ± 1.07	0 sec
MC-2	-	-	>10	99 ± 2.25	159 ± 0.91	0 sec
CM-3	-	-	>8	100 ± 1.71	159 ± 1.07	0 sec
CP-4	-	-	>2	100 ± 1.32	159 ± 1.21	0 sec

(n= 10) (±SD)

TABLE 4

Buoyancy, matrix integrity and total floating time of *in situ* gel.

Sl. NO	Formulation Code	Gelling time (in sec)	Floating time (in hours)	Graded Response	Floating lag time (in sec)	Drug Content (± SD)
1	**FG – 1**	25	< 1	**+**	27	99.14 ± 0.34
2	**FG – 2**	27	> 4	**+ +**	29	97.33 ± 0.53
3	**FG - 3**	35	> 8	**+ + +**	37	100.17 ± 0.6
4	**FG - 4**	28	> 4	**+ +**	30	98.4 ± 0.37
5	**FG - 5**	31	> 8	**+ + +**	33	99.11 ± 0.31
6	**FG - 6**	26	> 8	**+ + +**	28	97.34 ± 0.49
7	**FG - 7**	31	> 8	**+ + +**	33	99.24 ± 0.40
8	**FG - 8**	31	> 6	**+ +**	33	99.54 ± 0.45
9	**FG - 9**	33	> 6	**+ +**	35	98.74 ± 0.49

(n= 10) (±SD)

Hence, it was observed that capsules were faster in producing flotation as compared to that of gels. It could be rationalized due to lower density of the capsules but in the case of the gel, flotation only occurs due to the formation and entrapment of gas.

Determination of drug content

This is an important requirement for any type of dosage form. The amount of drug present in the formulation should not deviate beyond certain specified limits from the labeled amount. All capsule formulations were analyzed as per BP. It was found that, drug content was obtained in the range of 99-100% (±SD). All *in situ* gel formulations were found to having drug content in the range of 97-100% (±SD), indicating homogenous distribution of drug throughout the gel (Table 3, 4).

In vitro dissolution studies

Release from these formulations was as presented graphically in Figure 2. From the data presented, it was evident that a high proportion of HPMC is required not only for maintaining matrix integrity, but also extending release. Replacement of it with MC, CMC or carbopol had increased the rate of release in descending order. Similarly, concentrations of ethyl cellulose and stearic acid beyond 25 mg/capsule had a minimum effect on release. Hence, formulation HP-1 is considered the optimum formulation, with an extended release of up to 8 hours, longer than any other formulation.

A significant decreased rate and extent of drug release was observed with the increase of polymer concentration and attributed to increase in the density of the polymer matrix and also an increase in the diffusion path length which the drug molecules have to traverse. Formulations containing less amount of GG showed initial bursts of release and dissolution was completed in shorter period. Formulations containing higher amounts of GG released their contents for a longer period of time at slower rate. The role of SA was primarily in formations of *sol-gel* phenomenon, but it also did affected release from formulations to some extent. From all above mentioned information, FG-3 is considered the optimum formulation (Figure 2).

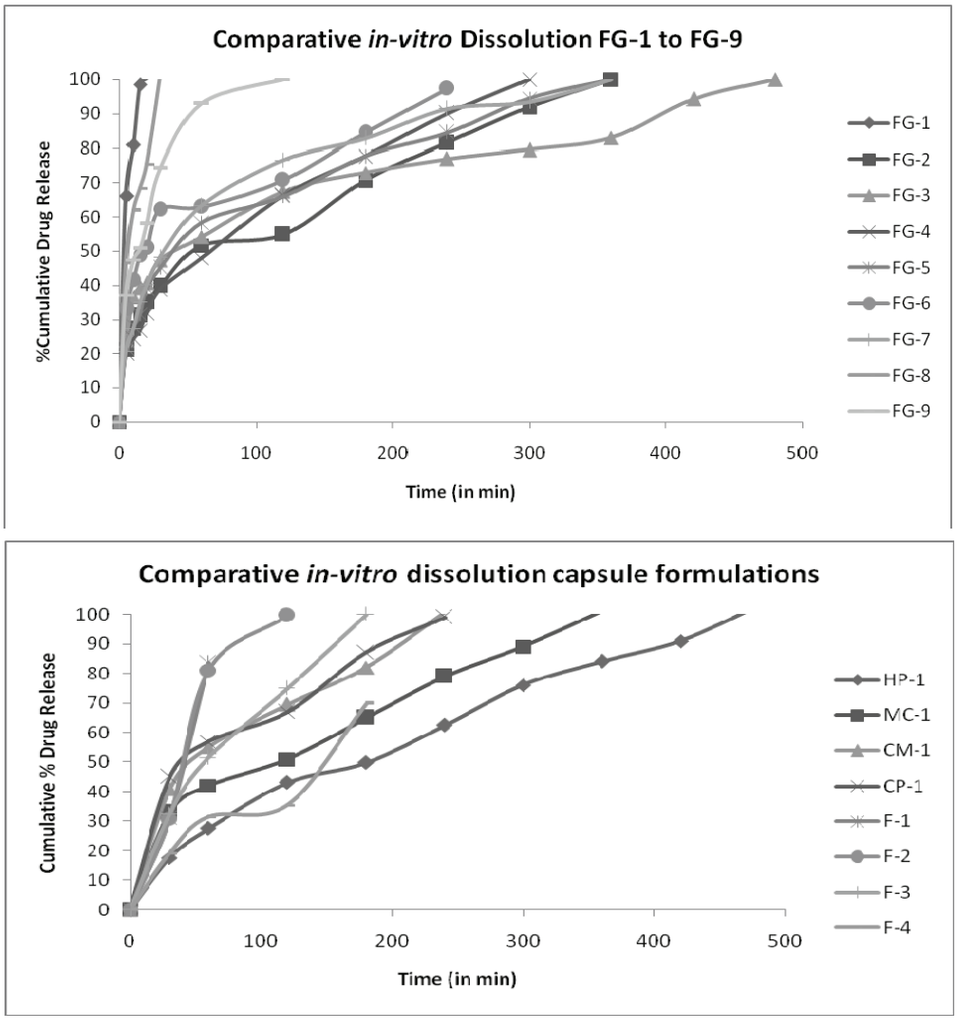

Fig. 2. *In vitro* dissolutions of floating capsule and *in situ* gel formulations of metoclopramide hydrochloride.

After both of the optimized formulations were compared, it was found that the rate of release from gel was faster compared to the capsule. This rationale for gel to release was retarded only after cross-linking completion. This was a time and cation-dependent process, which is evident from faster release at beginning (burst) period. As soon as the reaction was completed, it formed a stiff barrier which controlled release. Capsule release was slower, as the drug needs to get dissolved as well as diffuse through hydrocolloid barrier. But this process reached saturation on imbibing water and the rate reaches a steady state (Figure 3).

Stability study

The optimized formulations HP-1 and FG-3 were exposed to accelerated stability studies as per ICH-Q1A guidelines at 45°C and 75% RH for 6 months. At pre-determined intervals analysis of formulation was done for various parameters.

Samples withdrawn at the interval of one month for three months showed no change in their *in vitro* drug release profile. Results of the stability study show no remarkable change in the release profile, assay and other evaluation parameters of the MCP floating capsules and *in situ* gel after being exposed to accelerated stability conditions (Table 5).

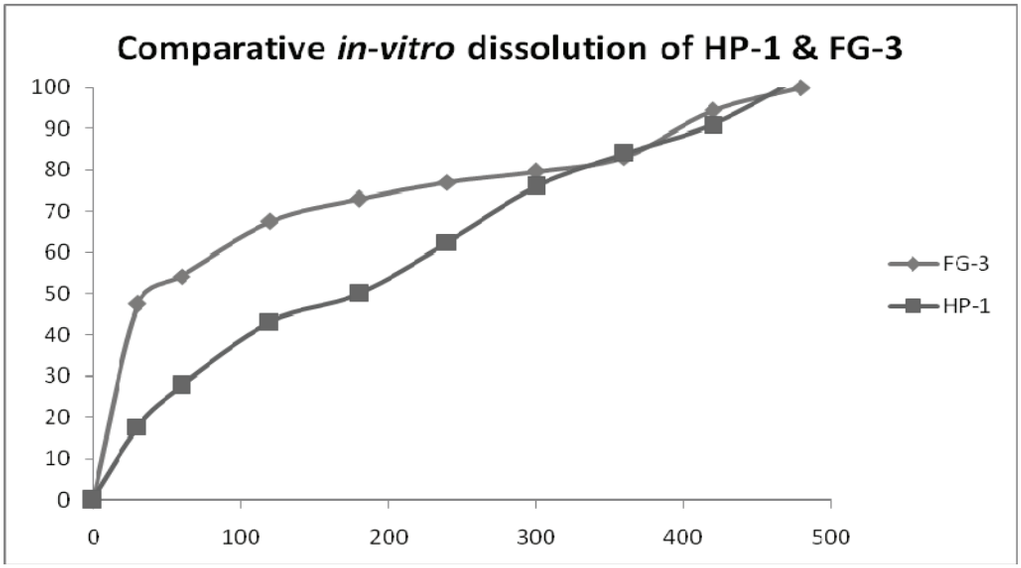

Fig. 3. Comparative *in vitro* dissolution of optimized capsule and *in situ* gel formulations of metoclopramide.

TABLE 5

Stability testing of HP-1 and FG-3 formulations.

Physical parameters after stability study of formulation HP-1

Parameter	Initial	Room temperature		40°C/75%RH		2°C-8°C	
		After 15 days	After 6 months	After 15 days	After 6 months	After 15 days	After 1 months
FLT (sec)	0	0	0	0	0	0	0
TFT (h)	> 12	> 12	> 12	> 12	> 12	> 12	> 12
Assay (%)	100.1	99.7	99.8	100.1	99.3	100.1	99.5
Matrix integrity	++	++	++	++	++	++	++

FLT: Floating Lag Time; **TFT:** Total Floating Time

Physical parameters after stability study of formulation FG-3

Parameter	Initial	Room temperature		40°C/75%RH		2°C-8°C	
		After 15 days	After 6 months	After 15 days	After 6 months	After 15 days	After 1 months
GT (sec)	31	30	32	28	36	37	43
TFT (h)	>8	>8	>8	>8	>8	>8	>8
Assay (%)	100.0	99.8	99.8	100.0	98.9	100.1	100.0
Matrix integrity	++	++	++	++	++	++	++

GT: Gelling time

Conclusion

Floating formulations of metoclopramide in the form of hydrodynamically balanced systems as well as stomach-specific *in situ* gel were formulated and evaluated. The floating capsules exhibited strong effect of the presence of HPMC on drug release as well as a floating nature. In the case of the *in situ* gel, sodium alginate played a pivotal role in the formation of *in situ* sol-to-gel conversion and guar gum was more prominent in controlling the rate of drug release from formulation. Both formulations were capable of sustaining release of the drug for 6-8 hours. Capsule formulations have the advantage of unit solid dosage form while gel formulations were liquid and easy for swallowing. During the accelerated stability period, both formulations were found to be stable. Hence, both formulations have promising market potential but still further studies are warranted for clinical and patient compliance.

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