ESTIMATING THE RELEASE EFFECT ON BSC-I DRUG BY USING A COMBINATION OF METHYLCELLULOSE AND EUDRAGIT® S-100 POLYMERS TO FORMULATE MINI-FLOATING TABLETS

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ABSTRACT

The purpose of the current research was to prepare a delayed-release system of mini-tablets (gastroprokinetic drug). The model drug (itopride hydrochloride) was formulated with the combination of methylcellulose (free-flowing agent) and Eudragit® S-100 (enteric coating agent) for delayed release. The research objective was to control the drug release in the stomach. The preparation of floating mini-tablets in three batches using different concentrations of polymers (methylcellulose in increasing order and Eudragit® S-100 remaining constant in two batches and the concentration decreased in the third batch) was utilized for the maintenance of the drug release pattern by evaluating the three batches for their weight variation, content uniformity, % drug release, thickness, hardness and friability tests. The selection of optimized formulation was based on the *in vitro* dissolution studies and floating lag time. As a result, Eudragit® S-100 showed a better-delayed release action. Formulation F2 gave better-delayed release (67.09 % for 360 minutes) and floating properties (1.34 minutes for lag time) in comparison to other batches i.e.; F1 and F3. The F3 results showed that the floating lag time (1.29 minutes) will decline, while methylcellulose concentration increases but Eudragit® S-100 concentration decreases, which reveals the enteric coating action of the Eudragit® S-100 polymer for delayed drug release in the studies.

Keywords: Itopride drug, floating mini-tablets, methylcellulose, Eudragit® S-100, evaluation test

INTRODUCTION

Itopride hydrochloride belongs to BCS-I (rapidly absorbed) class of drugs which exhibits both pharmacological effects i.e.; acetylcholine esterase inhibitory and dopamine D2 receptor antagonist[1-3], and the combination of these effects reflect a very beneficial role of gastroprokinetic agents for treating dyspepsia[4-7] and gastroesophageal reflux disorder[2]. The biological half-life of itopride is approximately 30 minutes, it requires multiple dosing which leads to the concentration of plasma fluctuation in the systemic circulation[8-9]. The conventional itopride-labeled dose regimen for oral administration is 50 mg, 3 times a day[1]. Therefore, maintaining the antidopaminergic action with a certain level of pharmacological effect is achieved by a delayed release pattern for the reduction of dose frequency for better patient compliance[10-12]. Hence, the rectification done by itopride DR formulation at 100 mg was to be developed and the direction for administration was instructed as once daily.

A common type of polymer used in medicinal formulations is called Eudragit® S-100. It is frequently used as an enteric coating material and is a member of the family of methacrylic acid copolymers. Eudragit® S-100 is renowned for its superior gastric acid resistance, biocompatibility, and film-forming abilities. Eudragit® S-100 is primarily used in pharmaceutical applications to shield medicinal compounds from the stomach's acidic environment. It creates a protective barrier around the dosage form to stop drug release and degradation in the stomach and to make sure the medication reaches the intestines where it will have the desired effect. While gastric acid renders Eudragit® S-100 insoluble, higher pH levels, such as those in the intestines, make it soluble.

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Numerous studies have been conducted on Eudragit® S-100, which is used in a range of pharmaceutical formulations, including tablets, capsules and pellets. Better pharmaceutical stability, decreased stomach angst, and tailored medicine distribution are just a few benefits it provides[13]. These polymers enable the creation of enteric, protective, or sustained-release medication formulations, which delay the drug's breakdown until it reaches a pH-appropriate location in the gastrointestinal (GI) tract. The medicine will disintegrate from the polymer matrix and be absorbed once it reaches the duodenum and stomach, which are its target areas of the digestive tract. Targeted drug delivery is widely used to prevent drug degradation in regions where the pH is insufficient for absorption or to relieve discomfort in the gastrointestinal tract[14].

Cellulose, a naturally occurring polysaccharide found in the cell walls of plants, is the source of methylcellulose, a hydrophilic polymer. Due to its special qualities and adaptability, it is widely used in many sectors. When combined with water, methylcellulose has a great capacity to bind water and create a gel-like substance. In food and pharmaceutical products, it is frequently employed as a thickening agent, stabilizer, and emulsifier[15]. Methyl cellulose is nearly insoluble in anhydrous ethanol, ether, and acetone but soluble in water at low temperatures. It is a hot gel which, when cooled to lower temperatures after forming a gel state at higher ones, transitions to a gel-sol state[16-17]. It is smooth, translucent, and has good mechanical characteristics[18-19].

The solubility of itopride in water is high and will not have much impact by pH increase[20]. Some common side effects of itopride are diarrhoea, nausea, headache, dizziness, stomach pain and constipation[21]. To overcome the side effects of itopride hydrochloride, methylcellulose, and Eudragit® S-100 were used in the development of formulation in combination, as methyl cellulose causes the highly viscous solution at the minimum concentration, and helps to treat constipation by increasing the stool bulk, which leads to the movements in the intestines. Hence, it has therapeutic action as a bulk laxative[22-23]. Eudragit® S-100 has some properties like being non-biodegradable, nonabsorbable, and non-toxic, which will be used as an enteric coating agent, while the Eudragit® S-100 category is easily soluble at pH > 7. Hence, it is used to modify drug delivery systems[24]. Its chemical composition, solubility, and swelling properties reflect as versatile in nature by promoting a delayed drug release at certain higher pH above pH 5.5, while protecting the drug release against the acidic nature of the gastric fluid[25-26].

In this research work, the formula designed to provide efficient floating and delayed-release mechanisms was chosen for *in vitro* evaluation to study the impact of methylcellulose and Eudragit® S-100 in combination with the drug release pattern of ITO HCl along with overcoming the drug side effects. Thus, the aim of the research was to improve the bioavailability of the model drug and also reduce the multiple dose intake.

MATERIALS AND METHODS

Itopride hydrochloride was received as a gift sample from Abbott Labs, Himachal Pradesh, India. Eudragit® (S-100) extra pure was purchased from Research Lab Fine Chem. Industries, Mumbai, India, Carbopol® 934P (Carboxypolymethylene-934) and methyl cellulose (low viscosity) from Qualikems Fine Chem. Pvt. Ltd., Industrial Estate Nandesari, Vadodara and sodium hydrogen carbonate (sodium bicarbonate) was purchased from AVARICE Industries, Ghaziabad, India. All other chemicals used were of analytical grades.

Determination of the maximum wavelength of the model drug

10 µg mL^{-1} of the first solution- stock I (model drug) was developed with 0.1N HCl in a volumetric flask. The spectrum was arranged the wavelength (200-400 nm) in a UV-double beam spectrophotometer and the detection of the maximum wavelength was recorded.

Table I: Composition of itopride floating mini-tablets

Ingredient (mg)	Purpose	Formulation batch		
		F1	F2	F3
Methylcellulose	Free-flowing agent	100	200	300
Eudragit® S-100	Enteric coating agent	300	300	200
Carbopol® 934P	Binder	600	600	600
Itopride	API	100	100	100
Sodium bicarbonate	Effervescent effect and neutralizer	150	150	150

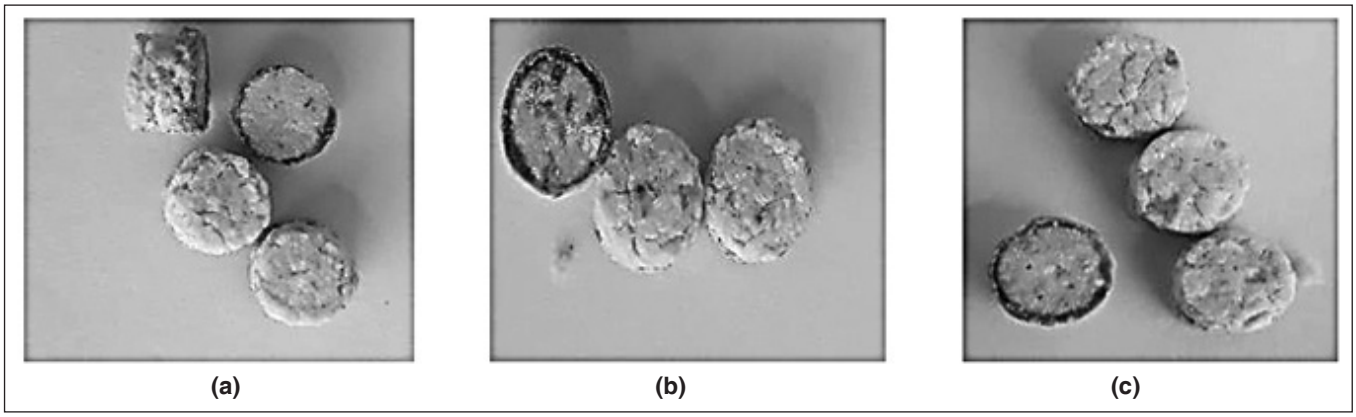

Fig. 1: Images of mini-tablets of different batches a) F1 b) F2 c) F3

Calibration graph of the model drug

The stock solution-II of 1000 µg mL^{-1} was prepared (100 mg of model drug was dissolved in 100 mL of 0.1N HCl). The dilution were prepared from the stock solution-II with concentrations ranging from 5 to 25 µg mL^{-1} and the volume madeup with 0.1 N HCl in a volumetric flask. The absorbance of all the dilutions was noted by using a UV-double beam spectrophotometer at 258 nm. The calibration curve developed the straight-line equation by plotting a graph between concentration (µg mL^{-1}) and absorbance.

Manufacturing of floating mini-tablets

The formulation composition was designed into different batches of itopride HCl floating mini-tablets (Table III)**.** Itopride hydrochloric acid, methyl cellulose, Eudragit® S-100, and Carbopol®934P were sieved through 80-size sieve no. individually, and bicarbonate sodium from 44-size sieve no. and all the excipients mixed in different proportions as mentioned in Table I. These mini-tablets were compressed by using a 4 mm single punching machine. Each batch of mini-tablet contained 100 mg of the model drug and the prepared formulations are shown in Fig. 1.

Evaluation of floating mini-tablets

The evaluation of prepared mini-tablets was done with related to post-compression parameters including the quality control tests of tablets.

Post-compression parameters

The tests of the the formulated floating mini-tablets were performed in triplicate for all test parameters, and results are expressed as mean ± SD. The official test includes a weight variation test, percentage content uniformity test, and *in vitro* dissolution test. All these tests were performed as per I.P. guidelines[27]. The unofficial tests include hardness test, friability test, tablet thickness, and diameter by using Pfizer hardness tester, Roche friability tester, and vernier calliper, respectively[27-28]. A specific test for the investigation of floating lag time was done by appearance on the liquid surface, after the addition of simulated gastric fluid without enzyme used as dissolution medium (pH 1.2, 37 ± 0.5 ˚C, 50 rpm) by using a stopwatch for the measurement[28-30].

Drug release analysis

The release pattern of the drug was carried out from an *in vitro* dissolution test by using apparatus-II (paddle method) with a 50-rpm speed of paddle adjusted in the artificial gastric medium, (pH 1.2) as dissolution medium (900 mL, 37 ± 1 ˚C). At predetermined intervals, 5 mL samples were taken out, filtration was done, and then the fresh medium was replaced (5 mL)[30]. When necessary, the filtrate samples were appropriately diluted with the medium before being tested using a double-beam UV spectrophotometer for the presence of itopride hydrochloric acid at 258 nm. The dissolution analysis was conducted, and the mean values were then calculated.

RESULTS AND DISCUSSION

Calibration graph of the model drug

The different dilutions of itopride hydrochloric acid were scanned (200-400 nm) against 0.1 N HCl and was used as a reference at 258 nm. The drug standard concentrations varied from 5-25 µg mL^{-1} revealing better linearity (R^2 = 0.9987) as per the Beer-Lamberts law, as shown in Fig. 2.

In vitro drug release analysis

The *in vitro* dissolution profile of formulated mini-tablets of itopride was performed in the artificial gastric medium. The drug release kinetics were deliberated at

different time intervals for 360 minutes as mentioned in Table II. The percentage variation of drug release was obtained due to the different proportions of polymers used in all the batches. The impact of polymers on the release pattern is shown in Fig. 3. Out of all the batches, batch F3 gave satisfactory drug release up to 27.11 % after 3 h for loading dose and drug release was delayed up to 8 h (71.28 %), as compared to the other two batches. Thus, batch F3 was the most favourable batch among all formulations studied.

Table II: *In vitro* percentage drug release profile of itopride hydrochloric acid

Time (minutes)	F1	F2	F3
10	1.15	1.76	1.25
30	3.97	4.53	4.04
60	8.24	8.94	8.79
120	16.24	16.14	16.85
180	26.09	25.59	27.11
240	38.15	36.07	39.81
300	50.99	50.31	54.73
360	66.30	67.09	71.28

Post-compression parameters data

The thickness of floating mini-tablets was recorded in the range of 2.4 - 2.8 mm. Hence, the impact of methylcellulose was reflected in the thickness of the formulations: as the polymer amount increases, the thickness also increases. Similarly, the other unofficial test of the mini-tablets within standard ranges indicated good mechanical resistance of the mini-tablet. But in batch F3, the concentration of Eudragit® S-100 decreases, which also decreases the thickness. Therefore, the impact of Eudragit® S-100 and methylcellulose in combination showed a response in the thickness. In the

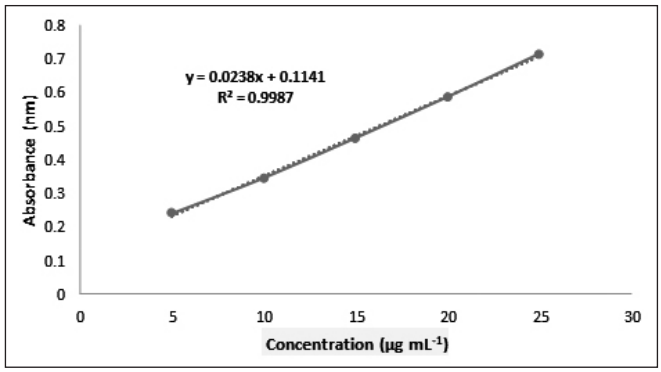

Fig. 2: Calibration curve of the model drug (Itopride Hydrochloride)

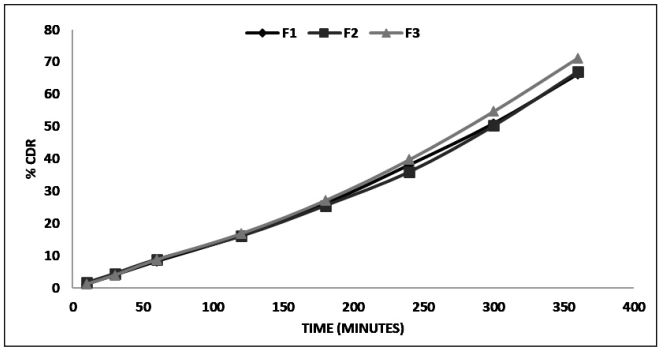

Fig. 3: *In vitro* drug release data of different formulations

different batches (F1 to F3), weight variation was shown as favorable data as per the Indian Pharmacopoeia (I.P) limit. The drug uniformity content percentage of each batch was obtained between the range of 66.30 to 71.28, as mentioned in Table III.

Table III: Results of post-compression parameters of itopride floating mini tablets

Parameter	Test	Batch code		
		F1	F2	F3
Official test	Weight variation (mg)	871.8	1423.9	1423.7
	Content uniformity (%)	64.60	64.77	66.22
	Drug release (%) (for 360 mins)	66.30	67.09	71.28
Unofficial test	Thickness (mm)	2.4	2.8	2.7
	Hardness (kg cm^{-2})	2.9	3.2	3.3
	Friability (%)	0.52	0.54	0.55
GFDDS evaluation test	Floating lag time (mins)	1.15	1.34	1.29

All batches were designed as per the effervescent methodology. The results of the floating mini-tablets are mentioned in Table III. When the formulations of each batch were soaked in the acidic medium, pH 1.2 and temperature 37 °C were to be maintained for floating which remained before the disintegration period. Sodium bicarbonate acts as an effervescent base in the formulations for induction of CO_2 formation when exposed to an acidic medium and the entrapment of the generated gas into the Eudragit®

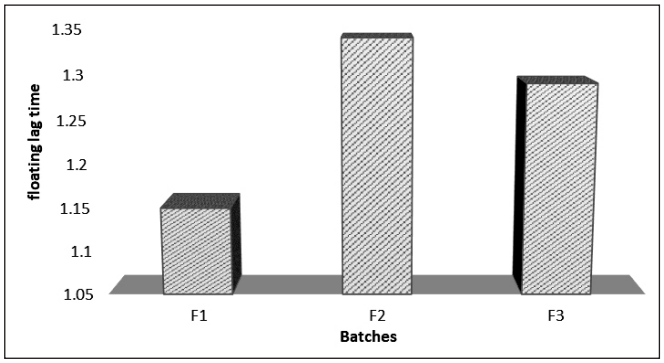

Fig. 4: Bar graph of floating lag time showing the variation between different batches

S-100 (swollen polymer with the protection of the outer layer), and thus, the dosage forms were floating in the medium. From all the prepared batches, the floating lag time increases as the concentration of methylcellulose polymer increases (F1 and F2) but the proportion of Eudragit® S-100 decreases in formulation F3, which ultimately decreases the floating lag time. Hence, the impact of Eudragit® S-100 retarded the drug release but reduced the floating lag time as compared to other F1 and F2 in which the concentration of Eudragit® S-100 was constant. From the above observation, it was concluded that, as the concentration of methylcellulose increases and the concentration of Eudragit® S-100 decreases, it will reflect the decline in the floating lag time and slight impact on the release pattern of the drug is observed as shown in Fig. 4. Hence, the F3 results showed that the floating lag time (1.29 minutes) will decline. Based on the observation, it was concluded that a decline in the floating lag time would be reflected by an increase in methylcellulose concentration and a decrease in Eudragit® S-100 concentration. Thus, it reveals that Eudragit® S-100 works as an enteric-coated agent for delayed drug release in this research project.

CONCLUSION

From the results obtained by experimental data, it can be concluded that floating mini-tablets of the model drug (itopride hydrochloride) were manufactured for the enhancement of gastric residence time, and thereby also for the improvement of the biological efficacy of the drug. Eudragit® S-100, used as an enteric coating agent respectively, shows better-delayed release effect of the model drug along with the combination of methylcellulose. As the polymer concentration increases the rate of release, it decreases accordingly due to the enhancement of diffusion path length. Formulation of mini-tablets exhibits satisfactory results for the various post-compression parameter tests performed like thickness, hardness, weight variation, content uniformity, floating lag time, total floating time, and *in vitro* drug release. The optimized formulation from the three batches was F2, as it provides better-delayed release action of the model drug and floating properties, in comparison to the other batches.

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