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FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF GASTROPROKINETIC DRUG ITOPRIDE HYDROCHLORIDE

R.MARGRET CHANDIRA*, DEBJIT BHOWMIK, CHIRANJIB, B. JAYAKAR

Vinayaka mission college of Pharmacy, Vinayaka missions University Salem, Tamilnadu, Email-debjit_cr@yahoo.com

ABSTRACT

As Itopride hydrochloride is gastroprokinetic drug, the site of action is stomach; and as the drug pH ranges from 3.5 to 5.5, the present work was aimed to formulate floating tablets of Itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. The present investigation concerns the development of floating tablets of Itopride hydrochloride, a novel prokinetic drug, which after oral administration are designed to prolong the gastric residence time and thereby increase drug bioavailability, and drug release rate. This would help in promoting gastrointestinal transit and speed up gastric motility, and thereby it will relieve the symptoms associated with it. Floating tablets were fabricated; using direct compression method; containing Itopride hydrochloride, polymers HPMC K100M, HPMC K15M and Carbopol 934 P, along with gas generating agent sodium bicarbonate and citric acid. The addition of Carbopol aided in the reduction of the drug dissolution due to their hydrophobic nature. The concentration of these agents was also optimized to get desired controlled release of drug. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, in-vitro drug release, hardness, friability and weight variation.The results indicated that gas powered floating tablets of Itopride hydrochloride containing 125 mg HPMC K100M, 40 mg HPMC K15M, and 40 mg Carbopol provides a better option for 24 hours release action and improved bioavailability. The drug release pattern of this optimized formulation was found to be non-fickian diffusion mechanism. The accelerated stability studies, at 40^0C / 75% RH, of the optimized formulation was carried out for one month and no significant change was observed.

Keywords: Gastroretentive drug delivery system, Gastroprokinetic drug, Swelling index, Hydrodynamically balanced tablet

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.[1] Floating Drug Delivery Systems (FDDS) [21] have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems. It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the

most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF or GRDS). Prokinetic agents help to speed up the passage of food through the stomach and may help with symptoms of bloating and feeling sick. Prokinetic agents often are touted as the most effective medications for the management of non-ulcer dyspepsia.Itopride hydrochloride is the drug of first choice in the therapy of upper dyspepsia at this time in Czech Republic. It is a prokinetic drug that activates the gastrointestinal motility through synergism of its dopamine D2 - receptor antagonistic action and its acetylcholine esterase inhibitory action. In addition to these actions it has an anti-emetic action that is based on its dopamine D2 receptor antagonistic action.The marketed conventional release products need to be administered 2-3 times daily. The continuing effort to improve pharmaceutical formulation in order to optimize therapy and patient compliance, various efforts have been tried to develop a modified release, once a day formulations. As a result of such efforts, many modified formulations are available.

As Itopride Hydrochloride is a rokinetic drug and its primary site of action is stomach and also the drug pH range is 3.5 to 5.5 it would be beneficial to formulate a floating drug delivery system of itopride hydrochloride, which would be once a day formulation.

MATERIALS AND METHODS

Itopride hydrochloride is procured by Micro Labs Ltd., Hosur, HPMC K100M, HPMC K15M are gifted by Colorcon Asia Pvt. Ltd., Goa, Carbopol 934 P is gifted by corel Pharma.Ahmedabad, Sodium bicarbonate, Citric acid (anhydrous) are procured by S.D.Fine-Chem Ltd., Vadodara, Poly Vinyl Pyrrolidine K30, Magnesium Stearate, Talc, Aerosil were procured by Loba Chemie

FORMULATION DESIGNING

Hydro-dynamically balanced tablets of Itopride HCl were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its local action and bioavailability.In the present work total ten formulations were prepared and complete composition of all batches shown in Table. The tablets were then characterized for various physicochemical parameters.

RESULTS AND DISCUSSION

Evaluation of hydrodynamically balanced tablet formulations:

1. **Pre-compression parameters**:

a) Angle of repose (θ): The values obtained for angle of repose for all formulations were tabulated in Table The values were found to be in the range from 24°.30' to 29°.88'. This indicates good flow property of the powder blend for direct compression.

b) Compressibility index: The values obtained for Compressibility index for all formulations were tabulated in Table Compressibility index value ranges between 12.30% to 16.34% indicating that the powder blend have the required flow property.

Table 1: Composition of all the formulations (Batch F1 – Batch F10)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Itopride HCl	150	150	150	150	150	150	150	150	150	150
HPMC K100M	---	100	---	50	---	100	100	100	110	125
HPMC K15M	100	---	---	100	100	---	50	50	40	40
Carbopol 934P	---	---	100	---	50	50	---	50	50	40
MCCP Ranq	100	100	100	50	50	50	50	---	---	---
Sodium Bicarbonate	60	60	60	60	60	60	60	60	60	60
Citric Acid	30	30	30	30	30	30	30	30	30	30
Polyvinyl Pyrrolidine K30	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10	5
Talc	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Total weight	470	470	470	470	470	470	470	470	470	470

*All the quantities are in mg

2. Post-compression parameters

a) Shape of the tablet

Microscopic examination of tablets from each formulation batch showed circular shape with no cracks.

b) Tablet dimensions

The dimensions determined for formulated tablets were tabulated in Table No.3. Tablets mean thickness (n = 3) were almost uniform in all the ten formulations and were found to be in the range of 5.12 mm to 5.18 mm. The diameter of the tablet ranges between 10.90 mm to 11.10 mm.

c) Hardness test

The measured hardness of tablets of each batch ranged between 4.1 to 4.5 kg/cm^2 (Table No.3). This ensures good handling characteristics of all batches.

d) Friability test

The values of friability test were tabulated in Table No.3. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

e) Weight variation test

The percentage weight variations for all formulations were shown in Table No.3. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Table 2: Pre-compression parameters

Batch	Angle of Repose (θ)	Compressibility Index (%)
F1	24° 30'	12.30
F2	26° 77'	15.67
F3	25° 28'	14.48
F4	28° 56'	16.34
F5	29° 88'	15.41
F6	24^0 36'	13.25
F7	25^0 22'	14.16
F8	27^0 29'	12.45
F9	26^0 54'	15.56
F10	28^0 48'	14.85

f) Tablet density:

To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (1.004g/cm^3). All the batches showed density below than that of gastric fluid (1.004). The values were shown in Table 4.

When tablet contacts the test medium, tablet expanded (because of swellable polymers) and there was liberation of CO_2 gas (because of effervescent agents, sodium bicarbonate and citric acid). Here, citric acid acts a dual action of effervescent agent as well as it maintains the pH of the environment. The density decreased due to this expansion and upward force of CO_2 gas generation. This plays an important role in ensuring the floating capability of the dosage form.

g) Buoyancy study:

On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Table No.4 showed the results of buoyancy study and Fig.18 and 19 showed buoyancy character of prepared tablet of optimized formulation (F10).

From the results it can be concluded that the batch containing HPMC polymers showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation F10 containing HPMC K15M, HPMC K100M and Carbopol 934P showed good BLT of 110 sec and TFT of more than 24 hrs. Carbopol was used as release retardant and it also provided an additional gelatinous layer to the formulation. The tablets floats may be due to the amount of polymer and gas generating agents, which gets partially entrapped in between, the gelatinous layer. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Table 3: Physical properties of tablets of batch F1 to F10

Batches	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)
F1	10.99 ±0.040	4.16 ±0.010	4.5 ±0.47	0.96	468.65 ±1.29
F2	10.98 ±0.006	4.14 ±0.012	4.4 ±0.32	0.72	465.50 ±1.74
F3	10.99 ±0.067	4.12 ±0.06	4.4 ±0.54	0.91	471.55 ±1.18
F4	10.98 ±0.070	4.16 ±0.011	4.3 ±0.42	0.86	470.05 ±1.37
F5	10.98 ±0.056	4.18 ±0.012	4.5 ±0.35	0.79	469.65 ±1.49
F6	10.98 ±0.006	4.16 ±0.010	4.5 ±0.54	0.97	472.55 ±1.19
F7	10.99 ±0.067	4.14 ±0.012	4.5 ±0.54	0.72	471.55 ±1.19
F8	10.98 ±0.072	4.12 ±0.06	4.3 ±0.42	0.72	470.55 ±1.19
F9	10.98 ±0.075	4.18 ±0.012	4.4 ±0.32	0.72	469.55 ±1.19
F10	10.98 ±0.065	4.12 ±0.06	4.4 ±0.32	0.86	471.55 ±1.19

*Each reading is an average of three determinations (Avg.± S.D)

Table 4: Tablet density, buoyancy lag time, total floating time

Batch	Tablet density (g/cc)	Buoyancy lag time (Sec)	Total floating time (hrs)
F1	0.93	133 sec	>12 hrs
F2	0.82	130 sec	>14 hrs
F3	1.12	FAIL	FAIL
F4	0.91	120 sec	>16 hrs
F5	0.97	102 sec	>16 hrs
F6	0.93	150sec	>20hrs
F7	0.88	140sec	>20hrs
F8	0.94	141sec	>24hrs
F9	0.97	138sec	>24hrs
F10	0.89	110sec	>24hrs

h) Swelling study:

Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups.

Swelling study was performed on all the batches for 5 hr. The results of swelling index were given in Table 10. While the plot of swelling index against time (hr) of optimized formulation (F10) is depicted in Fig. 20.

From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F10, containing HPMC K15M, HPMC K100M, and Carbopol 934P having nominal viscosity of 15,000 cps, 100,000cps and 934cps respectively. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Table 5: Swelling index of tablets of batch F1 to F10

Time	Swelling Index (%)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1 hr	80	82	79	76	76	75	82	88	79	89
2 hrs	129	135	130	120	125	131	135	127	130	129
3 hrs	148	162	156	140	142	144	162	168	159	161
4 hrs	168	185	172	161	163	182	185	172	166	187
5 hrs	185	207	189	170	179	197	207	199	186	208

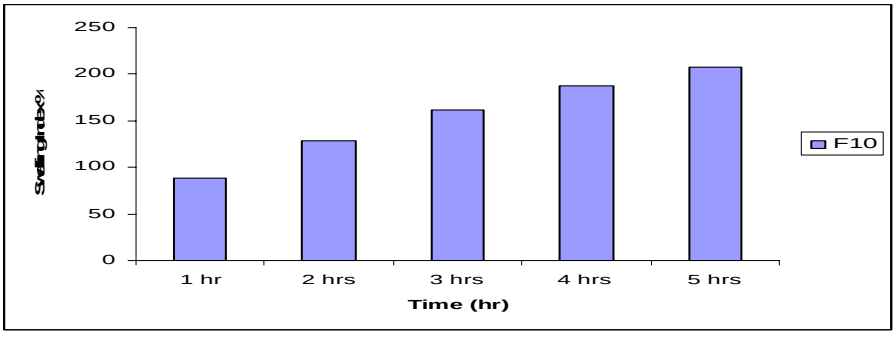

Fig. 1: Plot of swelling index against time of optimized formulation (F10)

Table 6: Drug content uniformity of tablets of batch F1 to F10

Batches	Drug content uniformity (%)
F1	97.01
F2	99.51
F3	98.01
F4	97.42
F5	98.41
F6	99.05
F7	99.05
F8	98.46
F9	98.45
F10	99.82

i) Drug content uniformity:

The percentage of drug content was found to be between 97.01% and 99.82% of Itopride hydrochloride, which was within acceptable limits. Table No. 11 showed the results of drug content uniformity in each batch.

j) Effect of hardness on buoyancy lag time:

The effect of hardness on buoyancy lag time for batch F10 was studied. The results of floating lag time of tablet having hardness of 4.5 kg/cm^2, 5.5 kg/cm^2 and 7 kg/cm^2 were 110 sec, 215 sec and 421 sec respectively as tabulated in Table 12. The plot of floating lag time (sec) vs. hardness (kg/cm^2) is depicted in Fig. 2 Batch F10 was selected for the study because it showed buoyancy lag time of 110 sec at hardness of 4.5 kg/cm^2.

Buoyancy of the tablet was governed by both the swelling of the hydrocolloid particle on surface when it contacts the gastric fluid that in turn results in an increase in the bulk volume and the presence of internal void space in the dry center of the tablet (porosity). On increasing the hardness of the tablets results in increased buoyancy lag time, which might be due to high compression resulting in reduction of porosity of the tablet. Moreover, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result of this, the capability of the tablet to float is significantly reduced.

Table 7: Effect of Hardness on Buoyancy Lag Time of Batch F10

Hardness in kg/cm^2	Buoyancy lag time (sec)
4.5kg/cm^2	110
5.5kg/cm^2	215
7.0kg/cm^2	421

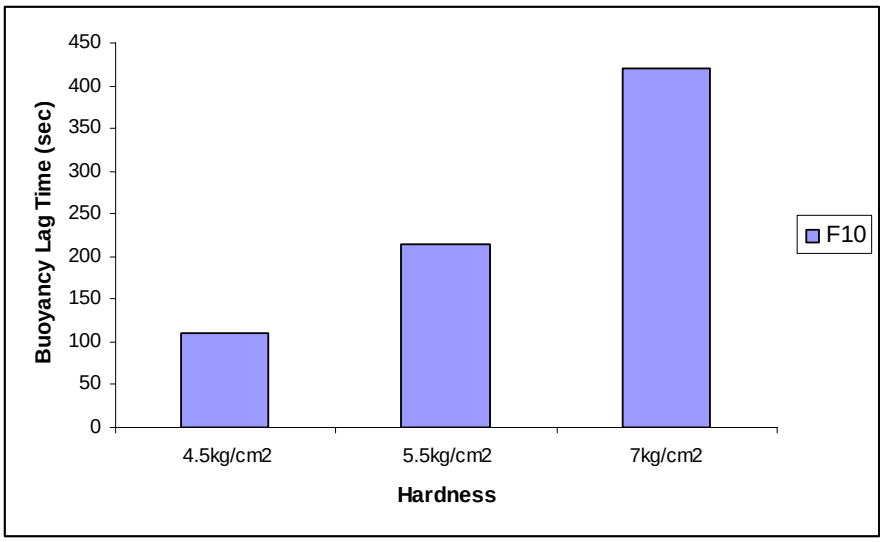

Fig. 2: Plot of Floating lag time vs. Tablet hardness

k) **In-vitro dissolution study:**

The in-vitro drug release profiles of tablet from each batch (F1 to F10) were shown in Table No. 13. The plot of cumulative percentage drug release versus time (hr) was plotted and depicted as shown in Fig. No 3 and Fig. No 4.

From the in-vitro dissolution data it was found that formulation F3 containing carbopol 934P alone released 97.2% of drug within 12 hr of the study indicating that the polymer amount was not sufficient to control the drug release. Formulation F10 containing carbopol 934P along with HPMC K15M and HPMC K100M showed better control of drug release than carbopol 934P or HPMC K100M alone, and F10 released 102.3% drug at the end of 24 hr. Tablet of batch F1, F2 and F3 contained same amount of polymer of different grades viz. HPMC K15M, HPMC K100M and carbopol 934P which showed various drug release rate. Out of all the ten formulations, batch F10 showed better control over drug release indicating that the release was decreased when the viscosity of the polymer was increased.

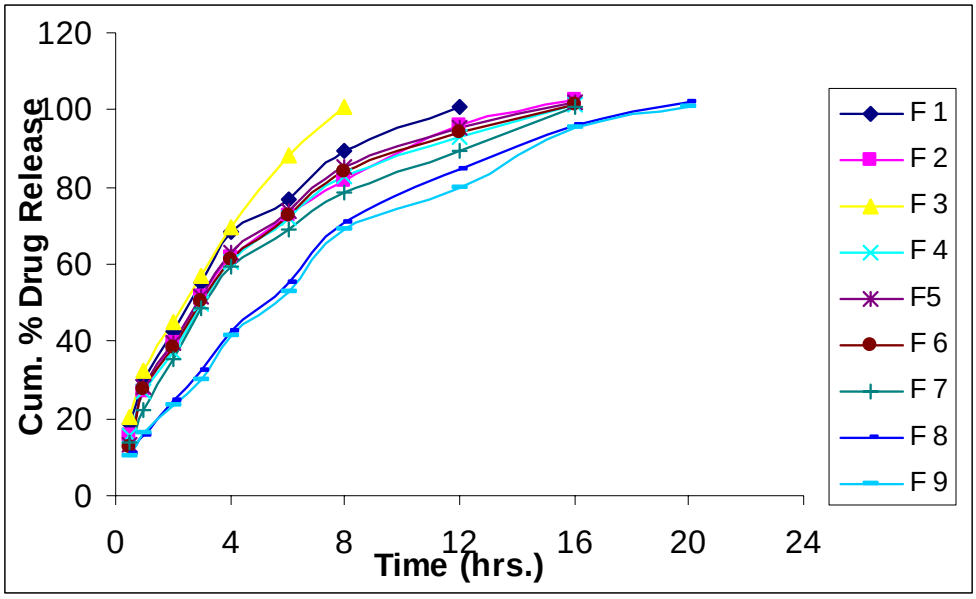

Fig. 3: In-vitro dissolution profile of formulations F 1 to F 9

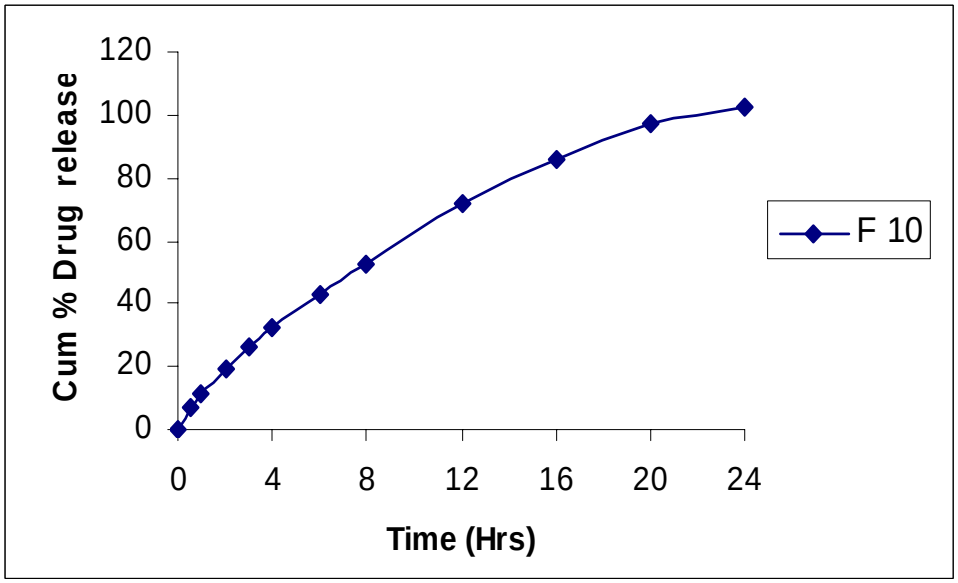

Fig. 4: In-vitro dissolution profile of optimized formulation (F 10)

n) Comparison with marketed sustained release product:

The promising formulation (F10) as found by evaluation studies was compared with marketed sustained released product Itopride SR, Intas (150mg). The evaluation parameters tested and compared were drug content uniformity and in-vitro dissolution profile. The values of comparative in-vitro dissolution study of optimized formulation (F10) and marketed product are recorded in Table No. 16 and shown graphically in Fig. 5.

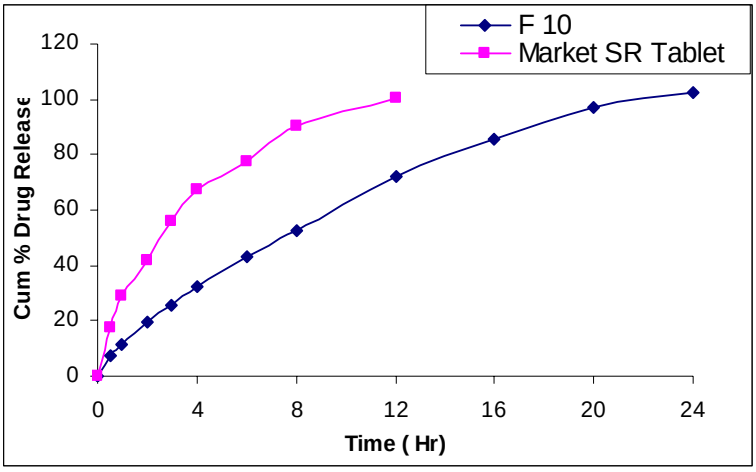

Fig. 5: Plot of Comparative dissolution profile of optimized formulation (F 10) And market SR tablet (MP)

SUMMARY AND CONCLUSION

Itopride hydrochloride is gastroprokinetic drug and the site of action is stomach and also the drug pH ranges from 3.5 to 5.5, the present work was aimed to formulate floating tablets of Itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system to improve the local action and ultimately its bioavailability. Itopride hydrochloride is the drug of first choice in the therapy of upper dyspepsia. It is a prokinetic drug that activates the gastrointestinal motility through synergism of its dopamine D2 - receptor antagonistic action and its acetylcholine esterase inhibitory action. In addition to these actions it has an anti-emetic action that is based on its dopamine D2 receptor antagonistic action.The tablets were formulated using hydrophilic polymers HPMC K100M, HPMC K15M and hydrophobic polymer carbopol 934P along with effervescing agent sodium bicarconate and citric acid. It was found that carbopol has a negative effect on floating behavior but it was used only for the drug release retardant characteristics. All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters, assay, swelling index, in-vitro drug release, floating lag time, total floating time, tablet density, hardness and friability. The main aim was to optimize the formulation for 24 hours in-vitro release and total floating time to more than 24 hours.Optimized formulation F10 containing 125 mg HPMC K100M, 40 mg HPMC K15M, and 40 mg carbopol 934P was consider as the best product with respect to in vitro drug release for 24 hours release action, total floating time and improved bioavailability and site-specific action. Tablets of batch F10 possessed quick buoyancy lag time of 110 sec. and good total floating time of 24 hrs. The results showed that the drug release rate was decreased as the viscosity of the polymer was increased. The formulation F10 was evaluated for effect of hardness

on floating lag time, and the results showed that the floating lag time increased as the hardness of the tablets was increased, due to reduction in porosity. Comparison study with marketed product GI Tune (Itopride hydrochloride SR tablets, Intas) showed that the optimized formulation F10 has better control over release rate in comparison to the marketed product. The marketed product released the drug 100.2% and the optimized formulation F10 was released the drug 72.1% within 12hrs. And the optimized formulation F10 remained floatable in the stomach for 24 hours.The present work can be continued further to prove its stability during shelf life, in-vivo dissolution, in-vivo gastric residence time by using gamma scintigraphy and establishment of in-vitro – in-vivo correlation.

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