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RESEARCH ARTICLE

FORMULATION AND DEVELOPMENT OF FLOATING DRUG DELIVERY OF ITOPRIDE HCL

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ABSTRACT

The aim of current research was to formulate floating tablets of Itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system,as itisgastroprokinetic drug, the site of action is stomach and as the drug pH ranges from 3.5 to 5.5. It was formulated as hydrodynamic balanced tablet using sodium bicarbonate and citric acid as gas generating agent, HPMC as hydrophilic polymerand Xanthan gum as drug release retarding agent with an objective to control the drug release and restrict the region of drug release to stomach. Tablets were prepared by direct compression method. Drug Excipient compatibility study was confirmed by FTIR & DSC studies.Floating tablets were prepared by direct compression using 3^2 factorial design using different polymers as independent variables in which HPMC K4M, Xanthan gum were used for maintaining drug release and dependent variables as % drug release, floating lag time & swelling index. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, in-vitro drug release, hardness, friability, weight variation.The formulations were investigated for % drug release, floating lag time by in-vitro dissolution study. Formulation was optimized on basis of acceptable tablet properties and in vitro drug release. Formulation F1 was selected on basis of factorial design dependent variable i.e. % drug release, floating lag time & swelling index.
Keywords: Floating drug delivery system, Gastroprokinetic drug, Swelling index, HPMC K4M, Xanthan gum.

INTRODUCTION

Oral route is considered most natural, uncomplicated,convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. Floating Drug Delivery Systems (FDDS) 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. This results in an increase in the Gastro Retentive Time and a better control of fluctuations in the plasma drug concentrations.[1] Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems. The gastric emptying time has been reported to be from 2-6h in humans in the fed state. When a sustained release dosage form is administered orally, sufficient bioavailability could not be obtained, especially for drugs having a limited absorption site in the intestinal tract. Therefore modern oral controlled release dosage forms must be based on gastrointestinal physiology, so that the drug is fully available for absorption[2-3]

Stomach specific floating drug delivery

Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix.[4-5]

Itopride hydrochloride is a novel gastroprokinetic drug, widely absorbed from the stomach and upper part of the small intestine and absorption becomes less as the drug passes beyond this. The bioavailability can be improved by making the drug completely absorbed in the stomach and upper part of the small intestine. It has a half life of 6hrs. The short half life of Itopride hydrochloride necessitates frequent administration. Therefore it is highly desirable to have a controlled release dosage form for Itopride hydrochloride[6]

Gastric emptying

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 - 3 hours . This is called the interdigestivemyloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington. PHASE I the quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretary, electrical and contractile activity. PHASE II, exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III. PHASE III is a short period of intense large regular contractions, termed "housekeeper waves" that sweep off undigested food and last 10-20 min. PHASE IV is the transition period of 0-5 mins between Phase III & I .[7-8]

Factors affecting gastric emptying

The most important parameters affecting gastric emptying and, hence, the gastric retention time oforal dosage forms include:Density, Size, Shape of dosage form, Single or Multiple unit formulation, Fed or Unfed state, Nature of Meal Gender, Age ,Biological factors, Frequency of Feed etc[9-10]

In the present study HPMC K4M, Xanthan Gum, Sodium Bicarbonate, Citric acid, Lactose was used for formulating floating drug delivery system. When tablet reaches to gastric fluid, it floats due to effervescence produced by

Sodium Bicarbonate & Citric acid. Drug release controlled by HPMC K4M Xanthan Gum due to their swelling &release retarding properties.The proposed formulation can be manufactured using currently available pharmaceuticaltechnology and materials recognized as safe.

MATERIALS & METHOD

Materials

Itopride HCL was purchased from Leo Chem researcher resources Ltd. Bangalore (India). HPMC K4M and Xanthan gum were obtained From Research lab Fine chem. (India).Other excipientsused to prepare the tablets were either of analytical or pharmaceutical grades purchased from local market.

Method

Drug Excipients Compatibility Study

Sample of pure drug, physical mixture of excipients and drug in (1 : 1) ratio was placed at accelerated stability condition 40±2 °C and 75±5% relative humidity for a period of 3 month. At the end of 3 month samples were evaluated for drug–excipients compatibility using Differential scanning colorimeter (DSC) (Mettler Toledo DSC 822e, Japan) and Fourier transformed infrared spectroscopy (FT-IR) (Shimadzu Corporation, Japan, 8400s).

Formulation of floating tablets

Floating tablets of itopride hydrochloride were prepared by direct compression method. The composition of formulation is given in the Table 1. ItoprideHCl, lactose and hydrophilic polymers were passed from sieve of # 40 and mixed for 10 min. All the Ingredients were weighed accurately.ItoprideHCl, lactose and hydrophilic polymers were passed from sieve of # 40 and mixed for 10 min blended in glass mortar uniformly. Then remaining excipients were also passed sieve of # 60 & mixed with drug blend. After sufficient mixing, powder blend was compressed into tablets on a 12 station single punch rotary tablet compression machine. A concave faced punch 10mm in diameter were used for tableting. Compression force of the machine was adjusted to obtain the hardness of 5 kg/cm2 and 7kg/cm2 for different batches.

Table 1: Composition of all the formulations (Batch F1 – Batch F9)

BATCH	ITOPRIDE	HPMC K 4M	XANTHAN GUM	NaHCO3	CITRIC ACID	LACTOSE	Mg. STERATE	TOTAL
F1	100	120	50	100	70	106	4	550
F2	100	120	70	100	70	86	4	550
F3	100	120	90	100	70	66	4	550
F4	100	140	70	100	70	66	4	550
F5	100	140	50	100	70	86	4	550
F6	100	140	90	100	70	46	4	550
F7	100	160	50	100	70	66	4	550
F8	100	160	70	100	70	46	4	550
F9	100	160	90	100	70	26	4	550

All ingredients are in mg.

3^2 Full Factorial Design

A 3^2 randomized full factorial design was used in this study. In this design2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of HPMC(X1) and Amount of Xanthan Gum (X2) were selected as independent variables. The times required to float, swelling index & % release were selected as dependent variables. The experimental design with corresponding formulation outline in Table 2.

Table 2: Composition of formulations

Batch code	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	0
F5	0	-1
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Levels	Amount of HPMC (X1)	Amount of Xanthan Gum (X2)
-1	120	50
0	140	70
1	160	90

EVALUATION

Thickness:

Thickness of tablets was determined using Vernier caliper. Five tablets from batch wereused, and average values were calculated.[11-12]

Weight variation test

To determine average weight, each tablet from formulation was weighed using an electronic balance (AUX-220, Shimadzu).[11-12]

Hardness:

The hardness was tested using Monsanto tester. The force is measured in kilograms.[11-12]

Friability:

For each formulation, the friability of 6 tablets was determined using the Roche friabilator (Lab Hosp.).[11-12]

In vitro drug release study of floating tablets

In-vitro dissolution studies were performed on floating tablets prepared by direct compression method using 0.1N HCL for 12 hrs. USP apparatus II with the paddle speed 50 rpm. 1 ml of filtered aliquot was withdrawn at pre-determined time intervals and replaced with 1 ml maintained at the same temperature. The samples were analyzed at 258 nm using a UV spectrophotometer. The floating lag time and percentage release was determined for the each formulation.[13-14]

RESULT AND DISCUSSION:

Compatability study

Drug-Excipient Interactions:

The IR spectra of Formulation were compared with the standard spectrum of Itopride HCL (Fig. 1). IR spectrum of was Itopride HCL characterized by the absorption of-C=O group at 1662 cm−1, –OCH_3 group at 1128 cm−1&N-H Stretching at 3281 cm−1. In spectra of Formulation,band was same absorption pattern as that of pure drug. Mentioned evidences thus lead to the conclusion that changes were not seen as there was no physical interaction between the drug and polymers.

In DSC study also drug was characterized by its melting point & formulation was also showing same results as drug, by these mentioned evidences lead to the conclusion that changes were not seen s there was no physical interaction between the drug &polymers (Fig 2).

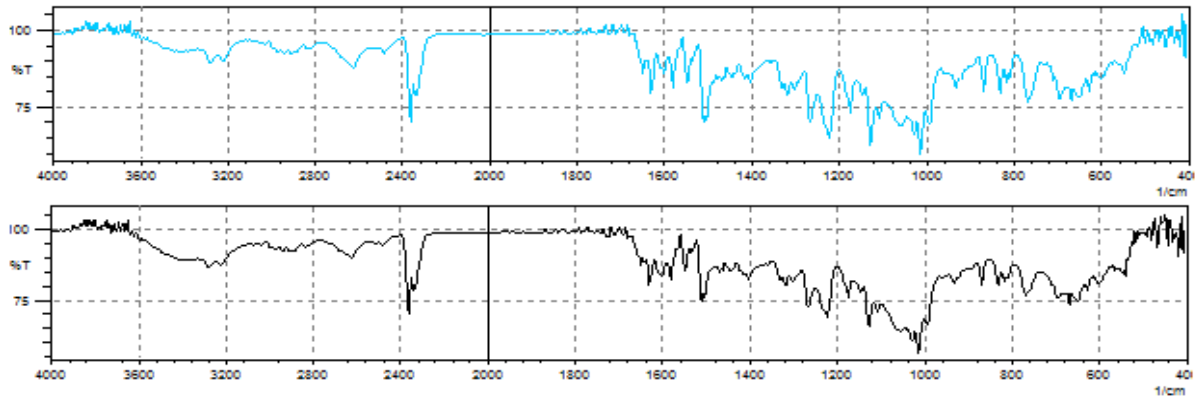

Figure 1: IR Spectrogram of Drug ItoprideHcl& formulation

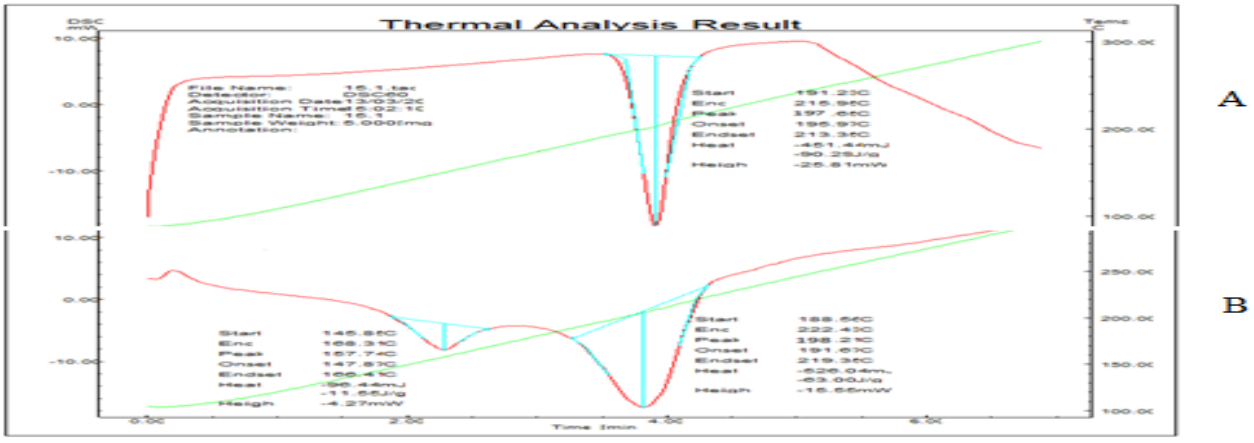

Figure 2: DSC Spectrogram of Drug ItoprideHcl (A) & formulation (B)

Preparation of floating tablets

Floating tablets were prepared by using 2 independent variables as different concentrations of polymers by using 3^2 factorial design. In formulation excipients used were HPMC K4M, Xanthan Gum, Sodium bicarbonate, Citric Acid, lactose & Magnesium Sterate. Carbon dioxide is formed within the tablet containing effervescent agent when the tablet is brought in contact with the acidic dissolution medium. Sodium bicarbonate is used

as gas generating agent which induces floatability of the tablet and it makes tablet remain to float in stomach The low density of hydroxypropyl methylcellulose assists in floating the tablet. Moreover, the gelling capacity of HPMC also helps to float the tablet by entrapping carbon dioxide gas in the gel network of HPMC. The gelling capacity of HPMC prevents disintegration of the tablet during the dissolution study. HPMC was choosen as swellable polymer because it is widely used as low-density hydrocolloid system, upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH. Xanthan gum is used in combination with HPMC to slow the drug release;xanthan gum ability to do this may be caused by the low solubility in gastric pH. Lactose is used as filler. Mg. stearate is used as lubricant and glidant to improve flow property of powder blend. Swelling index 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.

Precompression Parameters:

Angle of repose (θ): The values obtained for angle of repose for all formulations were tabulated in Table no.3The values were found to be in the range from 23°.30' to 28°.88'. This indicates good flow property of the powder blend for direct compression.

Compressibility index: The values obtained for Compressibility index for all formulations were tabulated in Table no.3 Compressibility index value ranges between 11.23% to 18.45% indicating that the powder blend have the required flow property.

Postcompression parameters

Tablet dimensions

The dimensions determined for formulated tablets were tabulated in Table No.4. 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 10.00 mm to 10.03mm.

Table 3: Pre-compression parameters

Batch	Angle of Repose (θ)	Compressibility Index (%)
F1	24.49	13.34
F2	23.30	12.98
F3	27.12	12.30
F4	27.89	16.29
F5	28.31	18.45
F6	28.88	11.23
F7	25.09	12.67
F8	27.34	14.30
F9	24.22	15.33

Hardness test

The measured hardness of tablets of each batch ranged between 5.5 to 6.5kg/cm2 (Table No.4). This ensures good handling characteristics of all batches.

Friability test

The values of friability test were tabulated in Table No.4. The % friabilitywas less than 1% in all the formulationsensuring that the tablets weremechanically stable.

Weight variation test

The percentage weight variations for all formulations were shown in Table No.4. 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 4: Postcompression parameters

Batches	Diameter (mm)n=3	Thickness(mm) n=3	Hardness(Kg/cm2) n=3	Friability(%) n=10	Weight Variation (mg) n=20
F1	10.00 ±0.034	6.04 ±0.012	5.5	0.78	551±1.29
F2	10.01 ±0.023	6.04 ±0.009	6.5	0.71	550±1.37
F3	10.01 ±0.045	6.03 ±0.002	6.5	0.70	550±1.33
F4	10.01 ±0.052	6.02 ±0.005	6.0	0.89	549±1.22
F5	10.02 ±0.024	6.03 ±0.009	5.5	0.77	552±1.21
F6	10.00 ±0.039	6.02 ±0.008	6.5	0.91	550±1.19
F7	10.00 ±0.048	6.04 ±0.003	6.0	0.85	551±1.23
F8	10.02 ±0.021	6.03 ±0.010	6.5	0.79	550±1.49
F9	10.01 ±0.046	6.04 ±0.011	5.5	0.80	551±1.19

Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake.The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of per cent weight gain, as given by the equation.

$$\text{Swelling index} = \frac{W2-W1}{W1} \text{ X } 100$$

W2 = Weight of dosage form at time t.

W1 = Initial weight of dosage form

From the following graph, it was concluded that as the time increases % swelling also increases.

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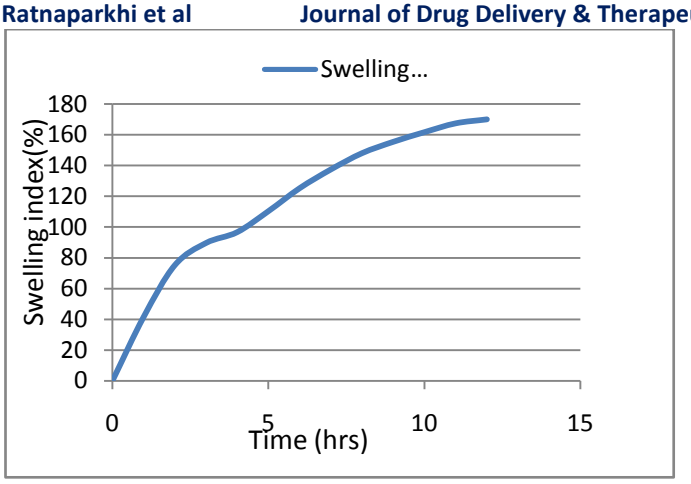

Figure 3: Plot of swelling index against time of optimized formulation F1

Buoyancy study:

On immersion in 0.1N HCl solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Fig.4 showed the results of buoyancy study and showed buoyancy character of prepared tablet of formulation. Formulation F1 shows floating lag time as 78sec. which was less compared to other formulations.

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. 5 showed the results of drug content uniformity in each batch.

Effect of hardness on floating lag time:

The effect of hardness on floating lag time for batch F1was studied. The results of floating lag time of tablet having hardness of 5.5 kg/cm2, 6.5 kg/cm2 and 7.5 kg/cm2 were 78 sec, 95sec and 120 sec respectively as tabulated in Table 6. Batch F1 was selected for the study because it showed floating lag time of 78 sec at hardness of 5.5 kg/cm2. From this study we can conclude that as hardness increases, floating lag time also increases.

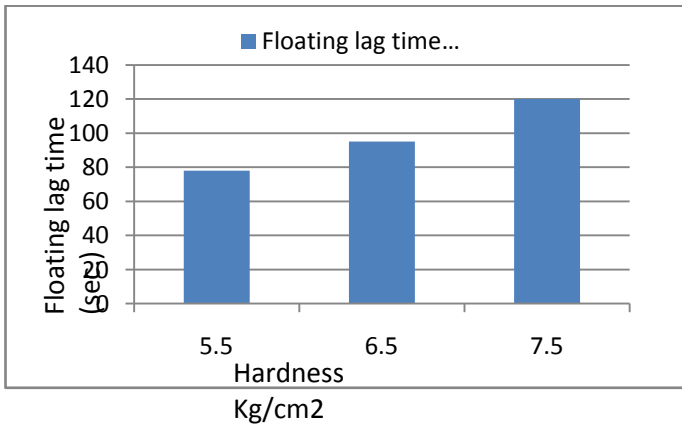

Figure.5: Plot of Floating lag time vs. Tablet hardness

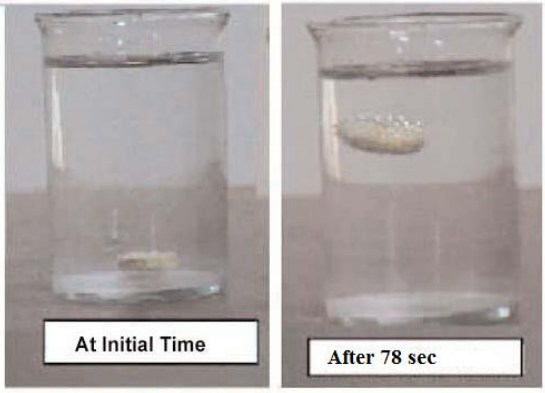

Figure 4:In vitro buoyancy study of batch F1.

Table 5: Drug content uniformity of tablets of batch F1 to F9

Batches	Drug content uniformity (%)
F1	99.03
F2	98.53
F3	97.89
F4	98.08
F5	99.01
F6	96.89
F7	97.33
F8	96.89
F9	95.09

Table 6: Effect of Hardness on Buoyancy Lag Time of Batch F1

Hardness	Floating lag time
5.5 kg/cm2	78 sec
6.5 kg/cm2	95 sec
7.5kg/cm2	120 sec

Effect of conc of sodium bicarbonate and citric acid on floating lag time:

The effect of conc of sodium bicarbonate and citric acid on buoyancy lag time for batch F1was studied. The results of floating lag time of tablet having conc sodium bicarbonate 60mg,80mg,100mg and citric acid 50mg,60mg,70mg was had floating lag time 120,90,78 sec respectively as tabulated in Table 7 . The plot of floating lags time (sec) vs. conc of sodium bicarbonate and citric acid is depicted in Fig. 2 Batch F1 was selected for the study because it showed buoyancy lag time of 78 sec at conc of sodium 100mg and citric acid 70mg. From this study we can conclude that as conc of sodium bicarbonate and citric acid increases, floating lag time also decreases.

Table no.7: Effect of conc of sodium bicarbonate and citric acid on floating lag time

Sodium bicarbonate (mg)	Citric acid(mg)	Floating lag time (sec)
60	50	120
80	60	90
100	70	78

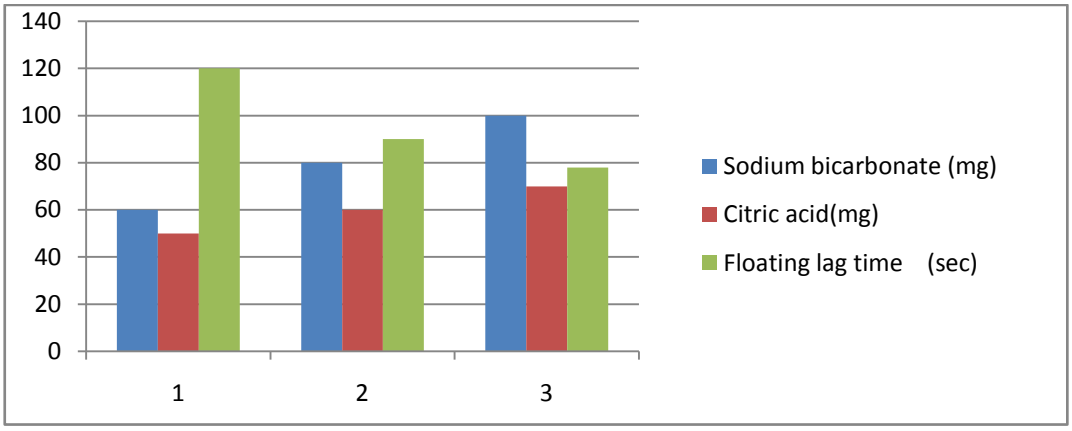

Figure 6: Effect of conc of sodium bicarbonate and citric acid on floating lag time

In vitro drug release study of floating tablets

From following graphs, we can observe that F1 formulation shows maximum drug release(99.40%) compared to other formulations.

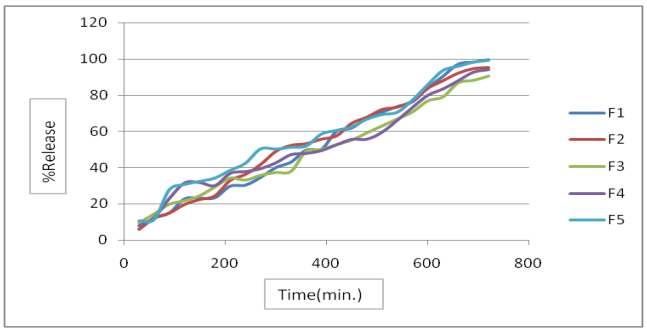

Figure 7: In vitro dissolution profile of formulations F 1 to F 5

Data fitting to the model

A two-factor, three-level optimal design as the response surface methodology (RSM) provides 9 runs. All the responses observed for 9 formulations were fitted to main effect model when using Design Expert (State ease – Ver. 8.0.7.1) and the values of R^2 and standard deviation are given in Table along with the regression equation generated for each response. Only statistically significant ($p < 0.05$) coefficients are included in the equations.

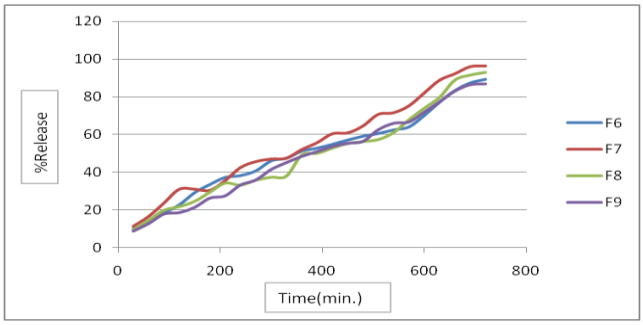

Figure 8: In vitro dissolution profile of formulations F 6 to F 9

Table 8:Summary of Results of Regression Analysis for Response Y1, Y2, Y3

Response	Models	F value	Prob > F	R^2	Adjusted R^2	Predicted R^2	S.D.	Remarks
Y1(Lag time)	Mean	40.33	0.0017	0.9758	0.9516	0.8775	4.47	Suggested
Y2(% release)	Mean	39.00	0.0018	0.9750	0.9500	0.8734	0.91	Suggested
Y3(Swelling Index)	Mean	47.68	0.0013	0.9837	0.9649	0.8952	1.62	Suggested
Equations:Y1=105-9.56X1-1.46X2-20.22X1X2 *Y2=93.69+1.56X1+1.44X2+2.47 X1X2* *Y3=185.78-13.78X1-2.37X2+1.04 X1X2*								

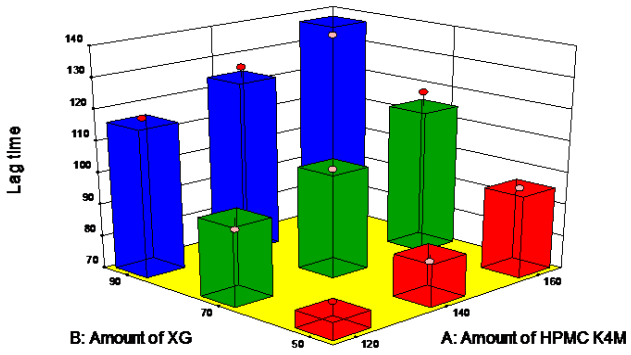

Figure 9: Effect of Xanthan gum & HPMC K4M on lag time

From above graph we can observe that, as concentration of xanthan gum and HPMC K4M increases, floating lag time also increases.So concentration of xanthan gum 50 mg and HPMC K4M 120 mg shows less floating lag time as compared to other concentrations.

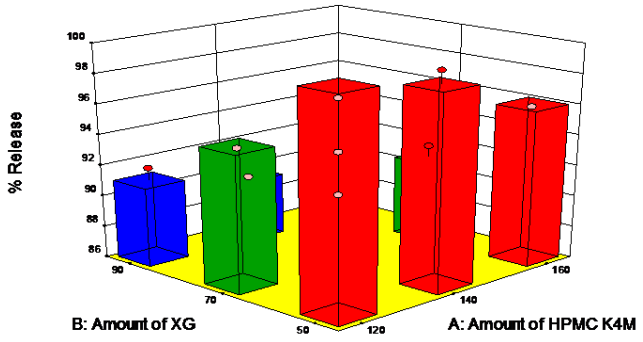

Figure 10: Effect of Xanthan gum & HPMC K4M on % Release

From above graph we can observe that, as concentration of xanthan gum and HPMC K4M increases, % release of drug decreases. So concentration of xanthan gum 50 mg and HPMC K4M 120 mg shows more % release of drug as compared to other concentrations.

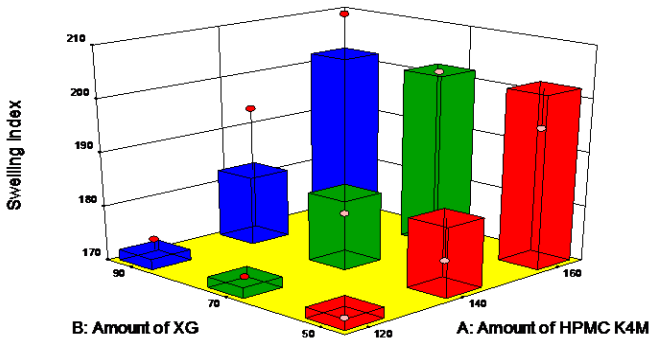

Figure 11: Effect of Xanthan gum & HPMC K4M on Swelling index

From above graph we can observe that, as concentration o HPMC K4M increases, swelling index also increases. So concentration of HPMC K4M 120 mg shows less swelling index as compared to other concentrations.

CONCLUSION

A lesser floating time and prolonged floating duration could be achieved by varying amount of effervescent mixture that is sodium bicarbonate and citric acid along with different polymer concentrations.The results of current study clearly indicate that the *in vitro* release of Itopride is significantly affected by the amount of HPMC K4M and Xanthan gum .HPMC K4M and Xanthan gum in combination help in maintaining the matrix integrity of the tablets. As the concentration of HPMC K4M and Xanthan gum increases the drug release decreases significantly; polymers concentration affects the drug release rate. The HPMC K4M and Xanthan gum in combination can be promising polymers for gastro retentive drug delivery system. The optimized formulation of batch F1 gave the best in vitro release of 99 % in 12 hrs.in simulated gastric fluid.

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