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Gastro retentive floating drug delivery system of model drug using central composite design

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Abstract

The work plans to build up a Gastro retentive floating drug delivery system of Model drug using central composite design. The model drug is a drug which is used in the treatment of antiulcer. Extended-release tablets of model drug provide constant plasma concentration with a less frequent administration and also reduce the side effects to some extent. This could extend its safe administration and improve patient compliance. The present study aims to develop floating tablets of model drug using HPMC K4M, Carbopol 934 and an effervescent agent which can float on gastrointestinal fluid for sustained release and evaluate the model drug tablets in-vitro for their TFT, FLT, and drug release pattern. Gastro retentive drug delivery system (GRDDS) refers to systems in which the drug retained in the stomach for a prolonged period that improves the bioavailability of drug substances. Any delivery system aims to deliver a therapeutic amount of drug to the specific site in the body to obtain rapid and then maintain a requisite amount of drug. The formulated tablets evaluated for both pre-compression and post compression parameters including weight variation, hardness, friability, in vitro drug release and different pharmacokinetic plots. Final formulation was agreeable when assessed for all assessment parameters.

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1. Introduction

GRDDS are prepared with the intention to retain drug in the gastric region for a prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract (GIT) thus leading its optimal bioavailability [1].

Floating drug delivery systems are bulk density as compare to gastric fluid and thus remain buoyant in the stomach for the prolonged period without affecting the gastric emptying rate, while the gastric floats gastric ion contents, the drug released is slowly at the predetermined rate from the system [2].

Desirable properties of the drug candidate for FDDS are drug should have site specific absorption, e.g., in stomach, the dose of drug should be small, aqueous solubility of drug should be limited, biological half- life should be short, therapeutic index should be high, analysis method of the drug should not be difficult and drug should be easily available [3].

Extended-release tablets of famotidine provide constant plasma concentration with a less frequent administration and also reduce the side effects to some extent. This could extend its safe administration and improve patient compliance. The present study aims to develop floating tablets of model drug using HPMC K4M, carbopol 934 and an effervescent agent.

The famotidine is an H2 blocker and used in the treatment of ulcer, Gastro esophageal reflux disease, Zollinger-Ellison Syndrome. The drug can be administered orally liquid by injection or in tablet forms (www.rxlist.com).

In statistic, a central composite design (CCD) is an experimental design, useful in response surface methodology, for building a second order (quadratic) model

for the response variable without needing to use a complete three- level factorial experiment. The advantages of CCD include variables and interactions are analyzed with the greatest effectiveness [5].

2. Materials and Methods

2.1 Materials

Model Drug (Famotidine) was gift sample from Synmedic Laboratories, HPMC K4M (Mark Healthcare Haridwar), Carbopol 934 (Rexin Laboratories,Ahmedabad), Sodium bi carbonate (Pearl Chemicals, Mumbai), Citric acid mono hydrate (Royal Chemicals, Mumbai), Lactose anhydrous (Capri enterprise, Mumbai), Magnessium Sterate (Capri enterprise, Mumbai), Talc (Jay shree Chemicals, Ahmedabad), Tablet punching Machine (Cadmach, Ahemadabad), FT-IR (Bruker), UV-spectrophotometer (Shimadzu Japan), Ultra Sonicator (Remi equipment), Paddle type Dissolution test apparatus (Electrolab), Digital weighing balance (Shinko Denshi Co Ltd Japan) and Hardness tester (Monsanto).

2.2. Preformulation Studies

2.2.1. The angle of repose

The angle of repose of blend was measured by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was maintained in such a way that the tip of the funnel simply touched the apex of the blend. Then the powder blend was allowed to pass through the funnel freely on to the surface. So as the diameter of the powder cone was determined and then the angle of repose was calculated using the equation as shown below [7].

$$tan\theta = \frac{h}{r}$$

Where, h is the height and r is radius of the powder cone.

2.2.2. Bulk Density (BD) and tapped density (TD)

Both densities were to be determined. A quantity of 2 g of the blend from each formula, previously shaken to break any agglomerates formed, was fed into a 10 ml measuring cylinder. The initial volume was noted, and the cylinder was permitted to fall under its particular weight on to a surface from the height of 2.5 cm at second intervals. Tapping proceeded until no further change in volume was observed [8, 9].

BD and TB were determined using the following equations:

$$BD = \frac{Weight\ of\ powder\ blend}{Untapped\ volume\ of\ packing}$$

$$TD = \frac{Weight\ of\ powder\ blend}{Tapped\ volume\ of\ packing}$$

2.2.3. Compressibility Index

One of the useful measures that can be observed from the bulk density and tapped density determinations, it is the Compressibility index of powder which is expressed in terms of percentage. The formula for Carr's Index is as below:

$$Carr's\ index = \frac{TD - BD}{TD} \times 100$$

2.2.4. Differential Scanning Calorimetry (DSC) analysis

DSC is useful in the investigation of thermal properties of the formulation, providing both qualitative and quantitative information about the physicochemical state of a drug with polymers. DSC measurements were carried out on DSC Q10 V9.9, US. The instrument was calibrated using Indium as standard. Samples were kept in sealed aluminum pans and heated from 30ºC to 300ºC at a rate of 10ºC/min under a nitrogen atmosphere (60 ml/min), with the empty pan as the reference [14].

2.2.5. Methods and preparation of tablets

Fourteen batches were prepared as per two level three factor design. Both HPMC K4M (20-40%), carbopol 934 (5-10%) and Sodium bicarbonate (5- 15%) were used as release rate controlling polymers in various concentration ranges (table no.1). Tablets were prepared by direct compression technique. The model drug, HPMC K4M, Carbopol 934, Sodium bicarbonate, Citric acid & Lactose were weighed and sifted through No. 40 mesh sieve and mixed well to form a uniform mass (in quantities as per the applied design). Talc and magnesium stearate was sifted through No. 60 mesh & added to the above blend and mixed well. The final blend was compressed into using 8.0 mm size rounds flat punches, and corresponding dies [3].

Table No.1 Formulation of Floating tablets

Batch No.	HPMC K4M (%w/w)	Carbopol 934 (%w/w)	Sodium bi carbonate (%w/w)
F1	30.00	3.30	10.00
F2	20.00	10.00	15.00
F3	40.00	5.00	5.00
F4	13.18	5.00	5.00
F5	30.00	7.50	10.00
F6	10.00	10.00	15.00
F7	20.00	10.00	5.00
F8	30.00	7.50	18.41
F9	30.00	7.50	10.00
F10	20.00	5.00	15.00
F11	40.00	5.00	15.00
F12	46.82	7.50	10.00
F13	30.00	11.70	10.00
F14	27.09	5.10	11.25

3. Evaluation of Floating Tablets

3.1. Weight variation

20 tablets from each batch were randomly picked, and their average weight was calculated. Then the individual weight

of each tablet was determined using digital electronic balance and was compared with average weight [10].

3.2 Hardness

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression) was measured using a Monsanto type tester. The test was executed on three tablets from each formulation and the average reading was noted (US Pharmacopoeia).

3.3 Friability

Friability of the tablets was calculated using a Roche friabilator. Ten preweighed tablets were placed in the friabilator, operated for 4 min at 25 rpm. The tablets were taken out, de-dusted and weigh again.

$$Percentage\ friability = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

3.4. Swelling index

The swelling properties of tablets were determined by putting the weighed tablet matrices (w1) in the dissolution apparatus in 900 ml of acidifying 0.1 N HCl at 37 ± 0.5°C. The tablets were removed intermittently from the dissolution medium and, after removing free water, the swollen weight (w2) was measured. Swelling Index was determined according to the equation [12].

$$S.I. = \frac{w2 - w1}{w1} \times 100$$

Where, w1 = initial weight of the tablet and w2 = final weight after swelling of tablet.

3.5. Floating lag time (FLT)

It is determined to assess the time taken by the dosage form to float on the top of the dissolution medium after it is placed in the medium [13].

3.6. Total floating time (TFT)

The time for which the dosage form continuously floats on the dissolution media is termed as floating time [13].

3.7. In-vitro release of drug

Dissolution study: In vitro dissolution study of model drug was performed in USP Dissolution apparatus type II, in 900 ml acidify 0.1 N HCl (pH 1.2), maintained at 37± 0.5ºC at a speed of 100 rpm. Samples of 10 ml were withdrawn, and replenished with fresh medium at pre-determined intervals for 8 h and analysed using UV spectrophotometer at 265 nm [15].

3.8. Plotting of Release Data in Various Models

In order to understand regarding the mechanism and kinetics of drug release, the outcomes of the in vitro drug release study were integrated with various kinetic equations like zero order (% release vs. t), first order (log% release vs. t) and Higuchi model. In order to represent a better fit for the formulation, drug release data were further analyzed by Peppas equation (F = kKP*t n , where F is the fraction of drug released at time t, KP is the release constant incorporating structural and geometric characteristics of the drug dosage form, n is the diffusional exponent indicating the drug-release mechanism).

3.9. Implementation of Central composite design

In the present study, three factors (n) were evaluated at the two levels (k) and accordingly, the CCD consisted of 4 (^{in}) batches of full factorial design (1F-4F), 4 (^{in}) batches on axial points (1S-6S) and 1 replicates at the centre points (1C). The factors selected were X1= concentration of HPMC K4 M (% w/w); X2= concentration of carbopol 934 (% w/w); X3= concentration of Sodium bicarbonate ((% w/w). Different concentration of HPMC K4M, Carbopol 934 and Sodium bicarbonate in formulations according to Central composite design of experiments. To implement central composite design we need to prepare all the fourteen formulations [5].

Results & Discussion

4.1. Pre-formulation studies results of powder blend

The powder blend was evaluated for their flow properties. The result of the powder blend pre-compression parameters was shown in table Pre-compression results it was found that powder blend has good flow (table no.2).

Table No.2 Pre-formulation studies of optimized batch

Batch No.	Angle of repose	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's Index
F14	28.81	0.424	0.513	17.34

4.2. Differential Scanning Calorimetry (DSC) analysis

The DSC analysis of polymers such as HPMC K4M, carbopol 934, sodium bicarbonate and drug with the polymer are shown in Figure no.1. On the basis analysis report of DSC, no interaction was confirmed in between the drug and polymer (figure no.1).

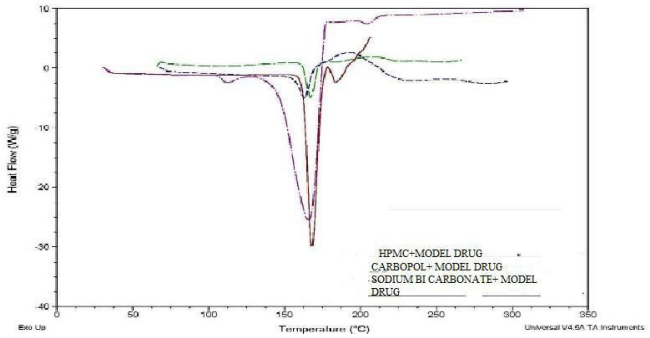

Figure no.1. DSC Thermogram of Drug with polymers

4.3. Weight Variation

Average weights of floating tablets of ideal batch varied in between 186.7 mg to 215.8 mg. Variation was within limits as prescribed in USP (7.5%). Results of weight variation are shown in Table no.3. Acceptance criteria: Variations limits as prescribed in USP (± 7.5 %). For ideal batch, it was found 186.7 to 215.8.

Table No.3 Results of weight variation

S.No.	F14
1	203.9
2	193.7
3	196.8
4	201.0
5	205.3
6	197.6
7	215.8
8	201.4
9	197.7
10	193.1
11	210.4
12	186.7
13	203.9
14	196.4
15	202.3
16	204.5
17	201.5
18	193.6
19	197.8
20	205.7
Avg.wt.	200.4

4. Hardness

The hardness of tablets was measured and found in a range of 3.43 kg/cm 2, sufficient to withstand shock. Results of hardness are shown in table no.4.

4.5. Friability

Friability was found to be less than 1% indicating good mechanical resistance. Results are shown in table no.4.

4.6. Swelling index

Swelling index, after 7 hrs, was found to 95.07%. Results were shown in table no.4.

Table No.4 Results of Hardness, Friability, Swelling index of optimized batch

Batch no.	Hardness (kg/cm2)	Friability (%)	Swelling index (%)
F14	3.05	0.74	95.07

4.7. Results of floating lag time and total floating time

Results of floating lag time and total floating time are shown in table no.5. All the formulations constantly floated on dissolution medium for more than 24 hrs. While the floating lag time varied from 5 to 57 seconds.

Table No.5 floating lag time and total floating studies of optimized batch

Batch no.	Floating lag time (sec)	Total floating time (hr)
F1	7	>24
F2	20	>24
F3	70	>24
F4	10	>24
F5	8	>24
F6	21	>24
F7	23	>24
F8	30	>24
F9	5	>24
F10	15	>24
F11	22	>24
F12	21	>24
F13	34	>24
F14	8	>24

4.8. In-vitro release study

The drug release from floating tablets for batches F1-F14 was found to vary from 70.61% to 97.23% are shown in table 6 and 7. In vitro, drug release data of different formulations of Model drug floating tablets are presented in table 6.The cumulative % drug release v/s time plots for different formulations are presented in figure 6 and 7.

Table No.6 The % Cumulative Drug released in batches (F1-F14)

Time (h)	1	2	3	4	5	6	7
F1	56.52	64.8	89.28	91.08	93.96	95.40	97.23
F2	38.81	48.3	52.88	72.85	75.14	75.79	79.72
F3	34.24	41.76	57.14	66.63	77.43	78.74	80.05
F4	43.39	61.72	75.79	93.4	93.89	94.56	95.79
F5	44.64	68.04	82.08	86.4	92.52	93.6	95.79
F6	43.72	51.22	63.76	71.84	76.77	87.57	93.46
F7	33.25	46.99	56.16	72.52	77.63	82.99	85.28
F8	63.03	70.19	75.47	77.68	81.97	87.92	85.28
F9	25.2	47.88	64.8	75.96	78.48	79.92	84.24
F10	23.46	37.45	49.23	59.05	62.73	67.64	70.61
F11	23.43	4012	55.83	63.68	.70.56	72.85	75.46
F12	36.19	46.99	55.5	64.34	76.77	82.26	83.65
F13	32.76	53.28	61.56	69.12	75.86	86.04	90
F14	31.94	43.39	56.16	66.30	75.19	82.99	85.61

Table No.7 In-vitro release data of various formulations

Formulations	Drug (mg)	HPMC K4M	Carbopol 934	Sodium bi carbonate	% drug release after 7hrs
F1	40	30	3.30	10	97.23
F2	40	20.00	10.00	15.00	79.72
F3	40	40.00	5.00	5.00	80.05
F4	40	13.18	5.00	5.00	95.79
F5	40	30.00	7.50	10.00	95.76
F6	40	40.00	10.00	15.00	93.46
F7	40	20.00	10.00	5.00	85.28
F8	40	30.00	7.50	18.41	89.25
F9	40	30.00	7.50	10.00	84.24
F10	40	20.00	5.00	15.00	70.61
F11	40	40.00	5.00	15.00	75.46
F12	40	46.82	7.50	10.00	83.65
F13	40	30.00	11.70	10.00	90
F14	40	27.09	5.10	11.25	85.61

4.9. Plotting of Release Data in Various Models

In order to understand regarding the mechanism and kinetics of drug release, the outcomes of the in vitro drug release study were integrated with various kinetic equations like zero order (% release vs. t), first order (log% release vs. t) and Higuchi model. In order to represent a better fit for the formulation, drug release data were further analyzed by Peppas equation (F = kKP*t n, where F is the fraction of drug released at time t, KP is the release constant incorporating structural and geometric characteristics of the drug dosage form, n is the diffusional exponent indicating the drug-release mechanism).

R2 values were determined for the linear curves obtained by the regression analysis of the below plots & shown in table 8.

Zero-order plot: A curve was plotted between the time taken on the x-axis and the cumulative percentage of drug release on the y-axis as shown in Figure no.2 and the value of R^2 is 0.993.

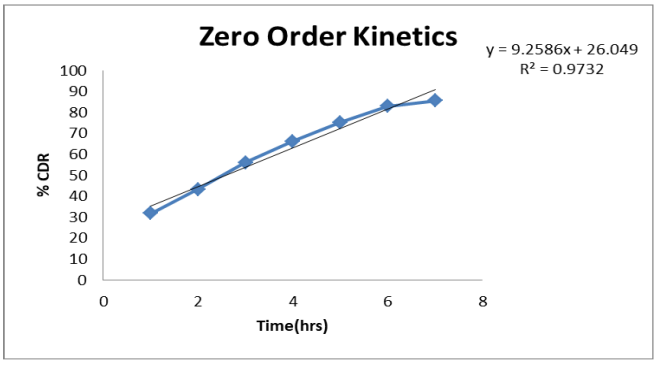

Figure no.2. Zero order plots

First order plot: A curve was plotted between time and the log of the amount of drug remaining to be released as shown in Figure no.3 and the value of R^2 is 0.953.

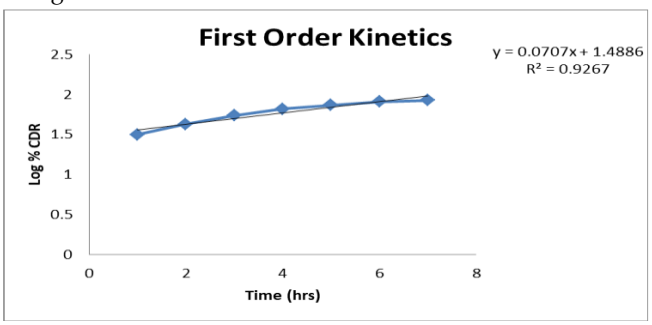

Figure no.3. First order plot

Higuchi model: A curve is plotted between the square root of time taken on the x-axis and the percent of cumulative drug release on the y-axis as shown in Figure no.4 and the value of R^2 is 0.891.

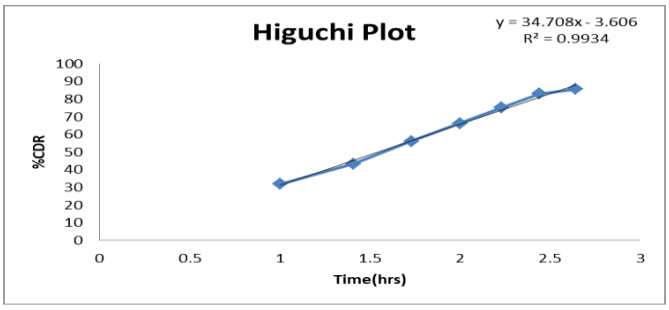

Figure no.4. Higuchi plot

Hixson Crowell Order Plot: A curve was plotted between cube root of the percent drug remaining and time as shown in Figure no.5 and the value of R^2 is 0.994.

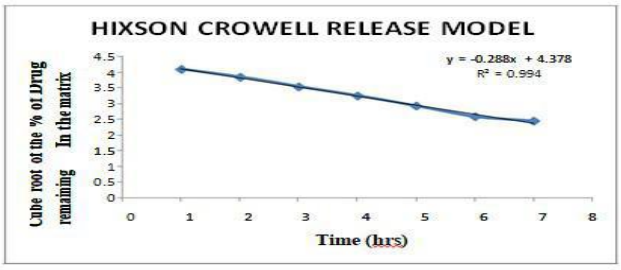

Figure no.5. Hixon Crowell plot

Korsmeyer-Peppas plot: A curve was plotted between the log of time and log of cumulative percent drug release as shown in figure no.6 and the value of R^2 is 0.985.

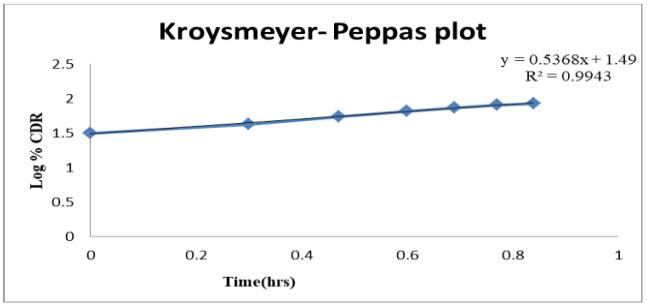

Figure no.6. Korsmeyer-Peppas plot

Based on above values Hixson Crowell order plot has greater R^2 value, i.e. 0.994. So the release rate was determined to

follow Hixson Crowell. R^2 values of different plots are shown in Table no.7.

Table No.7 R2 value of different plots

Formulation		R2 value of different plots			
	Zero order	First order	Higuchi plot	Hixson Korsmeyer-	Crowell Peppas
F14	0.973	0.923	0.993	0.994	0.985

Table No.8 Comparitive study of marketed formulation with the optimized batch

Time (hrs)	1	2	3	4	5	6	7
% Cumulative drug release of mkt. Preparation	82.12	89.73	94.64	95.19	95.93	96.57	97.88
% Cumulative drug release of optimized batch	31.94	43.39	56.16	66.30	75.19	82.99	85.61

4.10. Application of Central-Composite Design and ANOVA on drug floating lag time

The central composite design was applied to examine the effect of concentration of HPMC K4M (% w/w) (X1), the concentration of carbopol 934 (%w/w) (X2) and concentration of Sodium bicarbonate (% w/w) (X3) on the floating lag time. The real values of factors were transformed to facilitate orthogonality of results and easy calculation.

A mathematical model was designed for the estimation on floating lag time is as follows:

Y= 24.34 +7.48 X1+ 4.08 X2 -10.79 X3 -3.21X1X2 -11.04X1X3 +0.21X2X3.

Where Y= Floating Lag Time

X1= Concentration of HPMC K4M (% w/w) X2= Concentration of carbopol 934 (% w/w)

X3= Concentration of sodium bicarbonate (% w/w) X3, X1 X2, X1X2 and X1X3 show interaction terms

4.10.1. ANOVA of Regression (Floating Lag Time)

ANOVA was applied on the floating lag time (using Design Expert 7.0.0) to study the fitting and significance of model table no.9. F-test was carried out to compare the regression mean square with residual mean square, the ratio F= 3.64 show the model is significant. This is only 3.06 % chance that a "model F-value" this large could occur due to noise.

The 3-dimensional response surface plots and the corresponding contour plots for floating lag time are shown in figure no.7and 8, respectively. The estimated model, therefore, may be used as a response surface for floating lag time.

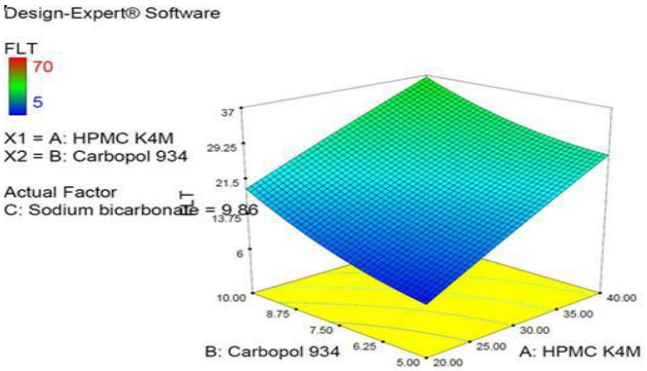

Figure no.7. D Response surface of FLT as a function of formulation variables

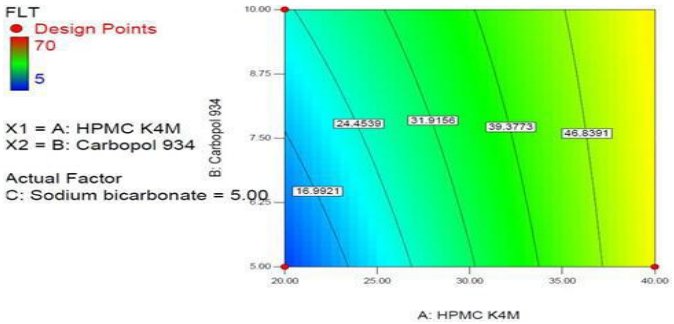

Figure no.8. Contour plot of FLT as a function of formulation variables

4.10.2. ANOVA of Regression (% Drug Release)

ANOVA was applied on the drug release (using Design Expert 7.0.0.) to study the fitting and significance of model. F-test was carried out to compare the regression mean square with residual mean square, the ratio F= 3.47 show the model is significant. This is only 4.3 % chance that a "model F- value" this large could occur due to noise.

Table no.9 ANOVA of Release rate study

	Degree of freedom	Sum of square	Mean square	F - value	F- Significance
Regression	9	792.66	88.07	3.57	0.0435*
Residual	3	197.34	24.67	-	-
Total	12	990	-	-	-

Conclusion

Percent release of formulation F14 was found better than other formulations after each interval of time. Tablets prepared according to formulation F14 showed good TFT and FLT. So, formulation F14 was selected for further studies. Floating tablets of the model drug were prepared with an objective to prolong its residence time in the stomach and upper intestine, to improve its absorption and bioavailability of drug and to prolong the drug release. HPMC K4M and Carbopol 934 was used as a gel-forming agent and Sodium bicarbonate was used as an effervescent agent, in different ratios according to central composite design opting three factors (HPMC K4M, Carbopol 934 and Sodium bicarbonate) and two levels (minimum and maximum). An effervescent technique was utilized for the preparation of Floating tablets. The technique was simple, reproducible and the formulated tablet shows good FLT and TFT. Among all the formulations, the optimized formulation exhibits a good percentage of drug release. As the ratio of sodium bicarbonate and carbopol 934 was raised significant increase in the drug release and HPMC K4M was raised significant decrease in the drug release was determined. Drug release data fitted better fit into Hixson Crowell plot. In-vitro drug release study of optimized batch F14 was compared with the marketed formulation.

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Conflict of Interest

There is no conflict of interest.

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