OPTIMIZATION AND EVALUATION OF CIPROFLOXACIN SWELLABLE FLOATING MATRIX TABLET ON GASTRIC RESIDENCE TIME

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ABSTRACT

In this study six formulations were developed using various non-active ingredients with different combinations like HPMC K4M, Ethyl Cellulose, Carbopol 934P, Sodium bicarbonate, Citric acid, Magnesium stearate, Talc and were characterized for *in-vitro* buoyancy lag time, total floating time, friability, hardness, thickness, weight variation, drug content uniformity, tablet density, swelling index and *in-vitro* drug release studies. Among the six formulations, the best (F3) was selected for optimization by 3^2 factorial design. In this design, Magnesium stearate (X1) and Citric acid (X2) are independent variables. Buoyancy lag time (Y1), total floating time (Y2), hardness (Y3), and *in-vitro* release studies for 24 hrs (Y4) are dependent variables. The results of the study showed that FB5 formulation was found to be optimized formulation. Statistically buoyancy lag time, total floating time, and *in-vitro* dissolution are significantly influenced by the independent variables. Hardness is not found to be significantly influenced by the independent variables. The promising formulation FB5 was found to be stable at 40 ± 2°C and 75 ± 5% relative humidity for three months. In conclusion, FB5 formulations were optimized and found to be statistically optimized formulation.

Keywords: 3^2 Factorial design, Floating matrix tablet, Ciprofloxacin, HPMC, Sustained release

INTRODUCTION

Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects such as gastrointestinal physiology, physicochemical properties of the drug and dosage form characteristics.[1,2] Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine.[3] Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for a longer period of time.[4] A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract are unstable in the lower parts of GIT or are poorly absorbed in the intestine.[5] It has been suggested for the following instances that an active material should be formulated in the form of an HBS to enhance bioavailability: (a) having a dissolution and/or stability problem in the small intestine fluids, (b) being locally effective in the stomach, (c) being absorbed only in the stomach and/or upper part of the intestine.[6]

Based on the mechanism of floatation, delivery system can be classified into two types namely,

- Effervescent floating drug delivery system and
- Non-effervescent floating drug delivery system.[7]

The excellent floating system is effective only in the presence of sufficient fluid in the stomach; otherwise, buoyancy of the tablet may be hindered.[8]

Ciprofloxacin is a broad-spectrum fluoroquinolone antibacterial agent that is active against both Gram-positive and Gram-negative bacteria. It is an ideal candidate for gastroretentive drug delivery technology. It functions by inhibiting DNA gyrase, a type II topoisomerase, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. It is rapidly absorbed orally and shows 60 to 70% oral bioavailability and 3 - 4 hours elimination half-life. Due to its elimination half-life, Ciprofloxacin is administered twice or thrice daily. It is predominantly absorbed from stomach and the proximal part of the small intestine. It reaches the peak plasma concentration to 2.5µg/ml in one to two hour after administration of 500 mg. Therapeutic uses of the ciprofloxacin include urinary and respiratory tract infections, GI, and abdominal infections, STDs, and bone, joint and soft tissue infections.[9]

The present study includes preparation and optimization of ciprofloxacin 100 mg swellable floating tablet using 3^2 factorial design. The scope of the study was to focus the development of floating tablets achieving an extended release for 24 hours targeting the stomach.

MATERIALS AND METHODS

Materials

Ciprofloxacin (Dr. Reddy's laboratories, Hyderabad), HPMC K4M, (Colorcon Asia Pvt, Ltd), Ethyl cellulose (SD fine chemicals Ltd), Carbopol 934P (Loba Chemie Pvt Ltd, Mumbai), Sodium bicarbonate (Loba chemie pvt Ltd, Mumbai), Citric acid (Loba Chemie Pvt Ltd, Mumbai), Magnesium stearate (Loba Chemie Pvt Ltd, Mumbai), Talc (Loba Chemie) are used. All the ingredients were of analytical grade.

Methods

Infrared spectra analysis[10]

Infrared spectrum of Ciprofloxacin was determined on Fourier Transform Infrared spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.

Infrared absorption spectrum of Ciprofloxacin: IR spectrum shows all prominent peaks of Ciprofloxacin. The major IR peaks observed in Ciprofloxacin were 3085.14 (C-H), 2620.34 (OH), 1707.76 (aliphatic), 1624.14 (N-H) and 1311.61 (C-N).

Preparation of floating tablets

Ciprofloxacin tablets are prepared by direct compression method containing Ciprofloxacin 100mg using HPMC K4M as hydrophilic polymer employing Sodium bicarbonate and Citric acid as effervescent agents and excipient. All the ingredients were mixed thoroughly except Magnesium stearate and Talc were passed through sieve no.60. Finally, the lubricants were added and mixed well. Prior to compression, the granules were evaluated for their compressibility parameters and flow characters. Granules were compressed into tablets using 8mm punch in a mega rotary punching machine.
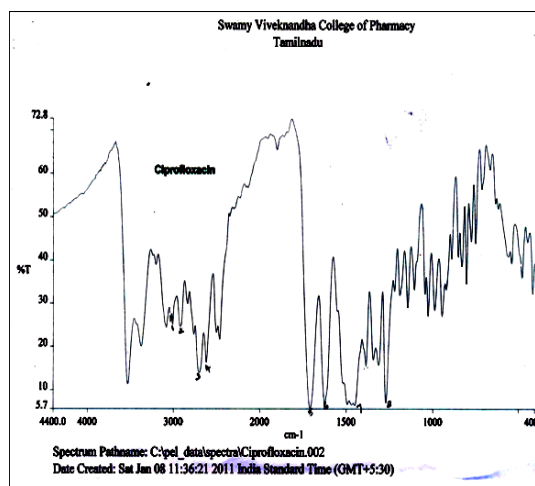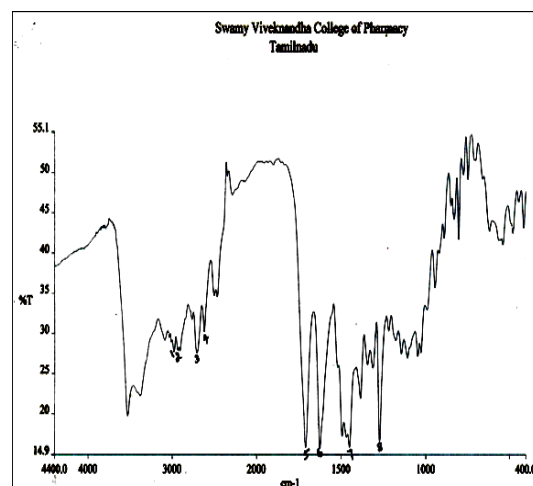
Fig. 1: FTIR of Ciprofloxacin

Fig. 2: FTIR of Ciprofloxacin and Polymers

Table 1: Composition of Ciprofloxacin floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ciprofloxacin	100	100	100	100	100	100
HPMC K$_4$M	70	50	35	25	0	0
Ethyl Cellulose	0	0	35	25	70	50
Carbopol 934 P	0	20	0	20	0	20
Sodium Bicarbonate	25	25	25	25	25	25
Citric Acid	20	20	20	20	20	20
Magnesium Stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total (mg)	220	220	220	220	220	220

Evaluation of tablet

The prepared Ciprofloxacin floating tablets were evaluated for thickness, diameter, hardness, friability, uniformity of weight, drug content, swelling index, buoyancy, total floating time, and in-vitro dissolution characteristics. The thickness and diameter of tablets were measured by Vernier Caliper. Hardness of tablets was tested using Monsanto hardness tester. Friability of tablets was determined by using Roche Friabilator. The drug content in each formulation was determined by taking 20 tablets from each batch were weighed and powdered.

In-vitro buoyancy study

The *in-vitro* buoyancy study was characterized by floating lag time and total floating time. The test was performed using a USP XXII type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5°C. The time required for the tablet to rise over the surface of the dissolution medium and the duration of time of the tablet constantly floated on the dissolution medium were noted as floating lag time and total floating time respectively.

In-vitro drug release study

The release rates of Ciprofloxacin floating tablets were determined by using dissolution testing apparatus USP XXII type II (Paddle type). The dissolution testing was performed using 900 ml of 0.1N HCl at 37 ± 0.5°C temperature with speed of 50 rpm. The sample solution was withdrawn from the dissolution testing apparatus hourly for 24 hours and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 278 nm.

Swelling study

Swelling of hydrophilic polymer such as Hydroxy propyl methyl cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium.

These eventually influence the release, slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 5 hours. The percentage weight gain by the tablet was calculated by using the following formula,

Swelling index (S.I) = {(Wt-Wo)/Wo} x 100

Where, S.I. = swelling index

Wt = Weight of tablet at time "t"

Wo = Weight of tablet before immersion.

Table 2: Physical characteristics of Ciprofloxacin granules

Batch No	Angle of repose(°) Mean ± S.D	Bulk density (gm/cc) Mean±S.D	Tapped density (gm/cc) Mean±S.D	Compressibility Index Mean ± S.D	Hausner's Ratio Mean±S.D
F1	27.25±0.196	0.451 ± 0.0049	0.519 ± 0.0028	12.943 ± 0.721	1.1500 ± 0.0089
F2	26.86±0.627	0.441 ± 0.0049	0.517 ± 0.0028	14.696 ± 0.954	1.1733 ± 0.0135
F3	28.95±0.648	0.457 ± 0.0049	0.522 ± 0.0051	12.486 ± 1.425	1.1483 ± 0.0183
F4	28.62±0.437	0.405 ± 0.0028	0.517 ± 0.0028	21.615 ± 0.860	1.2766 ± 0.0137
F5	27.85±0.359	0.421 ± 0.0014	0.522 ± 0.0023	19.397 ± 0.623	1.2415 ± 0.0084
F6	27.39±0.793	0.422 ± 0.0033	0.517 ± 0.0028	18.302 ± 0.921	1.2242 ± 0.0141

Table 3: Post compression parameters

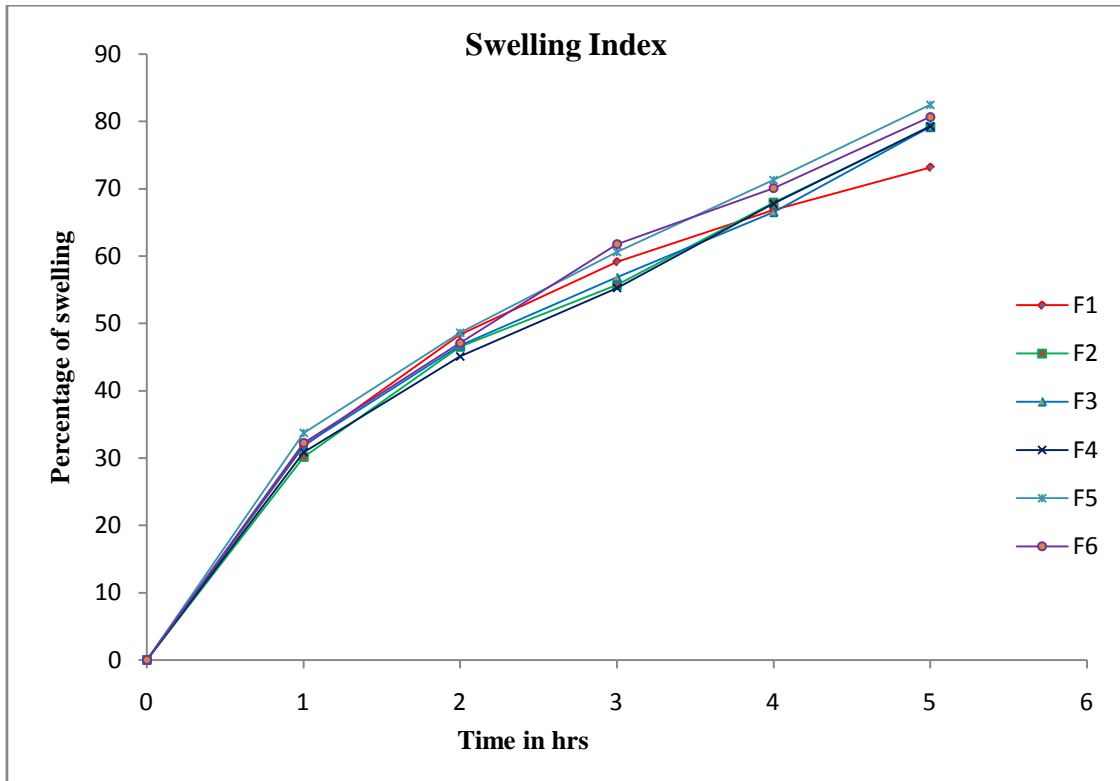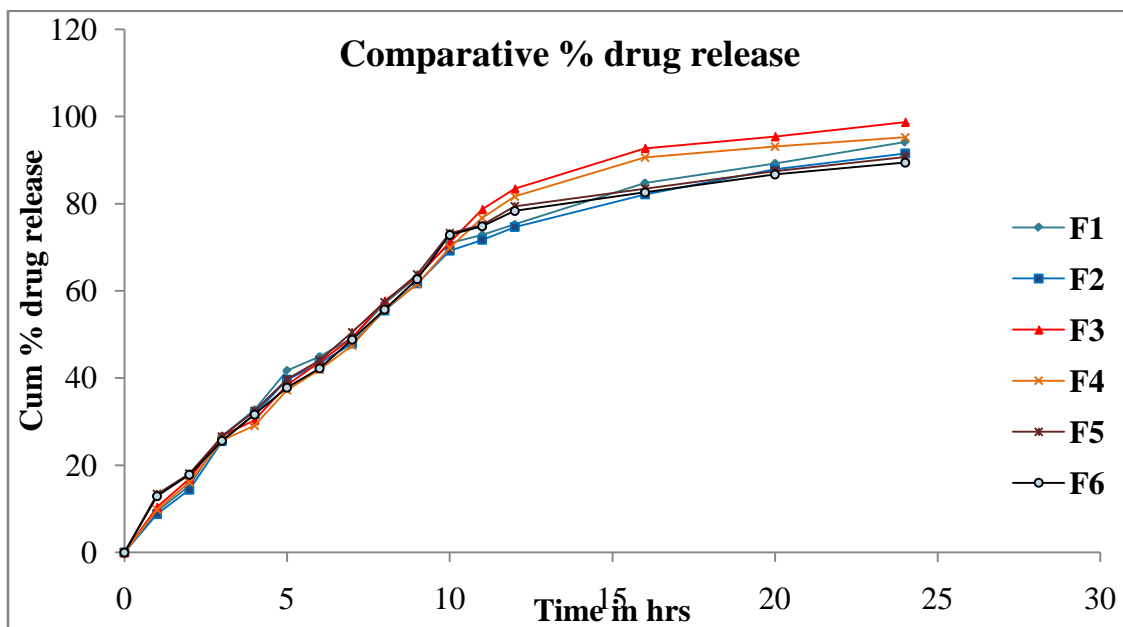| Batch No	Drug Content Uniformity (%)	Tablet density (g/cc)	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	96.87 ± 0.496	0.85 ± 0.017	52	22.1 ± 0.374
F2	97.18 ± 0.347	0.70 ± 0.016	54	23.0 ± 0.447
F3	98.67 ± 0.409	0.77 ± 0.0151	46	22.9 ± 0.734
F4	97.34 ± 0.502	0.66 ± 0.025	39	22.0 ± 0.707
F5	96.30 ± 0.422	0.81 ± 0.029	35	20.1 ± 0.800
F6	97.94 ± 0.229	0.68 ± 0.028	40	20.9 ± 0.916

Fig. 3: Swelling Index

Fig. 4: Comparative Cumulative % drug release

Table 4: Kinetic values obtained from different plots of formulations (F1-F6)

F. Code	Zero-order Regression Coefficient (R^2)	First-order Regression Coefficient (R^2)	Higuchi's Regression coefficient (R^2)	Korsmeyer and Peppa's Slope (n)	Korsmeyer and Peppa's Regression coefficient (R^2)	Possible Drug Release mechanism
F1	0.872	0.995	0.966	0.756	0.965	First order Non-fickian
F2	0.869	0.991	0.963	0.774	0.964	First order Non-fickian
F3	0.88	0.974	0.959	0.763	0.976	First order Non-fickian
F4	0.874	0.978	0.955	0.774	0.975	First order Non-fickian
F5	0.844	0.966	0.942	0.674	0.967	First order Non-fickian
F6	0.844	0.957	0.939	0.683	0.967	First order Non-fickian

Factorial Design

A study in which there are 2 factors with 3 levels is called 3^2 factorial design. A full factorial design was used in this study. Experimental trials were performed at all 9 possible combinations. The two independent variables are Magnesium stearate (X1) and Citric acid (X2)[11,12]. The buoyancy lag time (Y1), total floating time (Y2), hardness (Y3), and in-vitro dissolution (Y4) were selected as dependent variables[13].

Table 5: Composition of tablet as per 3^2 factorial design

Ingredients(mg)	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9
Ciprofloxacin	100	100	100	100	100	100	100	100	100
HPMC K4M	35	35	35	35	35	35	35	35	35
Ethyl Cellulose	35	35	35	35	35	35	35	35	35
Sodium bicarbonate	25	25	25	25	25	25	25	25	25
Citric acid	10	20	30	10	20	30	10	20	30
Magnesium stearate	1.5	1.5	1.5	3	3	3	4.5	4.5	4.5
Talc	2	2	2	2	2	2	2	2	2
Total (mg)	208.5	218.5	228.5	210	220	230	211.5	221.5	231.5

Table 6: Evaluation parameters of FB1-FB9 by 3^2 Factorial Design

Batch Code	Coded values X1	Coded values X2	Buoyancy Lag Time (in sec) ± SD	Total Floating Time (in hrs) ± SD	Hardness (kg/cm^2) ± SD	In-vitro dissolution for 24 hrs (%)± SD
FB1	-1	- 1	81.0 ± 0.81	15.1 ± 0.58	5.73 ± 0.04	91.4
FB2	-1	0	54.3 ± 0.94	22.7 ± 0.40	5.83 ± 0.04	96.7
FB3	-1	+1	30.6 ± 0.47	20.5 ± 0.70	5.80 ± 0.08	94.1
FB4	0	- 1	81.3 ± 0.94	14.9 ± 0.37	5.40 ± 0.08	90.8
FB5	0	0	51.3 ± 1.24	23.2 ± 0.37	5.06 ± 0.04	98.6
FB6	0	+1	30.3 ± 0.94	20.1 ± 0.73	5.33 ± 0.12	94.7
FB7	+1	- 1	79.0 ± 0.81	14.8 ± 0.50	5.06 ± 0.12	89.8
FB8	+1	0	56.6 ± 0.47	23.0 ± 0.31	5.13 ± 0.04	99.1
FB9	+1	+1	31.6 ± 0.47	19.5 ± 0.70	5.10 ± 0.08	95.2

A statistical model incorporating interactive and polynomial term was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$$

Where, Y is dependent variable, b0 is the arithmetic mean response of the 9 runs, and bi (b1, b2 , b12 , b11 and b22 is the estimated coefficient for the factor X1). The main effect (X1 and X2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X1X2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term (X12 and X22) are included to investigate nonlinearity. The buoyancy, total floating time, hardness, and in-vitro drug release for 9 batches (FB1-FB9) showed variation (i.e. 30.3 – 81.3 sec, 14.8 – 23.2 h, 5.06 – 5.83 kg/m^2, and 89.8 - 98.6 % respectively). The responses of formulation prepared by 3^2 factorial designs were indicated in Table no. 6. The data clearly indicate that the dependent variables were strongly influenced on the selected independent variables.

Table 7: The regression coefficients for each term in the regression model are summarized as follows

Polynomial Equations	R^2
Y1 = 55.4778 + 0.216667X1 - 24.8X2 - 0.116667X1X1 + 0.233333X2X2 + 0.75 X1X2	0.99
Y2 = 22.8889 – 0.166667X1 + 2.55X2 + 0.0333333X1X1 – 5.38333X2X2 – 0.175X1X2	0.99
Y3 = 5.38778 – 0.345X1 + 0.00666667X2 + 0.0783333X1X1 – 0.0366667X2X2 – 0.0075X1X2	0.99
Y4 = 98.1222 + 0.150X1 + 2.00X2 + 0.483333X1X1 – 5.13333X2X2 – 0.6750X1X2	0.98

Effect of Formulation Variables on Buoyancy

In the case of Y1 (buoyancy), b_2 was found to be more significant with an interaction of b_{12}, b_{11}, and b_{22}. However, the interaction of b_1, b_{11}, b_{12}, and b_{22} were not significant since P is > 0.05. When the X2 (Citric acid) content is increased the buoyancy is decreased. Similar results are seen earlier as Citric acid is increased, buoyancy is decreased[11]. The effect of X1 (Magnesium stearate) and X2 (Citric acid) on Y1 (buoyancy) is given in Fig. 5. At high levels of X2 (Citric acid), Y1 (buoyancy) is decreased.

Also at high level of X1 (Magnesium stearate), Y1 (buoyancy) is decreased. This was due to increase in X2 (Citric acid) makes more effervescence, so that Y1 (buoyancy) is decreased. Also,

increase in X1 (Magnesium stearate) decreased the hardness, so it results in decrease in Y1 (buoyancy). The surface plot of Y1 (buoyancy) at X1 (Magnesium stearate) and X2 (Citric acid) is indicated to be maximum of 81 when X2 (Citric acid) is increased and X1 (Magnesium stearate) remains the same as shown in the Fig. 5.

Effect of Formulation Variables on Total Floating Time

In the case of Y2 (total floating time), b_2 and b_{22} were found to be significant with an interaction of b_1, b_{11}, and b_{12}. The interaction of b_1, b_{11} and b_{12} are not significant since P > 0.05. When the X2 (Citric acid) level is decreased, (total floating time) Y2 also decreased[11]. The X1 (magnesium stearate) slightly influences the (total floating time) Y2. The effect of X1 (magnesium stearate) and X2 (Citric acid) on Y2 (total floating time) is given in the Fig. 6. At lower level of X2 (Citric acid), total floating (Y2) also lowered. The levels of X1 (Magnesium stearate) does not influence Y2 (total floating time) as shown in the Fig. 6. Y2 (total floating time) shows high value with high X2 (Citric acid) and no significant influence by X1 (Magnesium stearate). The surface plot for Y2 (total floating time) at X1 (Magnesium stearate) and X2 (Citric acid) indicates 23 hrs as maximum.

Effect of Formulation Variables On Hardness

In the case of Y3 (hardness), all the coefficients b_2, b_{11}, b_{22}, b_{12} are not found to be significant except b_1 since P > 0.05. As X1 (Magnesium stearate) is increased, Y3 (hardness) values are decreased to slighter extend. X2 (Citric acid) does not make any significant changes in the Y3 (hardness) as shown in Fig. 7. The X1 slightly increases the Y3 (hardness) since the lubricant has influence in hardness. Similar results are found earlier as X1 (Magnesium stearate) slightly influences Y3 (hardness). X2 (Citric acid) shows no influence on Y3 (hardness). According to the surface plot, the maximum hardness of 5.8 was found with the decrease in the level of X1 (Magnesium stearate).

Effect of Formulation Variables on In-Vitro Dissolution

In the case of Y4 (dissolution in 24 hrs), the coefficients b_1, b_{11}, b_{12} are not found to be significant. The significant coefficients are b_2 and b_{22} and are found to be significant with the interaction with b_{11}, b_{12}, and b_{22}, since the value of P > 0.05. According to the Fig. 8, X1 (Magnesium stearate) and X2 (Citric acid) does not influence Y4 (dissolution in 24 hrs). The surface plot of Y4 (dissolution in 24 hrs) at X1 (Magnesium stearate) and X2 (Citric acid) indicates 98% of maximum dissolution as shown in Fig. 8.
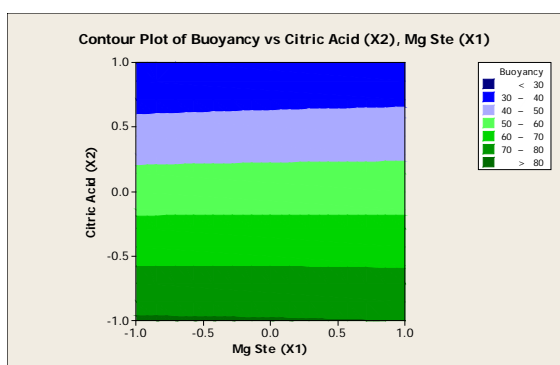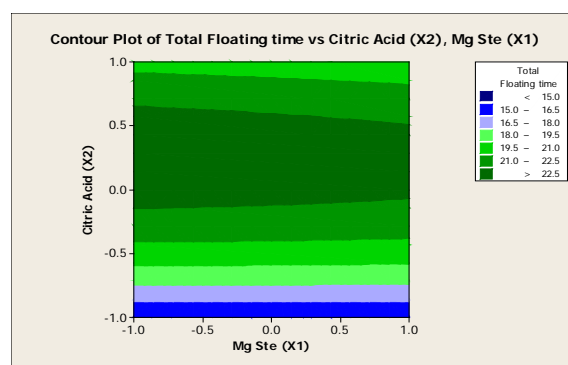

Fig. 5: Contour plot of Y1
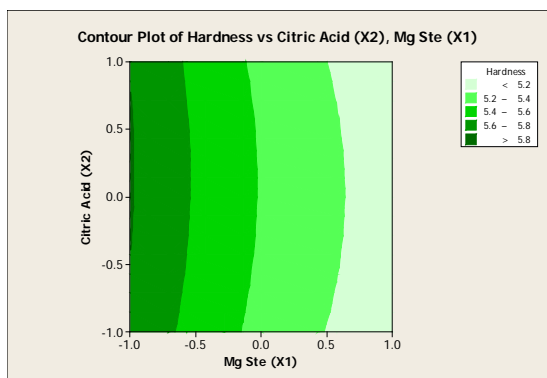

Fig. 6: Contour plot of Y2
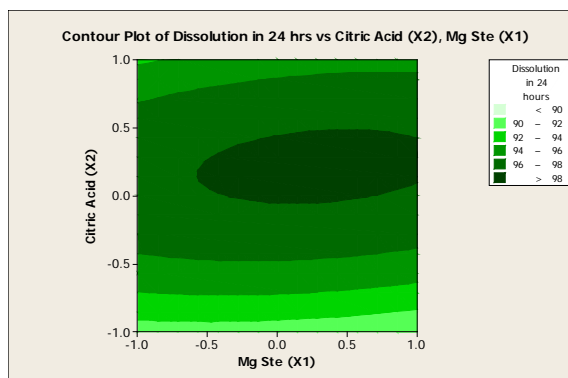

Fig. 7: Contour plot of Y3

Fig. 8: Contour plot of Y4

Stability study of batch FB5

The batch FB5 was selected as an optimum batch for the stability study and it was carried out at accelerated conditions of 40 ℃ / 75 % RH for period of three months as per ICH guidelines. Dissolution study was conducted after three months and dissolution profile was analyzed and find out cumulative drug release.

Table 8: Stability study of optimized formulation FB5

Parameters	1st month	2nd month	3rd month
Physical appearance	White smooth flat faced	White smooth flat faced	White smooth flat faced
Hardness(Kg/cm2)	5.09	5.12	5.14
Buoyancy lag time (sec)	51.2	52.3	53.7
Total floating time (hrs)	23.1	22.9	22.8
Drug content (%)	98.41	97.87	97.76
In-vitro release (%)	98.6	97.8	97.7

RESULTS AND DISCUSSION

The tablet was prepared by direct compression method by using Sodium bicarbonate and Citric acid as effervescent agents, Magnesium stearate and Talc as lubricants. The mixture of all formulation before compression were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The angle of repose value ranged from $26^o 86''$ ± 0.627 to $28^0 95''$ ±0.648. The results were found to be below 30^0 and hence the blend was found to have good flow property. Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.405 ± 0.0028 to 0.451 ± 0.0049 and 0.517 ± 0.0028 to 0.522 ± 0.0051 respectively. The compressibility index (%) was then calculated from the LBD and TBD and it ranged from 12.486 ± 1.425 to 19.397 ± 0.623. The blend was found to have free flowing property as the result were found to be below 20%. The Hausner's ratio ranged from 1.14 ± 0.01 to 1.27 ± 0.01. The result indicates the value of free flowing properties of the granules were below 1.2.

The results of all these tests were found to be satisfactory. The thickness of the tablets were uniform in all formulations and ranged from 5.01 ± 0.012 mm to 5.59 ± 0.069 mm. The hardness of tablets in all batches ranged from 5.2 ± 0.047 to 5.6 ± 0 .20 kg/cm². All the formulations (F1-F6) passed weight variation test as per the pharmacopeial limit of ± 5%. The percentage friability of all batches ranged from 0.15 to 0.31%, which was well below the pharmacopeial limit of <1 %. Drug content was also found to be uniform among the all formulations and ranged from 96.3 + 0.22% to 98.67 + 0.40 %.

In the present study *in-vitro* release profile could be expressed by Korsmeyer-Peppa's for all the formulations showed good linearity which indicates that drug release of F3 shows first order and non-fickian/anomalous transport. Three different polymers and their combination were used to prepare floating tablets. It was observed that the different type of polymer influences the drug release pattern. All the formulations contain equal amount of effervescent agents like Sodium bicarbonate and Citric acid.

Drug release from F6 is least due to high viscosity and permeability of water to Carbopol 934P along with Ethyl cellulose. Also combination of HPMC K_4M and Carbopol 934P significantly releases the drug. As expected, drug release depends on the polymer concentration and permeability of polymer. Tablets containing HPMC K_4M and Ethyl cellulose (F3) showed better drug release up to 24 hours of 98.6%.

Polymeric system with low viscosity polymer (HPMC K4M) yielded a faster initial burst effect. Shoufeng Li (2003) has reported that increased polymer concentration resulted in a corresponding decrease in the drug release. **Baumgartner *et al.*** reported similar results, in which they have demonstrated that HPMC with higher viscosity resulted in thicker gel layer formation.

Incorporation of Carbopol 934P decreased the release of Ciprofloxacin from the GFDDS. Carbopol 934P high viscosity grade is swellable in water and simulated gastric fluid, under the test condition (pH=1.2). Formulations without Carbopol 934P exhibited better drug release likely due to the fact that Carbopol 934P polymer with high molecular weight and viscosity, when contacted with water it would swell and adheres to the mucosa. This property may partially be responsible for the retarded release of Ciprofloxacin from the formulations with Carbopol 934P.

From the results of ANOVA it was observed that the independent factors X1 and X2 influences the dependent factors Y1 (buoyancy), Y2 (total floating time), and Y4 (dissolution in 24 hours). The other dependent factors Y3 (hardness) are not influenced, was found to have p value > 0.05. Further increase in Citric acid naturally decrease buoyancy lag time and total floating time. The role of X1 (Magnesium stearate) and X2 (Citric acid) does not play an important role for and hardness.

The formulation FB5 was found to be stable under the stability conditions as mentioned above since there was no significant changes found in the parameters such as physical appearance, hardness, buoyancy lag time, total floating time, drug content and *in-vitro* drug release.

CONCLUSION

The results demonstrated that the release of the drug is dependent on viscosity of different grades of HPMC K4M, Ethyl cellulose and Carbopol 934 P. It can be conclusively stated that the gastric floating tablet (F3) appears to be promising system for the sustained release Ciprofloxacin for antibiotic therapy. From the results it can be concluded that the release rate of HPMC K_4M and Ethyl cellulose combination shown greater drug release rate than the other formulations. The release kinetic of F3 indicates drug release by First order kinetics with non-fickian or anomalous transport. The dependent variables buoyancy, total floating time, and *in-vitro* dissolution are influenced by independent variables except hardness. The optimized formulation (FB5) was found to be stable when stored at 40 ± 2°C and 75 ± 5% relative humidity for three months under standard stability conditions.

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