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GASTRO RETENTIVE TABLET OF FEBUXOSTAT: FORMULATION, DRUG RELEASE DYNAMICS AND FACTORIAL DESIGN

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ABSTRACT

Present work highlights a strategy to develop a hydrophilic matrix based sustained release formulation for gastro-retentive drug delivery system (GRDDS) of Febuxostat. GRDDS is realized as a promising option for gout treatment, as the delivery system can control and prolong gastric residence time and supply high drug concentration in gastric region for better action. Swellable and floatable gastroretentive tablets were prepared by direct compression technique and evaluated for their swelling characteristics (Swelling index, water uptake), floating capacity (floating lag time and duration), Invitro drug release and stability studies. Factorial design was employed to optimize formulation components. Nine formulations were prepared using two independent variables, amount of Hydroxy Propyl Methyl Cellulose (HPMC) K_4M (60, 90, & 120 mg) and amount of Sodium bicarbonate (20, 30, & 40 mg). The floating lag time and time required for 90% ($t_{90\%}$) of drug release were selected as dependent variables. Optimized formulation showed zero order Invitro drug release for more than 10 hours with excellent buoyancy properties. The prepared tablets floated within 3 min and maintain for more than 18 h. The decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with lower viscosity (HPMC K4M) was shown to be beneficial than higher viscosity polymer (K15M and K100M) in improving the floating properties of GRDDS. These results suggest that prepared GRDDS has the improved release and retentive properties which will be translated into better treatment for gout and other disease.

KEYWORDS: Febuxostat, floating and swelling properties, HPMC, Sodium Bicarbonate, In vitro release, Factorial design.

ABBREVIATIONS

GRDDS = Gastro Retentive Drug Delivery System

HPMC = Hydroxy Propyl Methyl Cellulose

SB = Sodium Bicarbonate

FTIR = Fourier Transform Infra red

DSC = Differential Scanning Calorimetry

GI = Gastro Intestinal

GRT = Gastric Residence Time

DF = Dosage Form

MCC = Microcrystalline Cellulose

FLT = Floating Lag Time

DOE = Design of Experiment

HCl = Hydrochloric acid

1. INTRODUCTION

The oral route of drug delivery is typically considered as the most favoured and the user-friendly means of drug administration having the highest degree of patient compliance, as a result of which much efforts are aimed to identify orally active candidates that would provide reproducible and effective plasma concentration. However, several factors often impact the absorption of orally administered drugs. These factors include unfavourable physicochemical characteristics of the drug, high and frequent doses, and physiological conditions such as limited gastric emptying and retention time. [1] Majority of the drugs are having site-specific absorption in the G.I. tract and parameters like pH dependent solubility, stability and ionization of the drug in different portions of the G.I. tract influence their absorption. [2]

The current controlled release technology has made it possible to release drugs at a constant rate for longer periods of time ranging from days to years. [3] However this approach is not beneficial for variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the gastric or upper small intestine, (iii) are unstable in alkaline media, or (iv) exhibit low solubility at high pH values. [4,5] These limits promoted the development of GRDDS. This application is effective in delivery of sparingly soluble and insoluble drugs.

From the formulation and technological point of view, the GRDDS is considerably easy and logical approach. To extend the residence time of dosage form in the stomach, gastroretentive drug delivery systems can be adopted. The systems not only improve the bioavailability of drugs characterized by a narrow absorption window in the upper GI tract, but also provide multiple pharmacokinetic–pharmacodynamic advantages over conventional immediate-release dosage forms.

Several approaches has been developed in order to prolong the residence time of dosage form in the stomach such as floating[6], bioadhesive,[7] swelling[8] and expanding approaches[9] and has been developed to increase controlled[10] and predictable drug delivery[11] in the GI tract to increase the gastric residence time (GRT). [12-14]

GRDDS can be achieved by: (i) a low density dosage form (DF) that causes buoyancy above gastric fluid [15-16]; (ii) a high density DF that sinks in the bottom of the stomach; (iii) a bioadhesion to the stomach mucosa; or (iv) a limited emptying of the DF through the pyloric sphincter by swelling or unfolding to a larger size. [17-19] Effervescent tablets of Febuxostat were made of HPMC and SB so as to lengthen its stay in the absorption window. The floatability of drug caused by HPMC matrices depends on the porosity, and the porosity can be increased by generating carbon dioxide (CO_2) bubbles obtained from the reaction of SB with an acidic dissolution medium. Thus, prolonging the residence time of dosage form in the stomach is an important strategy to enhance the drug bioavailability. Floating drug delivery systems are considered preferable and promising since they do not adversely affect the motility of the GI tract.

Febuxostat is a non-purine selective inhibitor of xanthine oxidase (Figure 1). Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, Febuxostat inhibits xanthine oxidase and therefore reduces the production of uric acid, excess of which is responsible for the gout disease. Its oral bioavailability is about 80% and biological half life is about 5-8 hrs. Due to short residence time in upper GIT, effective concentrations cannot be achieved and thus fluctuation in plasma drug concentration occurs which leads to failure of therapeutic intervention.

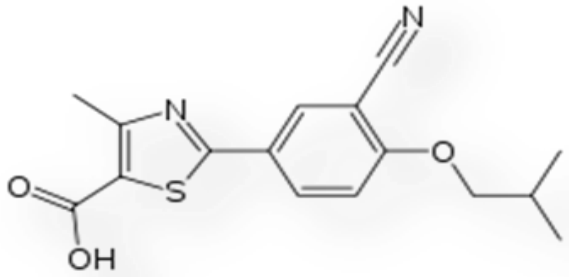


Figure 1: Structure of Febuxostat

The objective of this study was to systemically investigate the contribution of several formulation variables on the drug release rate and floating properties of GRDDS using Febuxostat as a model drug. Specifically, the In vitro release and floating studies of nine formulations, prepared according to a 2 × 3 full factorial design, were performed using USP type II dissolution apparatus and an online continuous floating monitoring system, respectively. Drug Release and tablet floating parameters were obtained directly from the drug release and floating lag time curve.

2. MATERIALS AND METHODS

2.1 MATERIALS

Febuxostat was received as a gift sample from Unimark Remedies, Ahmedabad, India. HPMC K4M, K15M, and K100M were purchased from Colorcon Asia Pvt. Ltd, India. SB was purchased from Finar Chemicals Ltd., India. Microcrystalline cellulose (MCC) (pH 101) was purchased from FMC Asia pacific Inc., Mumbai. All other chemicals and reagents were used of pharmaceutical or analytical grade.

2.2 Preparation of Gastro-Floating Tablets

The gastro-floating tablets containing 120 mg of Febuxostat with Poloxamer 188 complex equivalent to 40 mg of Febuxostat were prepared by direct compression with varying grades and concentrations of polymer such as HPMC as release retarding agent or matrix agent and sodium bicarbonate, as a effervescent agent. The drug and other inactive ingredients in each formulation were mixed homogeneously for 5 min in a mortar with pestle. Powder mixture mixed with 1% (w/w) magnesium stearate before being co-pressed into tablets using 11±0.1 mm round concave punches and corresponding dies on single punch compression machine. Table 1 shows the detailed formula compositions tested for gastro-floating tablets.

Table 1. Formulation of gastro retentive tablets of Febuxostat in a 3^2 Full Factorial Design

Batch	Febuxostat complex * (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)	SB (mg)	Talc (mg)	Magnesium stearate (mg)
F_1	120	60	-	-	20	3	3
F_2	120	60	-	-	30	3	3
F_3	120	60	-	-	40	3	3
F_4	120	90	-	-	20	3	3
F_5	120	90	-	-	30	3	3
F_6	120	90	-	-	40	3	3
F_7	120	120	-	-	20	3	3
F_8	120	120	-	-	30	3	3
F_9	120	120	-	-	40	3	3
F_{10}	120	-	90	-	30	3	3
F_{11}	120	-	-	90	30	3	3

Coded values	Actual values†	
	X_1 (mg.)	X_2 (mg.)
-1	60	20
0	90	30
+1	120	40

*All batches: 120 mg of Febuxostat+ Poloxamer 188 complex equivalent to 40 mg of Febuxostat (for solubility enhancement) (this complex reported separate manuscript under communication), MCC upto 350 mg of total weight of tablets

†X_1 is amount of hydroxypropyl methylcellulose K_4M (mg)

† X_2 is amount of sodium bicarbonate (mg)

2.3 Characterization of Febuxostat GRDDS

The prepared powder and tablets are evaluated for density, carr's index, angle of repose, crushing strength, friability, weight variation, swelling index, water uptake, in vitro drug release, In vitro floating lag time, and total floating time .

2.3.1 Fourier Transform Infrared (FTIR)

To investigate the chemical interaction, FTIR analysis of admixture of Febuxostat and the excipients used in the formulation were carried out over the range of 400-4000 cm^{-1} using FTIR spectrophotometer (Schimadzu, IR prestige 21, se Japan). The spectra produced by the pure drug and in combination with excipients were compared to confirm the interaction.

2.3.2 Differential scanning calorimetry (DSC)

DSC analysis was performed using Mettler Toledo (Star DSC1 SW 9.30). The instrument was calibrated with indium (calibration standard, purity >99.999%) for melting point and heat of fusion. A heating rate of 10 ºC/min was employed in the range of 25 ºC to 300 ºC. Analysis was performed under a nitrogen purge (50 ml/min). An empty pan was used as reference. The ratios of Febuxostat to excipients were similar to that of weight ratio in GRDDS. Pure drug, polymer and gastro-floating tablet were subjected to same thermal cycles.

2.4 Swelling index

The swelling of tablet is three dimensional and the extent of swelling can be measured either by the % weight gain of swollen tablet or by the % volume increment calculated by $\pi \times (\text{diameter}/2)^2 \times$ thickness with the assumption that the tablet swelled as a cylindrical form. The swelling studies of tablets were measured in glass containing 200 ml of SGF which was maintained at 37±0.5°C. At selected regular intervals, the tablet is withdrawn and weighed. [20] The swelling index (SI) was calculated according to the following equation:

$$\text{Swelling index} = \frac{S_t - S_i}{S_i} * 100 \qquad (1)$$

where S_i and S_t represent the initial diameter of the dry tablet and that of the swollen tablet at time t, respectively. The data represent mean ±SD from at least three samples per formulation (n=3).

2.5 In Vitro Buoyancy Studies

The In vitro buoyancy was determined by floating lag time, as per method described. [21] The time (floating lag time, FLT) that gastro-floating tablets take to emerge on the surface of medium and the time that the tablets constantly float on the surface of medium (duration of floating) were determined by the USP type II Apparatus filled with 900 mL of artificial gastric fluid without pepsin (pH = 1.2, 37 ± 0.5◦C,paddle rotation = 100 rpm). The FLT and the total floating time were determined for each formulation of gastro-floating tablets (n = 3).

2.6 In vitro Dissolution Studies

Drug release from GRDDS tablets were performed in 900 ml of simulated gastric fluid at 37±0.5°C at 50 rpm, using apparatus II method for 12 h. At appropriate time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12 h) 5 ml of sample was withdrawn and equal volume of medium

was added to maintain the volume constant. Samples were analyzed in spectrophotometer at 317 nm . A linear correlation ($r^2 > 0.999$) was obtained over the range of 2–20 µg/ml. [22] The dissolution data obtained were plotted as percent cumulative drug released versus time. Each in vitro dissolution test was performed in triplicate, as well.

2.7 Kinetics of Drug Release

An appropriate drug release test is required to characterize the drug product and ensure batch-to-batch reproducibility and consistent pharmacological/biological activity. The release of drug from a sustained release formulation is controlled by various factors through different mechanisms such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. [24] The drug release kinetics are studied by plotting all the data obtained from the in vitro release in various kinetics models like zero order[25], first-order[26], Higuchi[27], Hixon-Crowell[28], Korsemeyer and Peppas[29], and Weibull[30] models to ascertain the kinetic modeling of drug release. There are several linear and non-linear kinetic models widely used to describe release mechanisms and to compare test and reference dissolution profiles.

2.8 Factorial Design

Design of experiment (DOE) has been widely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables. [23] A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all possible combinations. The amounts of HPMC K4M (X_1) and sodium bicarbonate (X_2) were selected as independent variables. The times required for 90% drug release (Y_1), and floating lag time in second (Y_2) were selected as dependent variables. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (2)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1 X_2) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The statistical analysis of the factorial design batches was performed by multiple linear regression analysis

2.9 Stability study: The optimized formulation was packed in silver foil and subjected to stability studies at 40 °C ± 2 °C/75 ± 5% RH. Sample was withdrawn at predetermined time intervals of 0 (initial), 30, 60 and 90 days. Tablet was evaluated for the different physicochemical parameters viz. appearance, weight variation, hardness, friability, and in vitro release.

All results are expressed as mean±SD. Differences between two related parameters were performed by student's t-test or one-way ANOVA using software SPSS 17. Differences were considered significant at $P < 0.05$

3. RESULTS AND DISCUSSION

The data of physical parameters like bulk density, tapped density, hausner's ratio, thickness, content uniformity, weight variation, length of the tablet, floating lag time, and total duration of floating of all the formulations are provided in Table 2 and 3. The aim of this study was to develop a swellable and floatable GRDDS, based on combining HPMC K4M, and sodium bicarbonate to improve gastric retention by shortening the floating lag time (FLT) and prolonging the floating duration with controllable drug release profiles of Febuxostat. MCC is a diluent and imparts superior flow property. HPMC is capable of swelling in contact with aqueous fluids such as simulated gastric fluids leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance the floating abilities of the dosage forms.

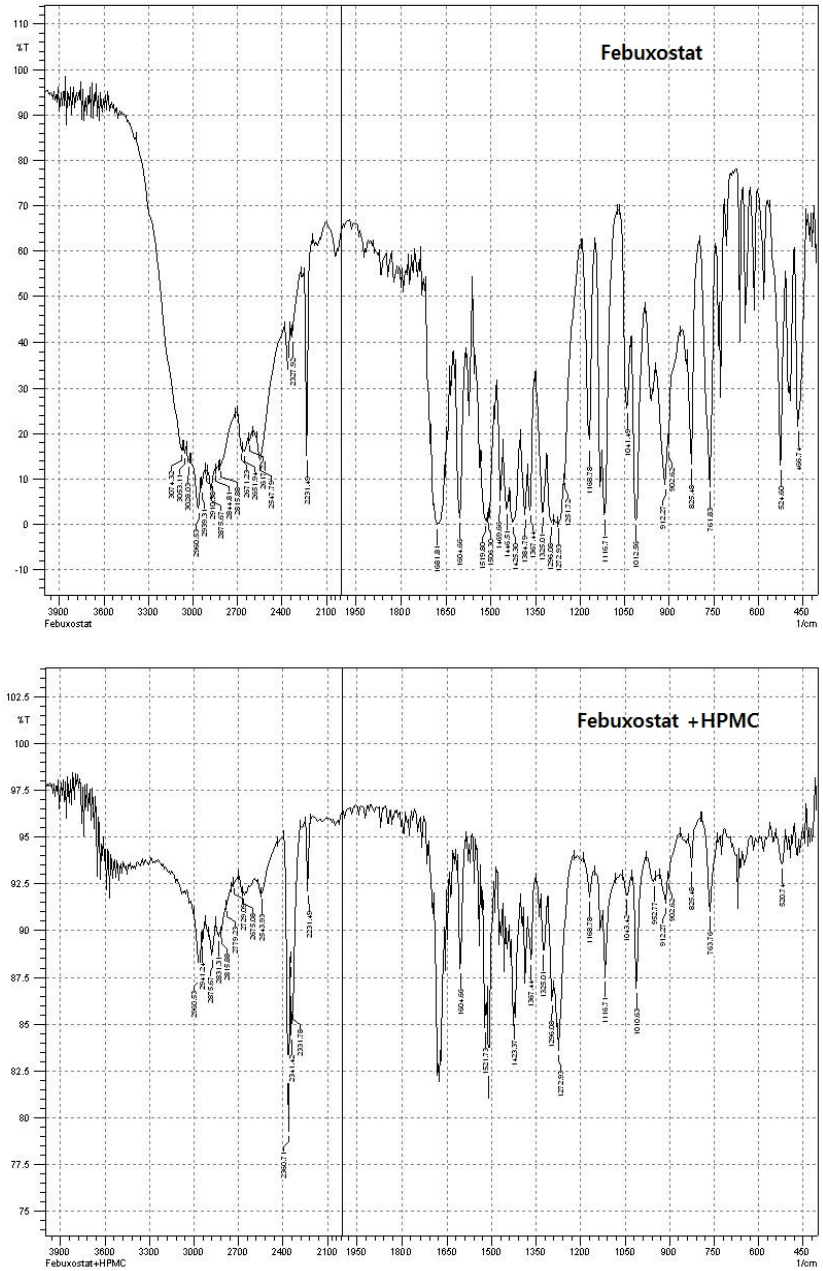
Table 2: Pre-compression parameters of gastro retentive tablets

Batch	Bulk Density (gm/cc)	Tapped density (gm/cc)	Hausner's ratio	Carr's index	Angle of repose (°)
F_1	0.71	0.83	1.17	14.45	20
F_2	0.66	0.76	1.15	13.15	22
F_3	0.75	0.90	1.2	16.66	23
F_4	0.67	0.83	1.23	19.28	21
F_5	0.72	0.76	1.05	13.89	22
F_6	0.83	0.93	1.12	10.75	25
F_7	0.88	1.02	1.16	13.73	23
F_8	0.87	1.05	1.21	17.14	21
F_9	0.88	0.99	1.13	11.11	24
F_{10}	0.71	0.79	1.11	14.08	26
F_{11}	0.77	0.91	1.18	15.38	23

3.1 Characterization of GRDDS Tablets

3.1.1 Fourier Transform Infrared

The FTIR spectra of pure Febuxostat and GRDDS are shown in Figures 2. The FTIR spectra of pure Febuxostat showed characteristic peaks at cm^{-1} (CH – stretching), (C-N – stretching), (C-HO - stretching alcoholic group), (C=O – stretching amidic group), (N-H - stretching), (C=C -bending), (C-F stretching), (O-H- bending). The spectrum of pure Febuxostat was equivalent to the spectra obtained by the addition of excipients. This shows that there is no physical and chemical interaction taking place between drug and excipients. The findings indicate that the drug and polymers are compatible with each other.



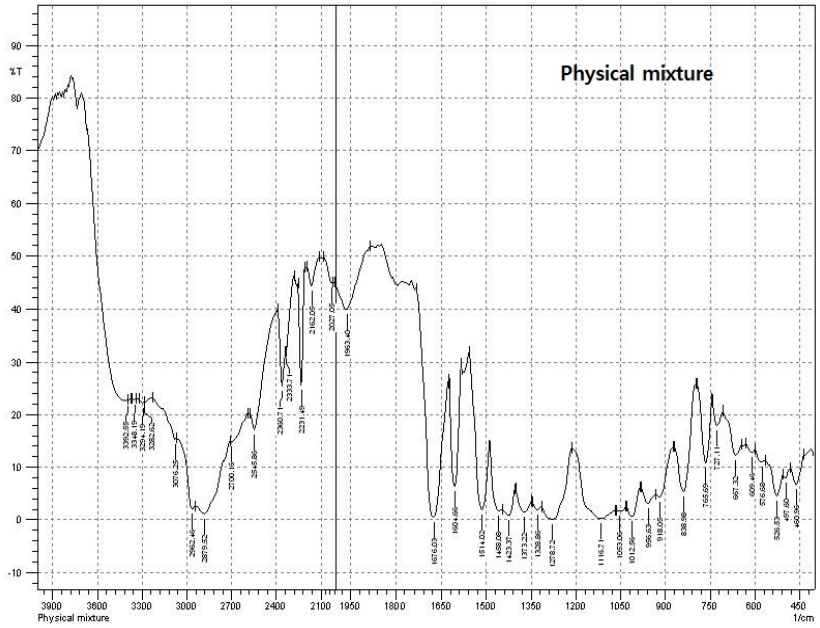


Figure 2: FTIR spectra of (a) pure Febuxostat, (2) Febuxostat + HPMC K4M (3) Physical mixture

3.1.2 Differential scanning calorimetry

Figure 3 shows DSC curve of Febuxostat, HPMC K4M and GRDDS tablet (Formulation). DSC of the resulting tablets revealed that there was no change in the peak temperature of the tablets when compared to that of pure Febuxostat, which showed a peak at 210.13°C to 148.79° C and 160.23°C with HPMC K4M and SB, respectively. These results indicate that there was no chemical interaction between the constituents of the tablet i.e. drug and excipients.

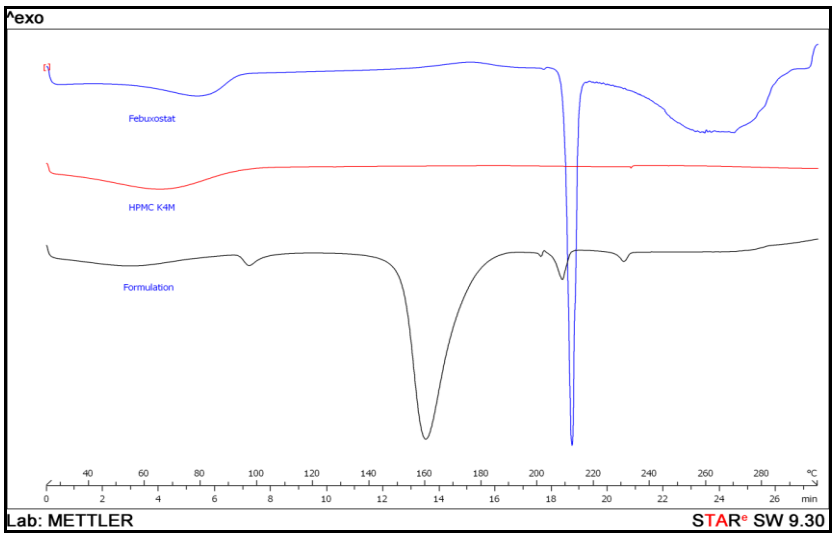


Figure 3: DSC thermogram of pure Febuxostat, HPMC K4M and Febuxostat GRDDS tablet

3.2 Swelling index

The swelling index of tablets was determined by the described method at different time intervals in section 2.3.4. Since the maximum swelling was observed after 12 h in most formulations, swelling was determined at the end of 18 h for all the developed tablets (Figure 4). The swelling ratio in SGF at 18 h for formulations with various concentration of HPMC K4M was measured, and the results are shown in Table 3.

Table 3: Post-compression parameters of gastro retentive tablets

Batches	Crushing strength (N) (n=10)	Friability % (n=20)	Floating lag time (sec) (n=10)	Total Floating time (h)	Swelling Index (%) (n=10)	$t_{90\%}$ (h)
F_1	56±3	0.40	142±3	> 18	180±12	10.9
F_2	61±5	0.43	94±7	> 18	175±21	11.2
F_3	60±2	0.53	59±5	> 18	213±10	11.9
F_4	53±4	0.60	159±3	> 18	171±13	11.5
F_5	54±6	0.56	101±8	> 18	159±09	12
F_6	57±5	0.62	74±9	> 18	240±11	12.5
F_7	56±2	0.67	167±5	> 18	186±13	12.7
F_8	60±5	0.65	111±7	> 18	209±18	13
F_9	52±3	0.63	82±4	> 18	261±14	14
F_{10}	55±4	0.61	169±6	> 18	191±19	14.1
F_{11}	61±3	0.59	159±4	> 18	215±20	15.8

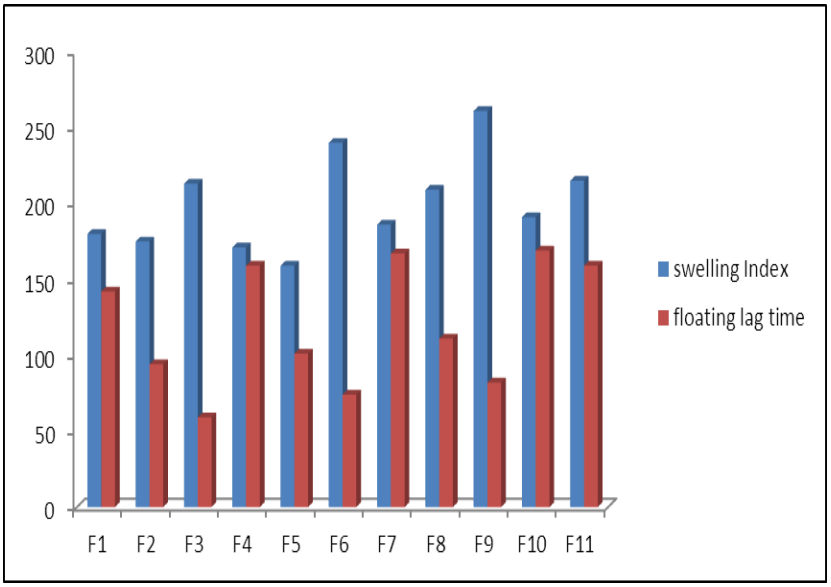


Figure 4: Swelling index (%) and Floating lag time (sec) of different tablets

3.3 In Vitro Buoyancy Studies: Different preliminary batches were prepared using HPMC; sodium bicarbonate was added as gas-generating agents and blend was compressed. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution media (0.1N

HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet till it becomes buoyant.

The amount of Sodium bicarbonate quantity employed is directly related to the floating lag time. The effects of sodium bicarbonate on buoyancy of the tablets were evaluated by using it at three different levels- 20, 30, and 40 mg per tablet. The results of in vitro buoyancy are shown in Table 3. The results show that the total floating time for the formulations were more than 18 hours irrespective to the amount of sodium carbonate whereas floating lag time decreases with increasing amount of sodium bicarbonate. The amount of carbon dioxide produced is exclusively proportional to the quantity of sodium bicarbonate in the tablet. Decrease in floating lag time of the formulations can be attributed to the availability of an increased amount of carbon dioxide as the concentration of sodium bicarbonate was increased, being entrapped in the formed gel to give rapid buoyancy. Floating lag time was less than 170 second for tablets studied. Buoyancy property is further facilitated by relatively good acid solubility of Febuxostat which causes faster penetration of dissolution media into the matrix. This in turn causes quicker initiation of reaction resulting in faster generation of carbon dioxide making the tablets more buoyant.

However in this study, quantity of HPMC K4M was also found to have a prominent effect on floating characteristics. Formulation containing higher amount of HPMC K4M had better buoyancy property. GRDDS prepared by using HPMC K100M exhibited lower floating properties compared to GRDDS prepared by using K4M. However, the difference between different floating curves of different polymeric system is small.

3.4 In Vitro dissolution studies: It is known that the drug release from gel matrices is controlled for water soluble drugs by diffusion through the gel layer or, for poorly soluble drugs, by erosion of the polymer. [33] When a polymer hydrogel matrix containing dispersed water-soluble drug is considered, the diffusion coefficient of drug in the dehydrated hydrogel matrix is extremely low but increases profoundly as the gel imbibes water. Drug release from the gel matrix is thus a function of the rate of uptake of water from the surrounding media and the rate of drug diffusion across the gel matrix. [34] Furthermore, diffusion in a swellable hydrogel matrix could encounter a swelling-controlled situation in which the diffusion coefficient depends significantly on both the concentration and time in which the rate of medium uptake into a polymer matrix is greatly determined by the rate of swelling and relaxation of the polymer chains.

Drug release from the hydrophilic matrix tablet is known to be a complex interaction between diffusion, swelling, and erosion mechanisms. These processes are controlled by the hydration of HPMC, which forms the gel barrier through which the drug diffuses. Drug release rate and extent are inversely proportional to the thickness of this hydrogel layer, because it takes time for drug molecules to travel across the gel layer and reach the dissolution medium. The higher proportion of polymer in the tablet enables the formation of a thicker hydrogel layer and subsequently delays the time required for drug release.

In vitro drug release and buoyancy study revealed that values of responses for these 9 formulations varied markedly indicating strong relationship between responses and the factors (Table 3). To evaluate the effect of the polymer concentration on drug release from GRDD tablets, HPMC K4M was used at 3 different levels- 60, 90 and 120 mg per tablet. The drug release profile as been shown in Figure 5. The result shows that the drug release can be reduced by increasing the concentration of polymer. At higher polymer concentration, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug and hence decreased drug release into the dissolution media.

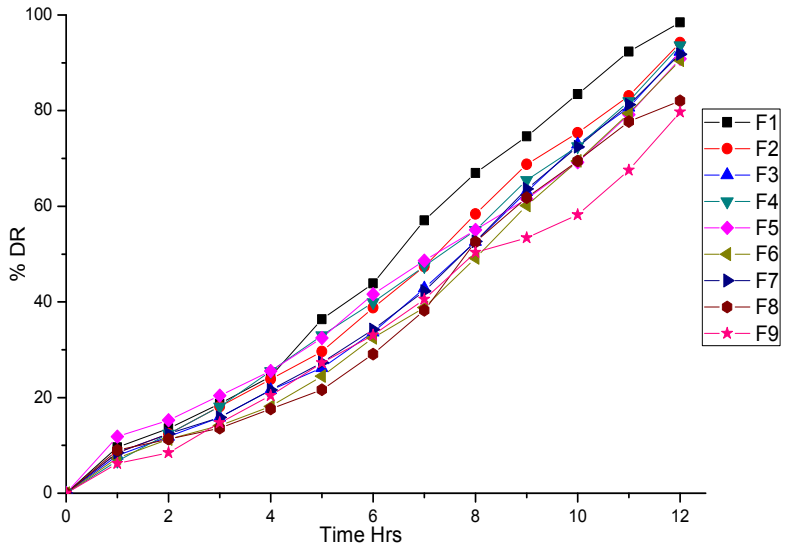


Figure 5: In vitro release of different batches (F1-F9)

The effect of sodium bicarbonate on drug release was evaluated at three different levels. The result shows that there is no significant difference in drug release profile upon changing the concentration of sodium bicarbonate. Sodium bicarbonate, upon contact with the dissolution medium, results in the formation of carbon dioxide gas. These carbon dioxide bubbles get

dispersed in the matrix and may cause partial obstruction of the diffusion path. The presence of the gas bubbles slows down the water transport in the direction of the matrix as well as the transport of the dissolved drug towards the outside of the matrix.

The difference in drug release effect is a result of difference in the viscosity of the polymer. The viscosity of HPMC K4M, K15M, K100M are 4000, 15000, and 100000cp respectively. As can been seen from Figure 6 polymeric system with low viscosity polymer (HPMC K4M) yielded comparatively higher drug release. The result has showed that increased viscosity results in a corresponding decrease in the drug release. Similar resulted were reported in which they have demonstrated that HPMC with high viscosity resulted in thicker gel layer formation. [35]

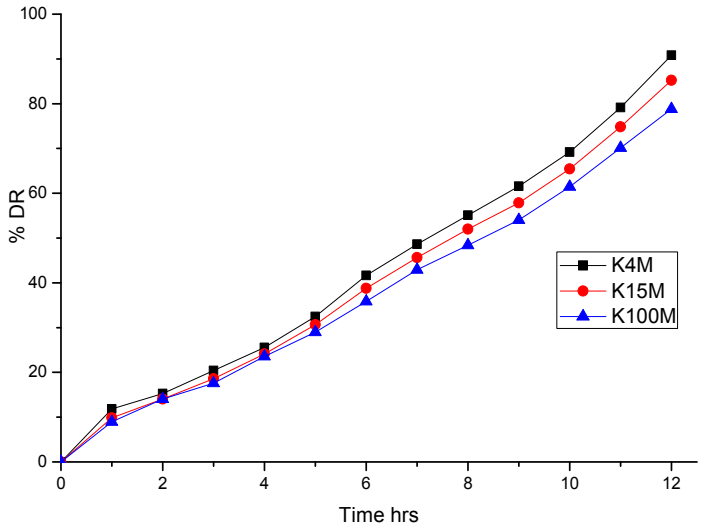


Figure 6: In vitro release of different viscosity grade polymer

3.5 Kinetics of Drug Release: The dissolution data of all batches F1 to F9 was fitted to zero order, first-order, Higuchi, Hixson Crowell, Korsemeyer and Peppas, and Weibull models. The method was adopted for deciding the most appropriate model. The results of F-statistics were used to select the most appropriate model. The release profile of the best batch F_6, fitted best to the zero order model (F = 32.92). The priority should be given to the model with the lowest F value. Thus, it may be concluded that drug release from gastroretentive Febuxostat tablets is best explained by the zero order model. The values of slope and intercept for the zero order model is 0.1236 and -6.1470, respectively. The value of the slope indicates that the drug released by diffusion of an anomalous type (Table 4).

Table 4: Drug release kinetic data of GRDDS (F_6)

Model	SSR	F-value	R-square	Slope	Intercept
Zero order	362.1358	32.9214	0.9651	0.1236	-6.1470
First order	3715.6970	337.7906	.7867	-.0028	4.9410
Higuchi	1846.4650	167.8604	0.8221	3.4151	-21.1542
Hixon-Crowell	1565.1180	142.2835	0.8680	0.0032	-0.3097
Korsmeyer	571.0681	57.1068	0.9566	1.0428	-3.1028
Weibull	798.0958	79.8096	0.8989	1.3468	-3.7252

3.6 Experimental design: The $t_{90\%}$, and floating lag time (sec.) values for the 9 batches (F_1 to F_9) showed a wide variation; the results are shown in Table 3. The data clearly indicate that the values of t_{90} and floating lag time (sec.) are strongly dependent on the independent variables. The fitted equations relating the response t_{90} and floating lag time (sec.) to the transformed factor are shown in Equation 2, and Equation 3, respectively.

$$t_{90\%}(Y_1) = 11.877+0.95X_1+0.55X_2+0.2833X_1^2+0.1833X_2^2+0.075X_1X_2 \quad (2)$$

($R^2 = 0.9935$)

$$\text{Floating lag time } (Y_2) = 123.333+10.833X_1-64.666X_2+0.5X_1^2+1X_2^2+3.25X_1X_2 \quad (3)$$

($R^2 = 0.9998$)

The values of the correlation coefficient indicate a good fit. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e, positive or negative).

Figures 7 (i) and (ii) show the plot of the amount of HPMC K4M (X_1) and amount of sodium bicarbonate (X_2) versus t_{90} and floating lag time, respectively. The plot was drawn using Sigma Plot software (Jandel Scientific Software, San Rafael, CA).The data demonstrate that both X_1 and X_2 affect the drug release (t_{90}) and floating lag time. It may also be concluded that the high level of X1 (amount of HPMC K_4M) and the higher level of X_2 (amount of sodium bicarbonate) favour the preparation of gastroretentive sustained release Febuxostat tablets. The high value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 has a significant effect on t_{90}. It can be concluded that the drug release pattern may be changed by appropriate selection of the X1 and X2 levels. When ANOVA was performed at 95% confidence interval to estimate the significance of the model, factors X_1 (HPMC) and X_2 (SB) were identified as critical influencing parameters for selected responses Y_1, and Y_2.

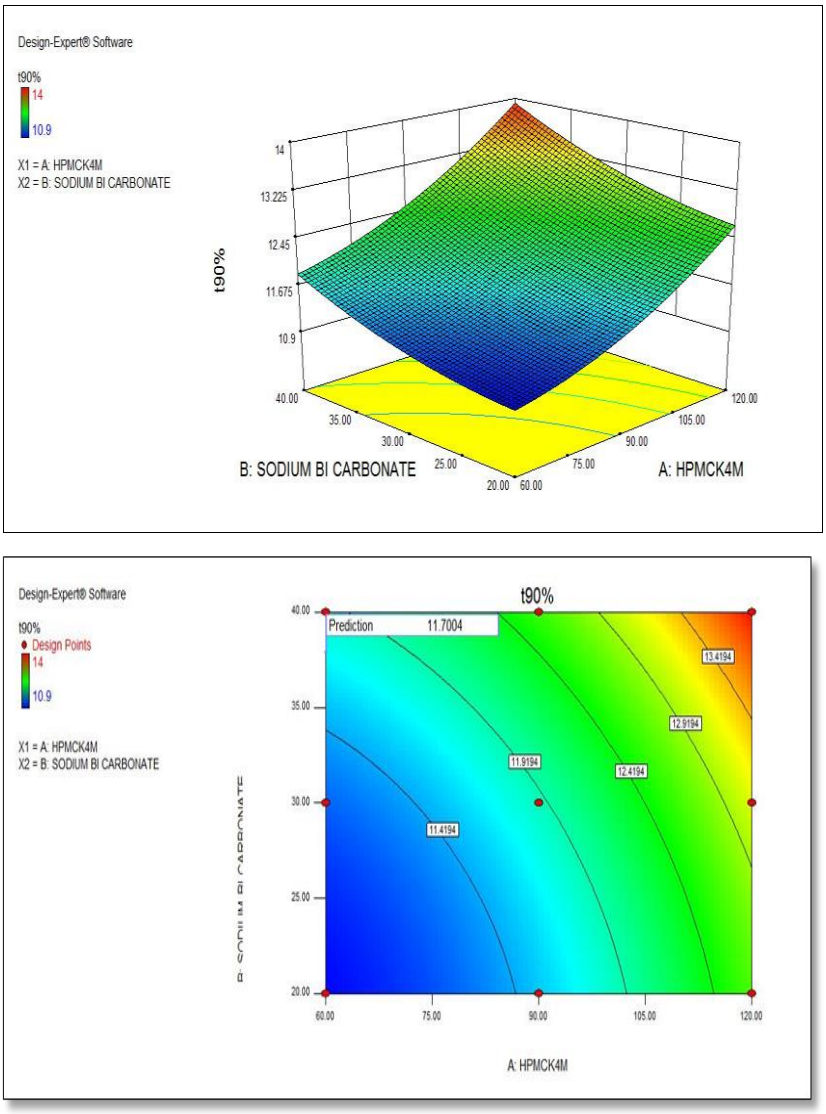


Figure 7 (i): Response surface plot for response t_{90} (min.)

All the factorial design batches showed good in vitro buoyancy (floating lag time). The results of the in vitro buoyancy study of batch F_1- F9 (for HPMC K4M polymer) are shown in Table 1. The table clearly indicates the floating lag time (3 minutes) of the Febuxostat tablets and the floating and swelling tendency of the formulation. The tablet swelled radially and axially. The Table 3 also indicates that the tablet remained buoyant more than 18 hours, but the tablet actually floated throughout the entire study. The in vitro buoyancy study was also conducted at an elevated SGF pH condition. The floating tendency remained unaltered at higher pH.

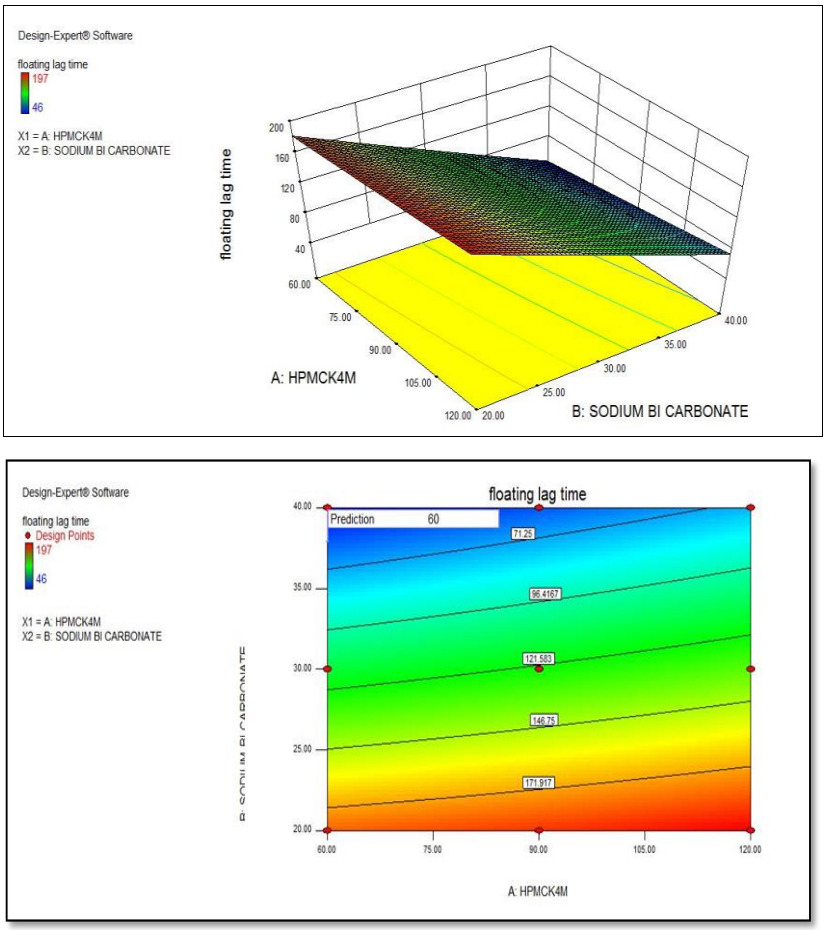


Figure 7 (ii) Response surface plot for response floating lag time (sec.)

3.7 Stability Studies: According to ICH guidelines, three months stability studies conducted at controlled temperature 40 °C ± 2 °C and humidity 75 ± 5% RH showed negligible changes in results as shown in table (5).

Table 5. Stability studies of tablet (F_6).

Parameters	**0 day**	**After 30 days**	**After 60 days**	**After 90 days**
Physical appearance	No change	No change	No change	No change
Weight variation (mg ± SD)[b]	350.1±0.98	349.33 ± 1.36	349.28 ± 1.1	350.86 ± 0.94
Thickness (mm ± SD)[a]	7.6 ±0.03	7.60 ± 0.02	7.61 ± 0.02	7.62 ± 0.02
Hardness (N ± SD)[a]	57 ±5	58 ± 7	57 ± 4	58 ± 2
Friability (% ± SD)[b]	0.62 ±0.21	0.62± 0.11	0.63 ± 0.08	0.63 ± 0.14
Assay	100	99.41±0.21	99.04±18	98.73±0.42
Buoyancy lag time (sec ± SD)[c]	74 ±9	75 ± 6	76 ± 7	76 ±4
Duration of floating (h)	>18	>18	>18	>18

a n = 10.
b n = 10.
c n = 10.

4. CONCLUSIONS

This study developed a GRDDS using HPMC as swellable and floatable polymers combined with SB as a gas generating agent in the tablets. A simple, rapid and high efficiency method was developed to prepare febuxostat containing HPMC tablets in the present study showed acceptable physical properties. Formulated tablets gave satisfactory results for various physiochemical evaluations for tablets like tablet dimensions, hardness, weight variation, floating lag time, total floating time, and In vitro drug release. IR spectra and DSC thermograms of Febuxostat, HPMC, SB and a physical mixture, indicated that there was no interaction between the drug and the polymer and confirmed the drug stability. The analysis of the factorial design revealed that tablets fulfilled the desired release pattern in combination with the desired floating lag time and floating time (> 18 h). These formulations best fitted to zero order kinetics. In vitro studies indicates that tablets remained in the stomach for more than 18 hr, which indicates the increase in the GRT due to floating and swelling principle.

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