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Research Article

Formulation and Evaluation of Gastroretentive Floating Tablets of Quetiapine Fumarate

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Abstract

The objective of the present study was to develop gastroretentive floating tablets of quetiapine fumarate. The gastroretentive floating tablets of quetiapine fumarate were formulated using natrosol 250 HHX as a sustained release polymer and sodium bicarbonate as a gas forming agents. A 3^2 factorial design was employed to study the influence of concentration of natrosol HHX 250 (X_1) and concentration of sodium bicarbonate (X_2) on the dependent variables % drug release at 1h (Y_1), % drug release at 8 h (Y_2) and floating lag time (Y_3). The optimized formulation (O1) showed floating lag time 49 ± 3 sec and % drug release 99.54± 0.81 at 12 h. The *in vitro* release of F1-F9 batches were found in between 99.95 ± 1.18 % to 86.32 ±1.71 % at 12 h. Floating lag time of F1-F9 batches were found to be 25± 2 sec to 178 ± 3 sec. FTIR studies shown that there was no interaction between quetiapine fumarate and excipients. From the factorial design batches it was found that floating lag time was decreased with increasing the amount of sodium bicarbonate and decreasing the amount of natrosol 250 HHX. Here % release of drug was decreased with increase the extent of natrosol 250 HHX. The *in-vitro* release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion.

Keywords: Quetiapine fumarate, Natrosol 250 HHX, Sodium bicarbonate, Gastroretentive floating tablets

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract.[1, 2] GRDDS provide extended residence time in the stomach is of specific interest for drugs having an absorption window in the stomach or in the upper portion of small intestine; acting locally in the stomach; those having low solubility at high pH values; or those unstable in the colonic or intestinal environments.[1, 3] Floating drug delivery systems(FDDS) is one of the great approaches of GRDDS to prolong gastric residence time and to obtain sufficient drug bioavailability. [4, 5] FDDS have a bulk density less than stomach fluids and so remain float in the stomach for a prolong period of time. While the system is floating in the stomach, the drug is liberated slowly at the desired rate from the system.[6-8] The controlled, slow delivery of drug in the stomach provides sufficient local therapeutic levels for long time and limits the systemic exposure to the drug. [5,9]

Quetiapine fumarate (QF) is a psychotropic drug used to cure schizophrenia, bipolar disorder, sudden episodes of mania or depression associated with bipolar disorder. It is an anti-psychotic agent showing serotonin/dopamine binding ratio, dopamine D2-receptor and 5-HT2-receptor blocking effects and resulting minimal extrapyramidal side effects.[10,11] QF has mean elimination half life of 6 h and hence there is a need for twice or thrice daily administration. Quetiapine fumarate shows pH depended solubility. Quetiapine fumarate is highly soluble in acidic pH and slightly soluble in basic pH. It would be more helpful to retain the drug in stomach for prolonged period so as to achieve maximum absorption and bioavailability.[12] So, gastroretentive floating tablet is desirable approach to prolong the residence time of the dosage form in the stomach or upper gastrointestinal tract until the drug is completely released from the system. The aim of this study was to prepare gastroretentive floating tablets of quetiapine fumarate by using natrosol 250 HHX (hydroxyethyl cellulose 250 HHX) as a sustained release hydrophilic polymer and sodium bicarbonate ($NaHCO_3$) as a gas forming agent.

MATERIALS AND METHODS

Materials

Quetiapine fumarate was obtained gift sample from Torrent Research Center, Ahmedabad. Natrosol 250 HHX, Avicel PH102 and polyvinylpyrrolidone (PVP K-30) were purchased from Yarrow chem Product, Mumbai. Sodium bicarbonate, citric acid, magnesium stearate and talc were purchased from Chemdyes Corporation, Rajkot, Gujarat.

Drug and excipient compatibility study by FTIR

FTIR study carried out to identify the drug sample and to establish drug polymer compatibility in physical mixture of drug and polymers. The FTIR spectra were obtained by using an FTIR spectrometer (FTIR- 8400S, Shimadzu, Japan). The samples were mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:1 (sample: KBr) ratio, respectively. FTIR study was accomplished in the range of 400-4000cm^{-1}

Preparation of floating Tablet

Direct compression technique was used to prepare floating tablets of QF. All ingredients were accurately weighed and passed through sieve # 40 and mixed thoroughly for 10 min. The blend was lubricated with talc and magnesium stearate for 2 min. The lubricated blend was compressed using single rotary tablet compression machine (Karnavati Engineering, Mehsana).

Experimental Design:

In this design, two factors were evaluated each at three levels and experimental trials were performed using all possible nine combination. In this present study, concentration of natrosol 250 HHX (X_1) and concentration of sodium bicarbonate (X_2) were selected as independent variables. The % *in-vitro* drug liberate at 1 h (% CDR at 1 h) (Y_1), *in-vitro* drug liberate at 8 h (% CDR at 8 h) (Y_2) and floating lag time (FLT) (Y_3) were elected as depended responses. A statistical design, incorporating interactive and polynomial terms was applied to check the response. [13]

Table 1: Variables in 3^2 Factorial designs

Independent Variables	Levels		
	-1	0	+1
X_1: Natrosol 250 HHX	60 mg (24 %)	75 mg (30 %)	90 mg (36%)
X_2: Sodium bicarbonate	25 mg (10 %)	35 mg (14 %)	45 mg (18%)

Dependent variables: Y_1: *in vitro* drug release at 1 h (% CDR at 1), Y_2: *in vitro* drug release 8 h (% CDR at 8 h), Y_3: floating lag time (FLT) (sec),

Table 2 Formulation of factorial batches

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Quetiapine Fumarate*	58	58	58	58	58	58	58	58	58
Natrosol 250 HHX	60	60	60	75	75	75	90	90	90
Sod. Bicarbonate	25	35	45	25	35	45	25	35	45
Citric Acid	15	15	15	15	15	15	15	15	15
Avicel PH102	78	68	58	63	53	43	48	38	28
PVP K30	8	8	8	8	8	8	8	8	8
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4	4
Average weight of tablet	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

* 58 mg of Quetiapine fumarate is equivalent to 50 mg of Quetiapine

Evaluation of floating tablets

Weight variation

Twenty (20) tablets from each batch were individually weighed in grams on a digital analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Tablets Thickness:

The thickness of the tables was determined by using digital vernier calipers. Randomly five tablets from each batch were taken and average values were calculated.

Hardness

Five tablets will select at random and the hardness of each tablet will measure with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2. [13]

Friability

The friability test will carried out in Roche friabilator. Ten tablets weighed ($W_{initial}$) at the start and kept in a rotating drum of friability apparatus for 100 revolutions. After ending of 100 revolutions, the tablets again weighed (W_{final}). The percent loss in weight or friability (f) determined by the formula given below. [13]

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} X\ 100$$

Drug Content

10 QF floating tablets were taken, powdered. The powder equivalent to 58 mg QF was shifted to a 100 ml volumetric flask and 0.1N HCl was added upto the mark. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 248 nm.[14]

***In-vitro* buoyancy studies**

Tablets were kept in a 100 ml beaker containing 0.1 N HCl (pH 1.2). The duration required for the QF floating tablet to increase to the surface and float was determined as floating lag time (FLT). The total duration of QF floating tablet continuously present on the surface was carried out as the total floating time. [15, 16]

***In-vitro* drug release**

It was conducted for a period of 12 h using USP XXIV type-II (Paddle) dissolution apparatus at 37±0.5°C at 50 rpm utilizing 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, ten ml of sample was taken from the dissolution medium and replaced with 0.1 N HCl to maintain the constant volume. After sample solution was filtered and diluted sufficiently, it was analyzed at 248 nm by UV-Visible spectrophotometer. [17]

***In-vitro* release kinetic study**

The drug release data of floating tablets was fitted to kinetics models, that is, zero order, first order, higuchi and Korsemeyer-Peppas to find out drug release pattern and mechanism. [18]

RESULTS AND DISCUSSIONS

Drug –excipients compatibility study by FTIR:

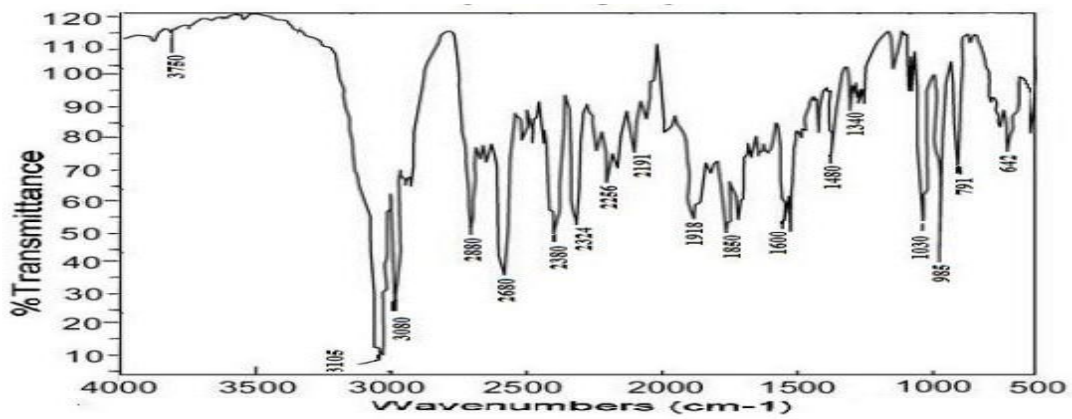

Figure 1: IR Spectra of Quetiapine Fumarate

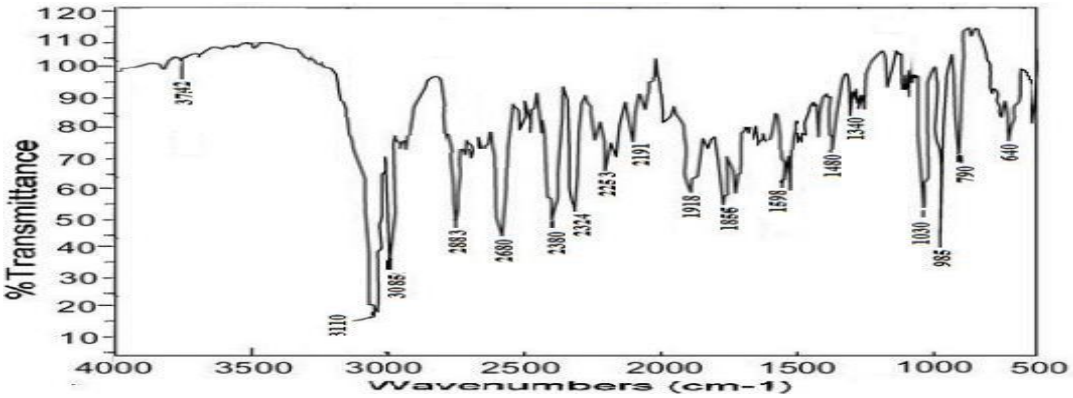

Figure 2: IR spectra of Physical mixture

From the IR studies (Figure 1and 2), important function group IR bands of QF and physical mixture were identified. Characteristic IR bands of QF includes the peaks at 3750 cm^{-1} (O-H stretching), 2880 cm^{-1} (C-H stretching), 2380 cm^{-1} (aromatic C=C stretching), 1600 cm^{-1} (C-N stretching), 1340 cm^{-1} (C-H bending) and 1030 cm^{-1} (C-O-C stretching) which remained unaltered in IR spectrum of physical mixture of QF and polymers. IR analysis showed that there was not any interaction between QF and polymers.

Factorial design batches tablet evaluation parameters

Prepared all batches QF tablets were assessed for weight variation, thickness, hardness, % friability and % of drug content. (Table 3).

Table 3: Results of factorial design batches tablet evaluation

Batch code	Weight variation (mg)*	Thickness(mm)#	Hardness (kg/cm^2)#	%Friability $	%Drug Content $
F1	252 ± 2.21	4.53 ± 0.10	5.9 ± 0.31	0.82 ± 0.12	98.81 ± 1.12
F2	251 ± 2.22	4.53 ± 0.14	5.0 ± 0.22	0.65 ± 0.08	98.72 ± 0.95
F3	250 ± 2.47	4.52 ± 0.19	5.8 ± 0.45	0.87 ± 0.13	98.65 ± 1.78
F4	253 ± 2.18	4.51 ± 0.09	5.1 ± 0.21	0.67 ± 0.11	99.85 ± 1.22
F5	251 ± 2.59	4.50 ± 0.12	5.2 ± 0.58	0.60 ± 0.18	99.53 ± 1.87
F6	250 ± 2.15	4.48 ± 0.18	5.2 ± 0.26	0.62 ± 0.17	99.16 ± 1.71
F7	252 ± 2.36	4.47 ± 0.17	5.4 ± 0.32	0.52 ± 0.12	98.32 ± 1.91
F8	254 ± 1.95	4.45 ± 0.12	6.3 ± 0.12	0.47 ± 0.15	99.44 ± 1.42
F9	252 ± 2.42	4.46 ± 0.16	5.4 ± 0.49	0.51 ± 0.14	98.60 ± 1.89

* n=20, # n=5, $= 10 (mean±SD)

The prepared tablets were smooth and white to off white color. Hardness of the QF floating tablets was in the range of 5.1-6.3 kg/cm². Weight variation in all above batches of QF tablets was within ±2.5% of theoretical tablet weight and within the acceptance criteria. The prepared tablets showed in range thickness of 4.45-4.53 mm. % drug content of QF floating tablets was found between 98.32% to 99.85%. Friability of QF tablets was less than 1% in all factorial batches.

In-vitro buoyancy studies (Table 4)

The floating lag time was found between 25 ± 2 sec to 178 ± 3 sec. QF tablets were prepared by effervescent technique using $NaHCO_3$ as a gas forming agent. $NaHCO_3$ produced CO_2 liberation in presence of acid. The liberated gas is protected within the gel. Then polymer is hydrated and reducing the tablet density. As the tablet density falls below 1 g/ ml, the tablet becomes buoyant.[1, 19-20] The effect $NaHCO_3$ on tablets buoyancy was evaluated by using it at three different levels 25, 35 and 45 mg per tablet. Lowest FLT was found in batch F3 which contain 45 mg $NaHCO_3$ and 60 mg natrosol 250 HHX. Highest FLT was found in batch F7 which contain 25 mg $NaHCO_3$ and 90mg natrosol 250 HHX. All QF floating tablets of factorial batches maintained their matrix integrity for more than 9 h. So from the result it was concluded that FLT decreases with increasing amount of $NaHCO_3$. It was due to increased amount of carbon dioxide as the concentration of $NaHCO_3$ was increased, being entrapped in the formed gel to give rapid buoyancy. [1]

Table 4: floating lag time and floating time of F1-F9 batches

Batch code	Floating LagTime (sec) *	Total FloatingTime (h)*
F1	153 ± 2	9
F2	38 ± 3	9
F3	25 ± 2	9
F4	165 ± 3	12
F5	48 ± 2	12
F6	40 ± 2	12
F7	178 ± 3	13
F8	60 ± 2	13
F9	48 ± 2	13

* n=5 (mean±SD)

% In-vitro drug release

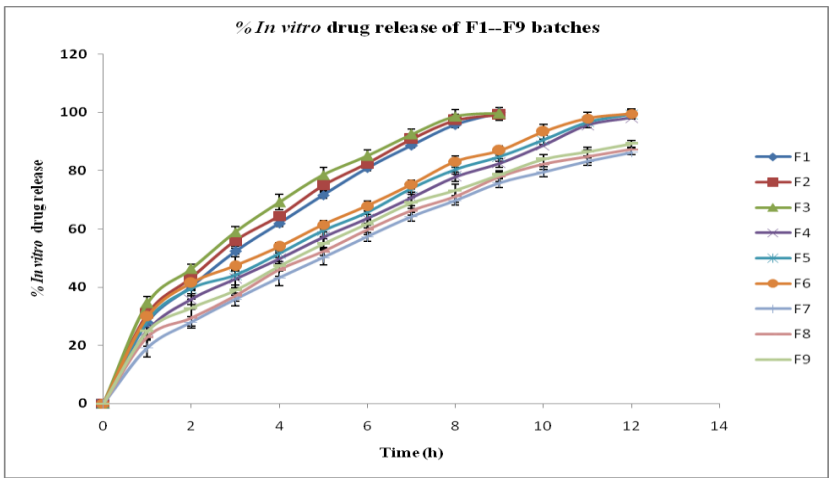

Figure 3: In vitro drug release data of F1-F9 batches

It was showed that the drug release was higher in case of F1, F2 and F3 batch while drug release was lower in case of F7, F8 and F9 batch. Batch F1 and F7 showed the 95.82 % and 69.67% at 8 h respectively. It indicates that as the amount of natrosol 250 HHX increase in formulation, the drug release decrease. It may be due to formation of more viscous gel layer around the tablet at high concentration of polymer.

Factorial design analysis

Analysis of factorial batches data was done using Design Expert DoE software. The data compiled for the selected responses and data analysis was done. Table 5 was used for data analysis.

Table 5: 3^2 factorial design layout

Batch code	Independent variable		Dependent Variables		
	X_1 Natrosol 250 HHX (mg)	X_2 Sodium Bicarbonate (mg)	Y_1 % drug release at 1 h	Y_2 % drug release at 8 h	Y_3 Floating lag time (s)
F1	60	25	27.94± 2.45	95.82 ± 1.89	153 ± 2
F2	60	35	30.81± 2.34	97.33 ± 2.11	38 ± 3
F3	60	45	34.82 ± 2.18	98.61± 2.45	25 ± 2
F4	75	25	24.92± 3.19	77.92± 1.69	165 ± 3
F5	75	35	28.52± 3.26	80.54 ± 1.67	48 ± 2
F6	75	45	29.93 ± 2.49	83.12 ± 1.98	40 ± 2
F7	90	25	19.24± 3.14	69.81± 1.62	178 ± 3
F8	90	35	22.92± 3.28	71.23 ± 2.16	60 ± 2
F9	90	45	24.52± 2.91	73.22± 2.11	48 ± 2

Regression analysis for the effect of X_1 and X_2 on Y_1

Table 6: ANOVA table for response Y_1

Source	Sum of Squares	DF	Mean Square	F-value	P-value	Remarks
Model (Quadratic)	177.05	5	35.41	136.98	< 0.0001	Significant
X_1	117.84	1	117.84	455.83	< 0.0001	Significant
X_2	50.87	1	50.87	196.77	< 0.0001	Significant
X_1^2	4.00	1	4.00	15.48	0.0056	Non- Significant
X_2^2	1.14	1	1.14	4.43	0.0735	Non- Significant
X_1X_2	0.42	1	0.42	1.63	0.2419	Non- Significant

$$Y_1 = +28.39-4.43* X_1+2.91* X_2-1.20 * X_1^2-0.64* X_2^2-0.32* X_1X_2 \quad (1)$$

Where, X_1=Natrosol 250 HHX, X_2=Sodium Bicarbonate

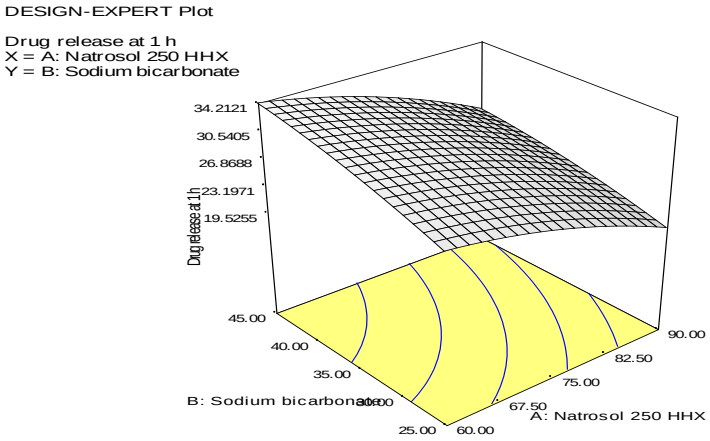

Figure 4: Surface plot for Y_1

From the equation (1), it was concluded that X_1 had negative & X_2 had positive effect on Y_1. So it was concluded that % drug release at 1 h decreased with an increase the amount of natrosol 250 HHX and decrease the amount of sodium bicarbonate.

Regression analysis for the effect of X_1 and X_2 on Y_2

Table 7: ANOVA table for response Y_2

Source	Sum of Squares	DF	Mean Square	F-value	P-value	Remarks
Model (Quadratic)	1069.51	5	213.90	978.04	< 0.0001	Significant
X_1	1001.04	1	1001.04	4577.13	< 0.0001	Significant
X_2	21.66	1	21.66	99.04	< 0.0001	Significant
X_1^2	39.69	1	39.69	181.46	< 0.0001	Significant
X_2^2	2.601	1	2.601	0.012	0.9162	Non- Significant
X_1X_2	0.096	1	0.096	0.44	0.5286	Non- Significant

$$Y_2 = +80.53-12.92* X_1+1.90* X_2+3.79* X_1^2+0.031* X_2^2+0.15*X_1X_2 \quad (2)$$

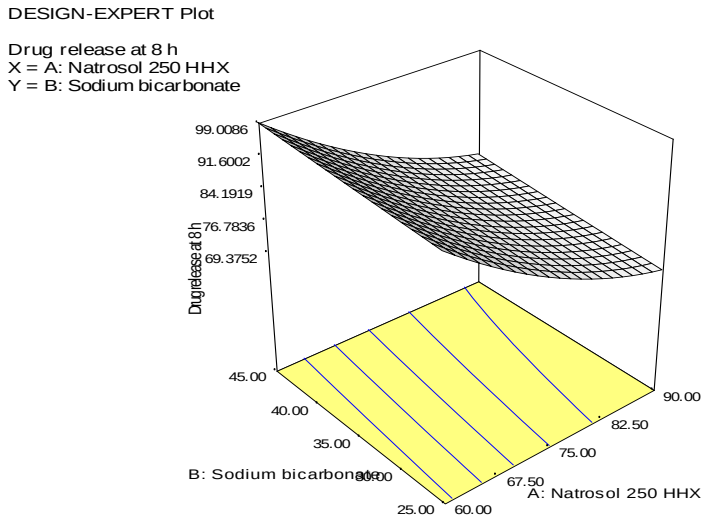

Figure 5: Surface plot for Y_2

From the equation (2), it was concluded that X_1 had negative & X_2 had positive effect on Y_2. So it was concluded that % drug release at 8 h decreased with an increase the amount of natrosol 250 HHX and decrease the amount of sodium bicarbonate

Regression analysis for the effect of X_1 and X_2 on Y_3

Table 8: ANOVA table for response Y_3

Source	Sum of Squares	DF	Mean Square	F-value	P-value	Remarks
Model (Quadratic)	1069.51	5	213.90	978.04	< 0.0001	Significant
X_1	1001.04	1	1001.04	4577.13	< 0.0001	Significant
X_2	21.66	1	21.66	99.04	< 0.0001	Significant
X_1^2	39.69	1	39.69	181.46	< 0.0001	Significant
X_2^2	2.601	1	2.601	0.012	0.9162	Non- Significant
X_1X_2	0.096	1	0.096	0.44	0.5286	Non- Significant

$$Y_3 = +48.34+11.67* X_1-63.83* X_2 -0.21* X_1^2+53.29* X_2^2-0.50* X_1X_2 \quad (3)$$

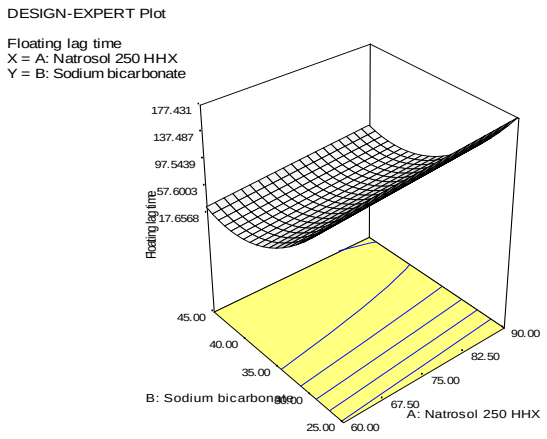

Figure 6: Surface plot for Y_3

From the equation (3), it was concluded that X_1 had positive & X_2 had negative effect on Y_3. So it was concluded that floating lag time decreased with decrease the amount of natrosol 250 HHX and increase the amount of sodium bicarbonate.

Check point batch analysis (Validation of design)

To assess the validity of prediction, a checkpoint batch C1 and C2 was prepared and evaluated under the same conditions as outlined for the other batches. The response data was compared with that of required data. The obtained response variables of check point batch compared with target response parameters. The bias for predicted versus observed responses was acceptable. The Check point batch C1 and C2were prepared and results of check point batches are shown in Table 9.

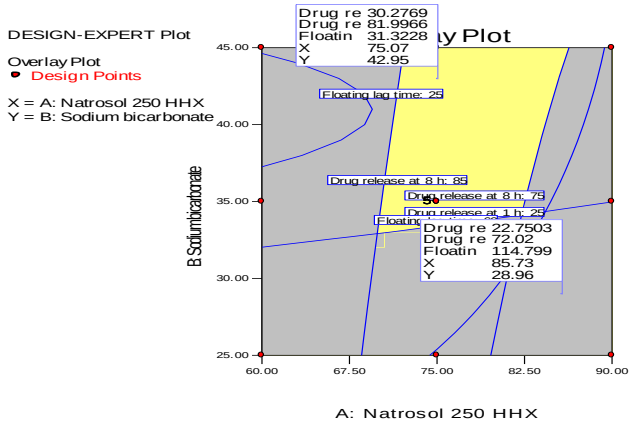

Figure 7: Overlay plot of check point batches

Table 9: Results of check point batches

Batch code	Natrosol 250 HHX (mg)	Sodium Bicarbonate (mg)	% Drug release at 1 h		
			Predicted	Observed	% Bias
C1	75.07	42.95	30.27	31.22	3.13
C2	85.73	28.96	22.75	22.16	2.59
Batch code	**Natrosol 250 HHX (mg)**	**Sodium Bicarbonate (mg)**	**% Drug release at 8 h**		
			Predicted	**Observed**	**% Bias**
C1	75.07	42.95	81.99	80.80	1.45
C2	85.73	28.96	72.02	71.15	1.20
Batch code	**Natrosol 250 HHX (mg)**	**Sodium Bicarbonate (mg)**	**Floating time (sec)**		
			Predicted	**Observed**	**% Bias**
C1	75.07	42.95	31	32	3.22
C2	85.73	28.96	114	110	3.50

Observed value of C1 and C2 batch was measured and compared with the predicted value of check point batch. % error was found to be less than 5 of all the responses. Hence, this model was valid and optimized batch can be selected from the overlay plot of this model.

Optimized batch

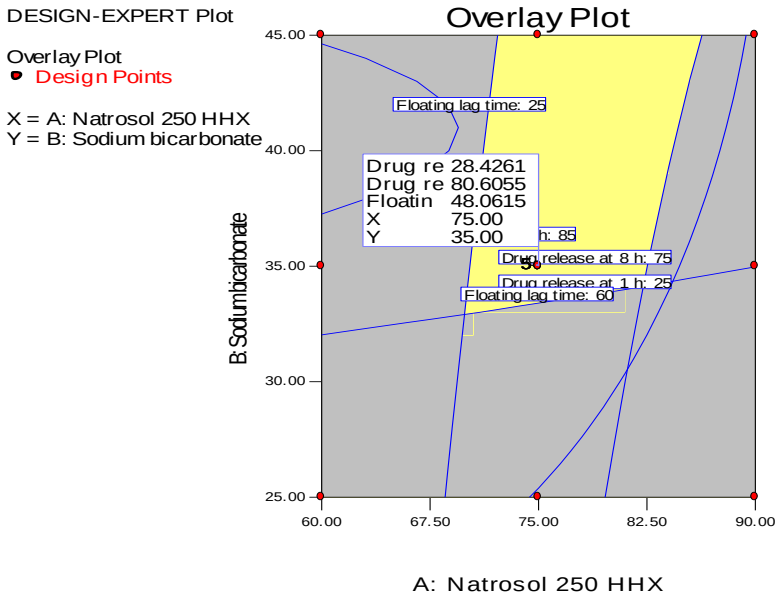

Figure 8: Overlay plot of optimized batch

Table 10: Results of optimized batch O1

Evaluation Parameters	Results	
Weight variation (mg)	252 ± 2.22	
Thickness(mm)	4.51 ± 0.11	
Hardness(kg/cm²)	5.2 ± 0.81	
Friability (%)	0.59 ± 0.09	
Drug Content (%)	99.2 ± 1.92	
Floating Lag Time (sec)	49 ± 3	
Total Floating Time (h)	12 h	
% Drug Release	Time (h)	% Drug Release
	0	0
	1	27.82± 2.92
	2	38.33± 2.23
	4	54.51± 1.95
	6	66.36± 2.61
	8	80.24± 1.74
	10	91.61± 1.12
	12	99.54± 0.81

Here in Figure 8 shows the yellow area was the optimized area and batch O1was fall in the yellow region. The optimized batch O1 was prepared and results of optimized batch are shown in Table 10.The tablets have uniform drug distribution hence drug content was found satisfactory. Weight variation also found well within acceptable range. Thickness was found uniform. In vitro buoyancy studies properties also found satisfactory. % CDR was found 27.82± 2.92, 80.24± 1.74 and 99.54± 0.81 at 1h, 8h and 12 h respectively.

***In vitro* release kinetic studies**

Table 11: *In vitro* release kinetic studies of optimized batch

Model	Zero order	1st order	Higuchi	Korsmeyer -Peppas
R^2	0.9872	0.9240	0.9968	0.9976
Slope (n)	6.51	0.0479	29.51	0.5182
Intercept	25.47	1.4841	-3.33	-0.5661

The in vitro release profile of drug from all the formulations could be best expressed by Korsmeyer-Peppas model, as the plot shows high linearity (R^2 = 0.9976). The "n" value was found to be 0.5182 in Korsmeyer- Peppas model, so it follows non-fickian diffusion or anomalous diffusion mechanism [Table 11].

CONCLUSIONS

Quetiapine fumarate floating tablets successfully prepared by using natrosol 250 HHX as a sustained release polymer and sodium bicarbonate as a gas forming agent. Concentration of Natrosol 250 HHX had significant effect on % *in-vitro* drug release and FLT. It was found that increase the concentration of polymer resulted that increased FLT and reduced the release rate. *In-vitro* release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion. From the study it can be conclude that floating tablets of quetiapine fumarate an innovative and promising perspective for the delivery of quetiapine fumarate as extended drug release over 12 h which is better formulation in the schizophrenia therapy with minimizing the adverse effects and improves patient compliance.

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