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Formulation and Evaluation of Gastroretentive Floating Tablets of Quetiapine Fumarate.

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ABSTRACT

The aim of the present investigation was to develop and evaluate gastroretentive drug delivery system (GRDDS) of Quetiapine Fumarate using a combination of hydrophilic polymers (HPMC K100M, HPMC K15M), natural gums (Guar gum, Xanthan gum and Karaya gum) and effervescent substances (sodium bicarbonate and citric acid). Floating tablets were prepared by direct compression method and were evaluated for physical characteristics such as hardness, thickness, friability, drug content and floating properties. The optimized formula Q13 showed better sustained drug release and also had good floating properties, it has shown zero order release with R^2 value of 0.990. As the n value for the Korsmeyer- Peppas model was found to be less than 0.447, it follows Fickian diffusion mechanism. FT-IR result showed that there is no drug excipient interaction.

Keywords: Gastro retentive tablets, Sustained release, Buoyancy, HPMC, Natural gums.

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INTRODUCTION

Quetiapine Fumarate (QF) has high solubility in the stomach pH and early part of small intestine compared to its solubility in the small intestine pH. As its solubility decreases with increase in pH, it would be more beneficial to retain the drug in stomach (acidic environment) for prolonged duration so as to achieve maximum absorption and bioavailability [1,2]. So gastroretentive drug delivery system is desirable 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 [3-5].

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system [6]. This results in an increased gastro retentive time and a better control of fluctuations in plasma drug concentration since When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response. The present work is aimed at formulating sustained release effervescent floating tablet dosage forms of Quetiapine Fumarate using various low-density and natural polymers. The prepared tablets were evaluated for physical characteristics such as hardness, weight variation, drug content uniformity, Floating lag time and floating capacity [7]. All the tablets were evaluated for *in vitro* release characteristics [8].

MATERIALS AND METHODS

Quetiapine Fumarate, HPMC K100M, HPMC K15M ,avicel 102 were generous gift samples from Dr.Reddy's Pharmaceuticals,Hyderabad,India. Guargum, Talc were supplied from Qualikems Pvt. Ltd, Delhi,India. Xanthan gum, Karaya gum were supplied by Himedia Laboratories, Mumbai,India. Ethyl Cellulose, Citric acid S.d. FiNE-CHEM Ltd. Mumbai,India. Other chemicals ,0were used of analytical grade.

Formulation Method: Direct Compression

Quetiapine fumarate(50 mg) and all the ingredients were accurately weighed. Quetiapine fumarate was well mixed with weighed quantity of polymer and then mixed with remaining ingredients i.e., sodium bicarbonate, citric acid and microcrystalline cellulose in geometric proportions in the composition as shown in the tables 1, 2, 3 and 4. Mixed homogeneously in a polybag for about 5 -10min. Then lubricated with the previously weighed and sieved magnesium stearate, talc to obtain the blend for compression. Then the lubricated blend was subjected to compression on a sixteen station rotary tablet punching machine using 9mm circular standard flat faced punches [9,10].

Table 1: Composition of floating tablets of Quetiapine Fumarate containingHPMC K_{100}M

Ingredient (weight in mg)	Formulations		
	Q1	Q2	Q3
Quetiapine Fumarate	50	50	50
HPMC K100M	150	175	200
Ethyl Cellulose	-	-	-
Xanthan gum	-	-	-
Guar gum	-	-	-
Sodium bicarbonate	53	53	53
Citric acid	18	18	18
Talc	4	4	4
Magnesium state	4	4	4
Avicel 102	71	46	21

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Table 2: Combination of HPMC $K_{100}M$ & Ethylcellulose/Xanthumgum/Guargum/Karaya gum/Sodium CMC

Ingredient (weight in mg)	Formulations				
	Q4	Q5	Q6	Q7	Q8
Quetiapine Fumarate	50	50	50	50	50
HPMC K100M	150	150	150	150	150
Ethyl Cellulose	50	-	-	-	-
Xanthan gum	-	50	-	-	-
Guar gum	-	-	50	-	-
Karaya gum	-	-	-	50	-
Sodium CMC	-	-	-	-	50
Sodium bicarbonate	53	53	53	53	53
Citric acid	18	18	18	18	18
Talc	4	4	4	4	4
Magnesium state	4	4	4	4	4
Avicel 102	21	21	21	21	21

Table 3: Composition of floating tablets of Quetiapine Fumarate containingHPMC $K_{15}M$

Ingredient (weight in mg)	Formulations		
	Q9	Q10	Q11
Quetiapine Fumarate	50	50	50
HPMC K15M	150	175	200
Ethyl Cellulose	-	-	-
Xanthan gum	-	-	-
Guar gum	-	-	-
Sodium bicarbonate	53	53	53
Citric acid	18	18	18
Talc	4	4	4
Magnesium state	4	4	4
Avicel 102	71	46	21

Table 4: Composition of floating tablets of Quetiapine Fumarate containing combination of HPMC $K_{15}M$ and Ethyl cellulose/Xanthan gum/Guar gum/Karaya gum/Sodium CMC

Ingredient (weight in mg)	Formulations				
	Q12	Q13	Q14	Q15	Q16
Quetiapine Fumarate	50	50	50	50	50
HPMC K15M	150	150	150	150	150
Ethyl Cellulose	50	-	-	-	-
Xanthan gum	-	50	-	-	-
Guar gum	-	-	50	-	-
Karaya gum	-	-	-	50	-
Sodium CMC	-	-	-	-	50
Sodium bicarbonate	53	53	53	53	53
Citric acid	18	18	18	18	18
Talc	4	4	4	4	4
Magnesium state	4	4	4	4	4
Avicel 102	21	21	21	21	21

Evaluation Parameters of Floating Tablets: Weight Variation Test

Twenty (20) tablets from each batch were individually weighed in grams on an 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

Weight Variation limits as per USP [11,12].

Average weight (in mg)	**% ± deviation allowed**
130 or less	10
130-324	7.5
More than 324	5

Thickness Test

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliperse [11,12]. The average thickness and standard deviation were reported.

Hardness Test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness [11,12], and the standard deviation was reported.

Friability Test

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friablator. The tablets were then dusted and re-weighed to determine the loss in weight [11,12]. Friability was then calculated as per weight loss from the original tablets.

Total floating time: Time for which the tablet remains buoyant is measured and taken as total floating time.

Floating Lag Time

Around 100 ml of 0.1N HCl was taken in a 100 ml beaker and a tablet was dropped in the beaker. The stopwatch was started and the time duration was noted till the tablet reached the top of the fluid in the beaker.

Determination of Drug Content

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 250 nm. The drug content of the Standard containing the drug powder was also determined [13,14]. The Drug content was determined by the formula.

$$\text{Drug content} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100$$

The tablet passes the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

In-Vitro Drug Release Studies

The release rate of Floating matrix tablets of Quetiapine Fumarate was determined using USP Type 2 Apparatus. The dissolution test was performed in triplicate, using 900ml of 0.1 N HCl at 37± 0.5˚C at 50 rpm for 24 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at specified wave lengths described in developed simultaneous analytical methods using Elico SL -159, U.V-Visible Spectrophotometer.

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RESULTS AND DISCUSSION

Physical Parameters

All of the Quetiapine Fumarate formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability drug content. The results of the tests were as shown in tables 5and 6 . The Hardness of the tablets was found in the range of 4.0-5.5 Kg/cm^2 indicating satisfactory mechanical strength. The thickness of the tablets was found to be between 3.50 and 3.84mm . The variation in weight was within the range ±5% complying with pharmacopoeial specifications. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. Assay of the prepared matrix tablets was found in the range of 98-100% clearly indicating the good cotent uniformity. This study indicated that all the prepared formulations were good.

Table 5: Physical parameters of the prepared formulations Q1-Q8

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
Q1	350±3	4.5±0.3	3.84±0.05	0.32±0.04	98.23±0.89
Q2	348±2	4.6±0.5	3.76±0.06	0.19±0.05	99.65±0.68
Q3	346±3	5.0±0.5	3.50±0.04	0.29±0.06	98.45±0.47
Q4	347±2	4.0±0.5	3.76±0.04	0.33±0.06	98.44±0.69
Q5	348±3	4.5±0.2	3.63±0.06	0.29±0.07	99.23±0.53
Q6	349±3	4.2±0.5	3.50±0.04	0.29±0.03	98.45±0.42
Q7	346±2	4.5±0.4	3.86±0.03	0.26±0.04	99.12±0.39
Q8	348±2	5.0±0.2	3.55±0.25	0.23±0.07	98.65±0.78

Table 6: Physical parameters of the prepared formulations Q9-Q16

Formulation code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability(%)	Assay(%)
Q9	343±3	5.2±0.5	3.50±0.04	0.29±0.08	98.45±0.67
Q10	347±3	5.5±0.5	3.50±0.04	0.29±0.05	98.45±0.54
Q11	344±3	5.0±0.5	3.50±0.04	0.29±0.03	98.45±0.65
Q12	348±2	4.5±0.2	3.60±0.04	0.24±0.07	99.72±0.52
Q13	349±3	4.2±0.5	3.50±0.04	0.29±0.05	98.45±0.46
Q14	345±2	4.5±0.5	3.76±0.06	0.19±0.04	99.65±0.76
Q15	350±3	5.0±0.5	3.50±0.04	0.29±0.07	98.45±0.86
Q16	348±3	5.2±0.5	3.50±0.04	0.29±0.06	98.45±0.65

Floating Properties

Table 7: Floating Properties of Quetiapine Fumarate Tablets

Formulations	Floating lag time (sec)	Floating time(hrs)
Q1	85	>24
Q2	134	>24
Q3	98	>24
Q4	60	>24
Q5	168	>24
Q6	145	>24
Q7	166	>24
Q8	125	>24
Q9	78	>24
Q10	188	>24
Q11	196	>24
Q12	98	>24
Q13	139	>24
Q14	153	>24
Q15	129	>24
Q16	148	>24

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The floating lag time and Total floating time of all the formulations of Quetiapine Fumarate floating matrix tablets are shown in Table 7. All the formulations were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. The floating ability of the tablets was due to the presence of sodium bicarbonate at a concentration of 15%. All the formulations showed floating time of 24hrs.

Fourier Transform Infrared (FTIR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure QF, pure polymers and optimized formulations were analyzed over the range 400–4000 cm^{-1}. The results are shown as figures 1, 2and 3.

Figure 1: FT-IR Spectra of Quetiapine Fumarate

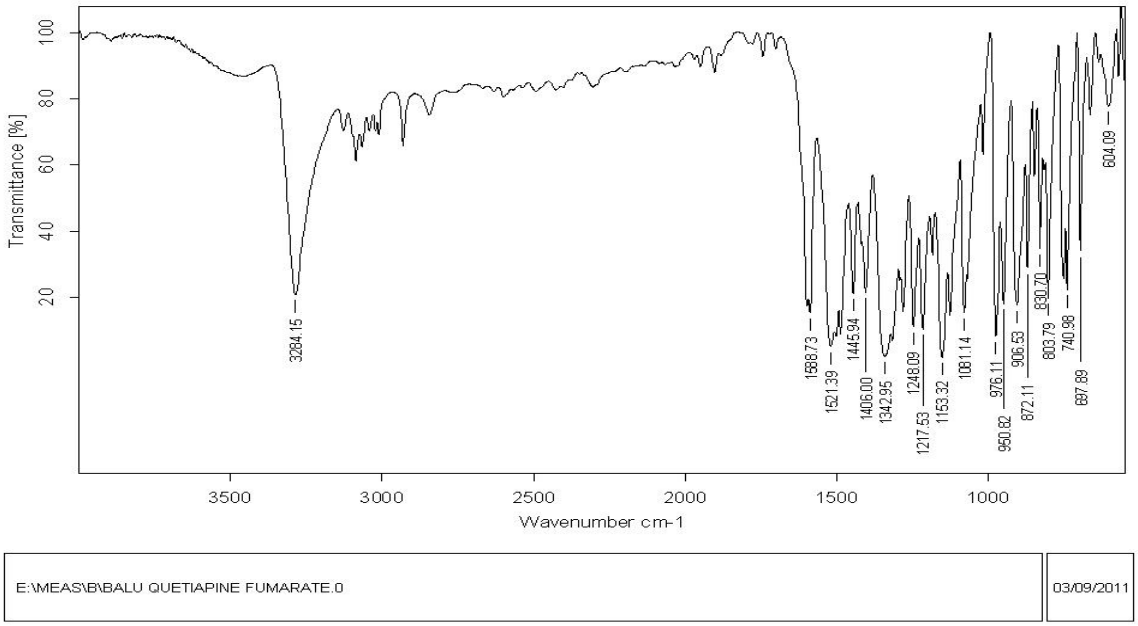

Figure 2: FT-IR Spectra of formulations containing HPMC K100M

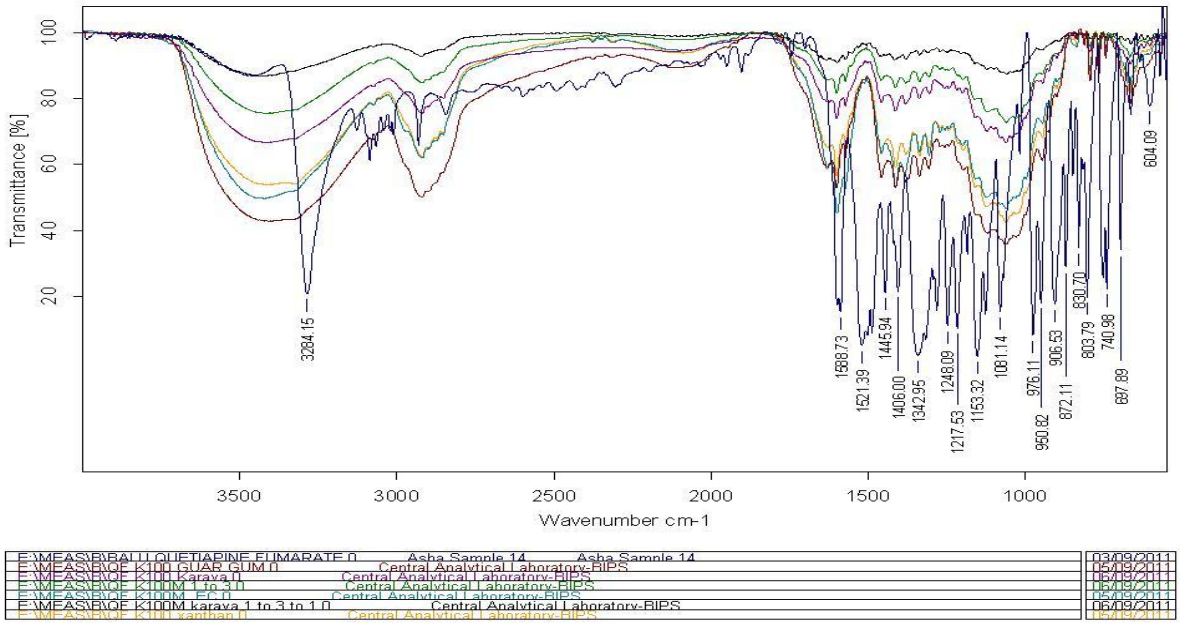

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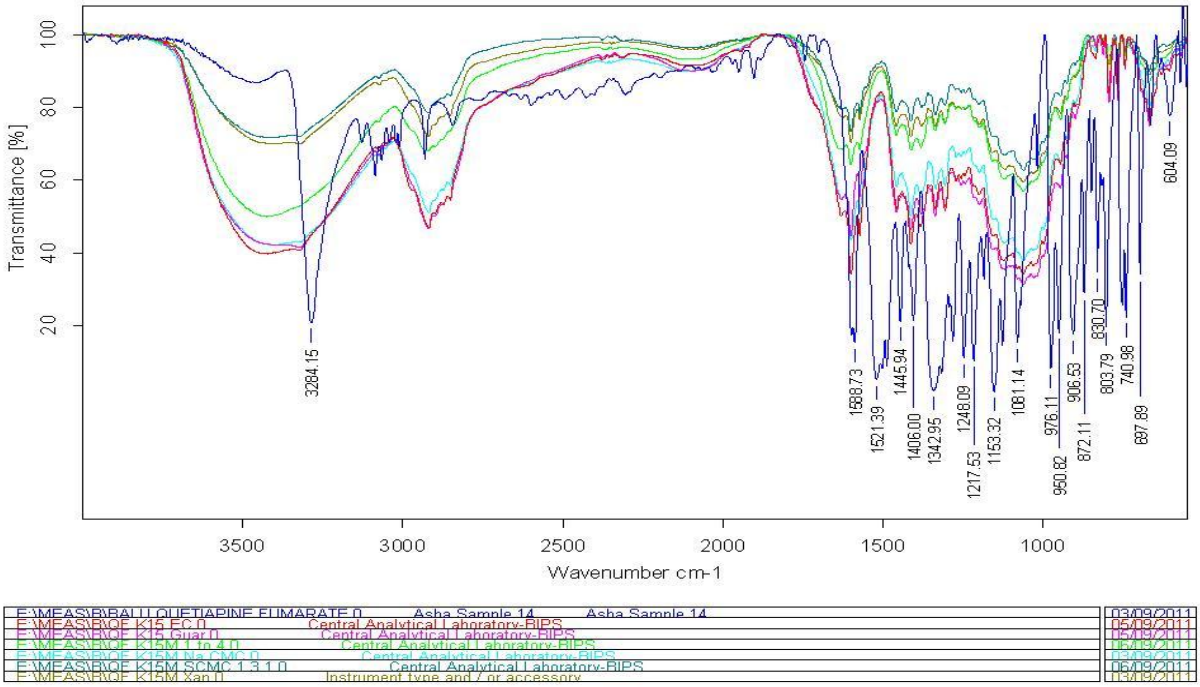
Figure 3: FT-IR Spectra of formulations containing HPMC K15M



In-Vitro Drug Release Studies

The cumulative percent of drug released from the formulations Q_1, Q_2 and Q_3 at the end of 24hrs is 98.50, 96.50 & 94.96 respectively and that from Q_4, Q_5, Q_6, Q_7 and Q_8 at the end of 24hrs is 90.83, 97.80, 96.73, 92.60 and 98.68 respectively. Formulations of Quetiapine Fumarate (Q_4 to Q_8) containing a combination of HPMC K100M and EC/Xanthan gum/Guar gum/Karaya gum/Na CMC did not show any significant retarding effect with respect to drug release pattern when compared with formulations of Quetiapine Fumarate containing HPMC K100M in different drug polymer ratios 1:3, 1:3.5 and 1:4 respectively for Q_1 Q_2 Q_3. To compare the dissolution profile of the developed formulations with theoritical drug release profile, statistically derived mathematical parameter, "similarity factor (f2)" was employed. The data obtained from *In Vitro* dissolution studies were fitted to different kinetic models i.e Zero order, First order, Higuchi and Korsmeyer-peppas equations.

The similarity factor (f2) values for the formulations Q_1 to Q_8 were calculated. Out of all the formulations of Quetiapine Fumarate containing HPMC K100M, the formulation Q_1 is the optimal formulation as it showed highest similarity factor (64.02). The formulation Q_1, Q_3, Q_6 and Q_8 followed Zero order kinetics whereas formulations Q_2, Q_4, Q_5 and Q_7 followed first order kinetics as indicated by their high regression values. All the formulations (Q_1 to Q_8) showed good correlation in Higuchi Kinetics clearly indicating that the drug release mechanism was predominantly diffusion controlled. Peppas release exponent (n) values indicated that the drug release from formulations Q_1, Q_2, Q_4 and Q_5 followed non-fickian diffusion (n>0.5) whereas formulation Q_3 , Q_6, Q_7 and Q_8 followed Fickian diffusion (n<0.5).

Among the Formulations of Quetiapine Fumarate containing HPMC K15M , Q_9, Q_{10} and Q_{11} having different drug polymer ratios 1:3, 1:3.5 and 1:4 respectively retarded the drug release as a function of polymer concentration. The cumulative percent drug released from the formulations Q_9, Q_{10} and Q_{11} at the end of 24hrs was 98.89, 98.34 and 96.50 respectively. Formulations of Quetiapine Fumarate (Q_{12} to Q_{16}) containing a combination of HPMC K15M and EC/Xanthan gum/Guar gum/Karaya gum/Na CMC did not show any significant retarding effect with respect to drug release pattern, the drug release of Q_{12}, Q_{13}, Q_{14}, Q_{15} and Q_{16} formulations at the end of 24hrs is 98.78, 96.73, 97.35, 94.37 and 98.50 respectively. The similarity factor (f2) values for the formulations Q_9 to Q_{16} were calculated. Out of all the formulations of Quetiapine Fumarate containing HPMC K15M, the Formulation Q_{15} is the optimized Formulation as it showed highest Similarity Factor (73.16). The formulations Q_9, Q_{10}, Q_{12}, Q_{13} and Q_{16} followed first order kinetics as indicated by their high regression values compared to Zero order kinetics where as Formulations Q_{11} Q_{14} and Q_{15} followed Zero order Kinetics. Peppas exponent (n) values indicated that drug release from formulations Q_9, Q_{12}, Q_{13}, Q_{14} and Q_{15}

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followed Fickian diffusion (n<0.5) whereas formulations Q_{11}, Q_{10}, and Q_{16} followed Non-Fickian diffusion (n>0.5). All the formulations (Q_9 to Q_{16}) showed good correlation in Higuchi kinetics clearly indicating that the drug release mechanism was predominantly diffusion controlled cumulative drug release was calculated from the developed methods and shown in the tables 8 and 9 and the release kinetic profiles in Table10 and Figures 4, 5, 6 and 7.

Table 8: Cummulative Percent Drug Release of Quetiapine Fumarate from floating tablets

Time (hrs)	**Cummulative % drug released**							
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
0	0	0	0	0	0	0	0	0
1	17.82±1.3	15.40±1.2	18.82±1.0	17.76±1.4	22.83±3.1	19.12±1.3	17.76±1.4	19.71±1.1
2	24.54±1.4	22.60±1.8	23.48±1.1	26.43±1.2	30.15±2.6	25.49±1.2	28.74±1.3	26.85±1.1
4	35.17±0.8	42.07±2.1	33.10±0.9	41.36±1.4	52.11±0.8	40.13±0.5	35.82±1.6	42.01±0.6
6	41.31±1.6	53.64±1.2	35.23±1.9	51.40±1.5	63.68±1.7	53.23±1.2	41.66±0.4	53.29±0.9
8	50.22±1.5	56.01±0.6	38.41±2.1	54.24±1.1	69.58±1.5	56.01±1.1	54.24±0.7	56.60±0.2
10	57.83±0.9	63.68±1.5	50.75±1.6	59.55±1.0	79.61±1.0	63.09±1.1	63.09±0.6	68.40±1.2
12	72.53±1.7	71.35±1.6	57.78±2.6	62.50±1.6	84.92±1.2	75.48±1.9	72.53±1.3	76.66±1.3
20	86.10±1.8	84.92±2.4	77.84±0.6	76.66±0.3	94.37±1.3	83.74±0.8	84.92±1.2	82.56±1.3
24	98.50±0.9	96.50±1.4	94.96±1.2	90.83±1.1	97.80±1.3	96.73±0.2	92.60±1.3	98.68±0.4

Table 9: Cummulative Percent Drug Release of Quetiapine Fumarate from floating tablets

Time (hrs)	**Cummulative % drug released**							
	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
0	0	0	0	0	0	0	0	0
1	25.37±0.9	21.48±0.8	15.34±1.2	19.88±1.1	23.25±1.3	20.24±0.9	22.42±1.2	19.29±1.4
2	29.68±1.3	30.03±1.8	25.84±1.0	30.39±1.2	32.04±1.8	27.97±1.2	26.20±1.1	28.56±0.9
4	47.50±1.2	44.91±2.0	39.95±1.1	55.76±0.6	48.51±0.7	42.60±1.3	38.47±1.4	47.97±1.7
6	54.05±1.5	53.52±2.3	50.75±2.0	59.55±0.7	53.64±1.3	55.76±0.5	44.96±0.8	56.47±1.6
8	74.89±1.4	65.45±1.0	57.06±1.5	64.86±1.3	57.19±1.5	57.78±1.9	51.46±0.8	57.78±1.3
10	84.92±1.2	73.71±1.5	62.50±0.8	69.58±1.5	69.58±1.2	68.40±0.7	56.60±1.9	70.76±1.7
12	97.32±1.6	84.92±1.3	68.40±1.1	76.66±1.3	75.48±1.1	75.48±1.3	63.68±1.3	78.43±1.4
20	98.25±0.5	97.32±0.8	79.61±1.4	87.29±1.1	89.06±1.3	84.33±0.8	83.15±1.2	93.19±0.8
24	98.89±0.5	98.34±0.8	96.50±1.1	98.78±0.4	96.73±1.1	97.35±0.6	94.37±1.5	98.50±0.2

Table 10: Regression coefficient (R^2) values for different kinetic models

Formulation code	**Zero order R^2**	**First Order R^2**	**Higuchi R^2**	**Korsmeyer R^2**	**Korsmeyer n**	**Similarity factor(F2)**
Q1	0.966	0.863	0.986	0.990	0.545	64.062
Q2	0.907	0.927	0.982	0.977	0.576	54.725
Q3	0.990	0.865	0.954	0.954	0.497	58.514
Q4	0.917	0.938	0.980	0.983	0.490	57.79
Q5	0.816	0.993	0.939	0.964	0.481	39.462
Q6	0.915	0.911	0.981	0.988	0.518	55.430
Q7	0.935	0.984	0.984	0.985	0.518	60.060
Q8	0.901	0.828	0.974	0.986	0.508	52.64
Q9	0.780	0.917	0.898	0.949	0.489	36.019
Q10	0.882	0.982	0.970	0.987	0.505	44.306
Q11	0.914	0.874	0.982	0.982	0.550	57.099
Q12	0.851	0.859	0.951	0.954	0.483	44.92
Q13	0.921	0.956	0.986	0.990	0.447	51.33
Q14	0.901	0.900	0.978	0.987	0.495	52.14
Q15	0.982	0.933	0.993	0.987	0.460	73.16
Q16	0.899	0.955	0.979	0.981	0.515	48.25

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Figure 4: Drug release profiles of Q1, Q2, Q3

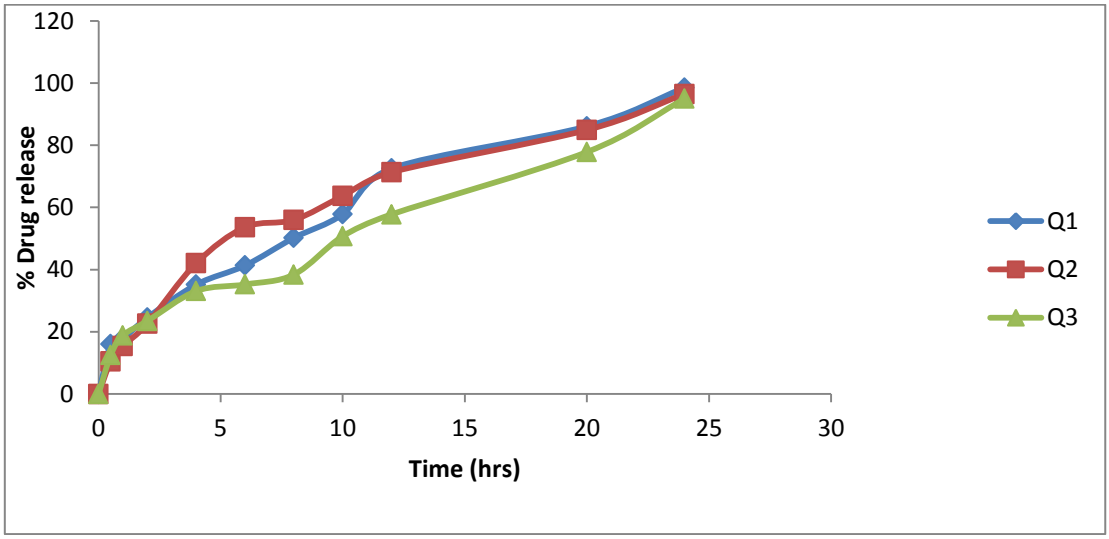

Figure 5: Drug release profiles of Q4, Q5, Q6, Q7, Q8

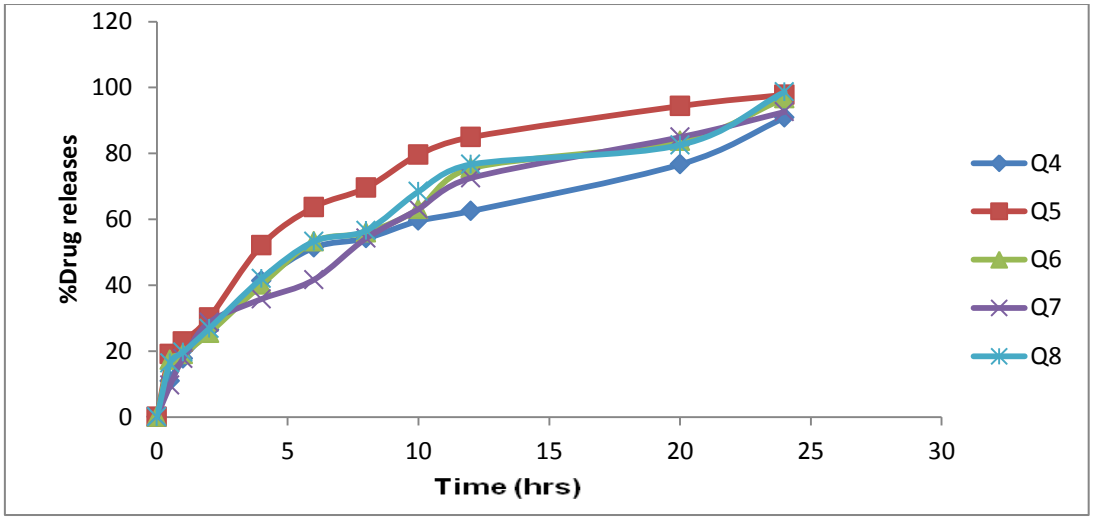

Figure 6: Drug release profiles of Q9, Q10, Q11:

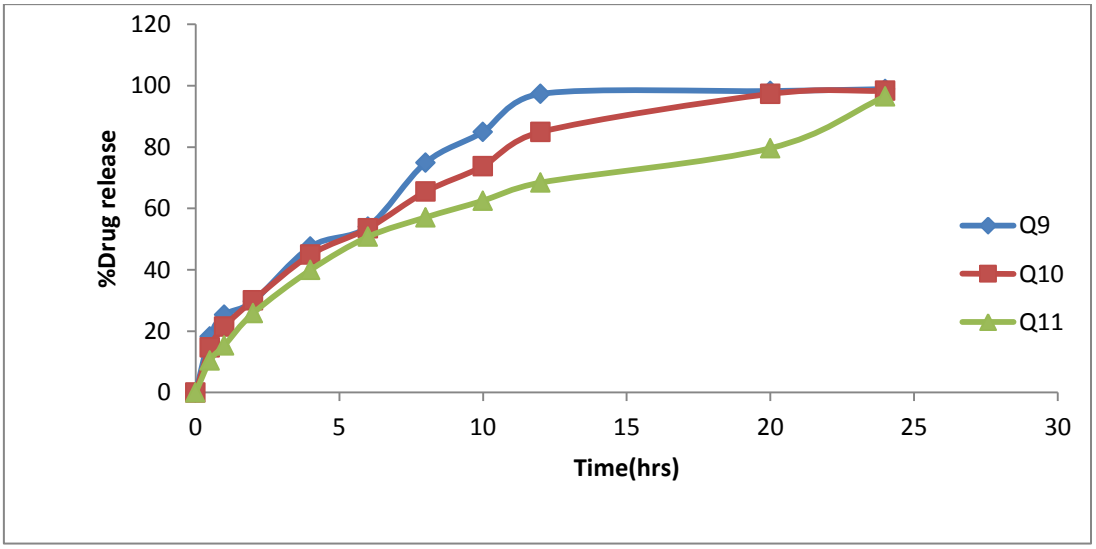

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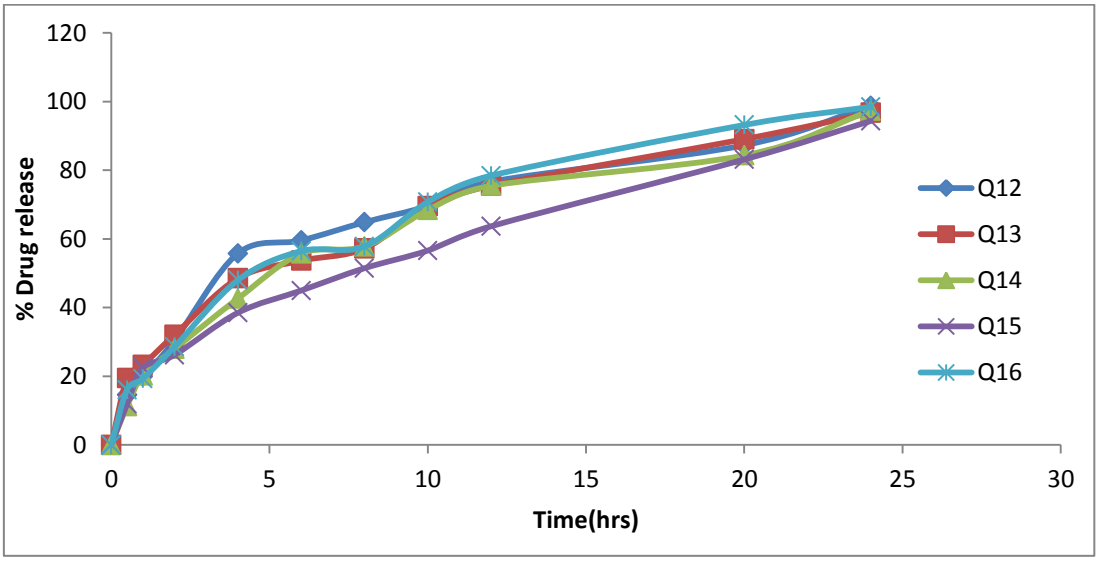
Figure 7: Drug release profiles of Q12, Q13, Q14, Q15, Q16



CONCLUSION

Different swelling polymers such as HPMC K100M, HPMC K15M individually and in combination with, other polymers such as Xanthan gum, Guar gum, karaya gum, Sodium CMC and Ethyl cellulose can be successfully emplyed in the preparation of controlled release floating tablets of Quetiapine Fumarate. The optimized formula Q_{13} showed better sustained drug release and which also had good floating properties and fitted best to be Korsmeyer-Peppas model with R^2 value of 0.990. As the n value for the Korsmeyer- Peppas model was found be less than 0.447 it follows Fickian diffusion mechanism. The research study provided useful information for the formulation scientists on formulation, characterization during development of controlled drug delivery systems of Quetiapine Fumarate using these polymers.The prepared formulations can be successfully commercialized after establishing the safety and efficacy in human volunteers.

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