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In Vitro and *In Vivo* Evaluation of Quetiapine Fumarate controlled gastroretentive floating drug delivery system

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Abstract

The aim of the present work was to develop and optimize gastroretentive floating system of Quetiapine fumarate (QF) for the effective treatment of Schizophrenia. The present study was carried out with an objective of preparation and in vivo evaluation of floating tablets of using QF as a model drug using HPMC polymers, Gelucire 43/01 and Polyox WSR 301 to improve oral bioavailability of QF floating tablets by increasing gastric residence time. The tablets were prepared by direct compression method. The effect of polymers concentration and viscosity grades of HPMC on drug release profile was evaluated. The result of in vitro dissolution study showed that the drug release profile could be sustained by increasing the concentration of HPMC K15M and Polyox WSR 301. The optimized formulation (F12) containing HPMC K15M and Polyox WSR301 showed 98.6% drug release at the end of 12h. Changing the viscosity grade of HPMC from K15M to K100M had no significant effect on drug release profile. The optimized formulations (F12) containing sodium bicarbonate 40mg per tablet showed desired buoyancy (floating lag time of about 32seconds and total floating time of >12h). Optimized formulation (F12) followed diffusion controlled zero order kinetics and non-fickian transport of the drug. FTIR and DSC studies revealed the absence of any chemical interaction between drug and polymers used. The best formulation (F12) was selected based on in vitro characteristics and was used in vivo radiographic studies by incorporating $BaSO_4$. These studies revealed that the tablets remained in the stomach for 6h in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. Studies to evaluate the pharmacokinetics in vivo showed better bioavailability, area under the concentration–time curve, elimination rate constant and half-life than marketed product.

Keywords: Quetiapine fumarate, Floating drug delivery system, HPMC, Polyox WSR 301, Radiographic studies.

Introduction

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [1].

Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem [2]. Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract [3]. The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [4]. One of the novel approaches in the area of oral sustained release drug delivery is gastro retentive drug delivery system (GRDDS) [5]. Gastric retention devices are designed to prolong the gastric residence time of oral controlled release dosage forms. Thus result in increased contact time for drugs that act locally, increased absorption of drugs that have absorption windows in upper part of gastrointestinal tract (GIT), and better absorption for drugs less soluble in the intestinal fluid [6]. Gastro retentive drug delivery systems (GRDDS) can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an

absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [7]. Extended-release dosage forms with prolonged residence time in the stomach are highly desirable for drugs with i) narrow absorption windows, ii) stability problems in the intestinal or colonic environment, iii) local action in the stomach, and iv) low solubility at high pH values [8]. Floating matrix tablets are designed to prolong the gastric residence time after oral administration at a particular site. It is useful for achieving controlled plasma level as well as improving bioavailability [9]. Quetiapine fumarate (QF) is an atypical psychotropic agent approved for the treatment of schizophrenia, bipolar disorder and along with an antidepressant to treat major depressive disorder [10]. Biological half life of QF is 6h, due to which frequent administration is required. To avoid the drawbacks of frequent administrations such as plasma level fluctuations and patient non-compliance it is desirable to have a controlled release dosage forms of QF. It has been reported that bioavailability of QF is strongly dependent on the local physiology of GIT. It is readily soluble in the acidic environment of the stomach and thus is preferentially absorbed from the upper part of GIT. In the alkaline environment of intestine, precipitation of the drug occurs decreasing its absorption. This study was conducted with an aim to develop gastro retentive floating tablet using different polymers like HPMC K100M, HPMC K15M, Gelucire 43/01 and WSR 301, incorporating 200mg QF into hydrophilic polymeric matrix which would release the drug in stomach and upper part of GIT in a controlled manner. The site specific absorption of QF provides a strong rationale for its use as a model drug for gastro retentive dosage form.

Materials and methods

Materials

SEROQUEL SR 200mg tablet was purchased from AstraZeneca, Bangalore. Quetiapine fumarate was received as a gift sample from Aurobindo Pharma Ltd, (Hyderabad, India), Hydroxy propyl methyl cellulose K-15M and K-100M were obtained from Rubicon labs, Mumbai, India, POLYOX WSR 301 was obtained from Dow chemical's, New York. Gelucire 43/01 and PVP K 30 were gifted from MSN Labs Ltd, Hyderabad. All other excipients and chemicals used were of analytical grade.

Preparation of Quetiapine Fumarate Floating Tablets

The tablets were prepared by direct compression method. All the ingredients except Quetiapine fumarate were passed through # 80 mesh prior to mixing. The ingredients were weighed separately and mixed to get a uniform polymer mixture. The drug was then mixed with the polymer mixture for a period of 30 minutes to ensure uniform mixing of the drug. These powder mixtures were lubricated with magnesium stearate and compressed to obtain tablets. The Composition of Quetiapine fumarate floating tablets were shown in Table 1.

Buoyancy lag time determination & total floating time

The in vitro buoyancy was determined by the floating lag time. The tablet was placed in a 250 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total floating time of all tablets was determined by visual observation [11].

In vitro dissolution studies

In vitro drug release studies for the prepared immediate release tablets were conducted for a period of 12h using USP XXIV type-II (Paddle) dissolution apparatus at 37±0.5oC at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed for Quetiapine fumarate by UV/Visible spectrophotometer Shimadzu 1800 at 231 nm.

Kinetic modeling of drug release

The dissolution profiles of all the batches were fitted to zero order, first order, Higuchi and Peppas equations [12,13].
(Equation 1-4 respectively).

$Mt = M0 + k0t$ (1)

$\ln Mt = \ln M0 + k1t$ (2)

$Mt = M0 – kHt1/2$ (3)

$Mt/M\alpha = Ktn$ (4)

In these equations, Mt is the cumulative amount of drug released at any specified time (t) and M0 is the dose of the drug incorporated in the delivery system and Mt/Mα is a fraction of drug released at time (t). k0, k1, kH and K are rate constants for zero order, first order, Higuchi and Korsmeyer model respectively, n is the release exponent. The n value is used to characterize different release mechanisms for cylindrical shaped matrices.
The dissolution data were also fitted according to the well-known exponential Zero Order equation, which is often used to describe drug release behavior from polymeric systems.
The best fit with higher correlation (r2 > 98) was found with Higuchi's equation for all the formulations.

Table 1: Composition of Quetiapine fumarate floating tablets

FORMULATION CODE	Quetiapine fumarate (mg)	HPMC K15M (mg)	HPMC K 100M (mg)	WSR 301 (mg)	GELUCIRE 43/01 (mg)	PVP K30 (mg)	$NAHCO_3$ (mg)	MCC (mg)	TALC (mg)	Mg Stearate (mg)
F1	230.4	-	75	20		10.6	30	10	2	2
F2	230.4	-	80	25	-	10.6	35	15	2	2
F3	230.4	-	85	25	-	10.6	40	15	2	2
F4	230.4	40	35	20	-	10.6	30	10	2	2
F5	230.4	40	40	25	-	10.6	35	15	2	2
F6	230.4	45	45	30	-	10.6	40	15	2	2
F7	230.4	-	80	15	15	10.6	30	15	2	2
F8	230.4	60	---	20	20	10.6	35	20	2	2
F9	230.4	65	---	25	15	10.6	35	15	2	2
F10	230.4	70	---	30	-	10.6	40	15	2	2
F11	230.4	75	---	25	-	10.6	40	15	2	2
F12	230.4	80	---	20	-	10.6	45	10	2	2

Drug excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for Quetiapine fumarate, HPMCK15 M, and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer (PERKIN ELMER BX1) samples were prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. The samples were scanned from 4000 to 400/cm-1

Stability studies

The stability studies were carried out as per ICH guidelines. The best formulation F12 was subjected to accelerated stability test by storing at 40±20C/75±5% relative humidity in an accelerated stability chamber (Remi, Mumbai). After specified period of time (1, 2 & 3 months) samples were withdrawn and floating lag time, total floating time and in vitro dissolution studies were conducted [14].

Radiographic studies

The radiographic and In-vivo bioavailability study protocol was approved by the Institutional Human Ethics Committee (IHEC), bearing No: IHEC/VGOPC/051/2015. Vaagdevi Group of Pharmacy Colleges, Warangal, India.

Determination of In vivo gastric residence time

For this study, the tablets are prepared by replacing half the amount of drug with barium sulfate. After overnight fasting, the volunteers were fed with a low calorie food. After half an hour, a barium sulfate-labeled tablet was given to every subject with 200ml of water. The volunteers were asked to take 200ml water after every 1h. At different time intervals (0.5, 2, 4, and 6h post administration of tablets), the volunteers were exposed to abdominal X-ray imaging in standing position. The distance between the source of X-rays and the subject was kept constant for all images. Thus, the observation of the floating tablet movements could be easily noticed15. The mean gastric retention period was estimated.

In vivo bioavailability studies Quetiapine fumarate *In vivo* study protocol[16]

Six healthy male subjects with a mean age of 28.83±3.60 years (ranging from 24 to 34 years), mean weight 69.33±7.61Kg (ranging from 61 to 79 Kg) and a mean height of 173.17 ± 10.46cm (ranging from 157 to 182cm) participated in this study. Informed and signed consent and approval of the Human Ethical Committee were obtained. The volunteers were judged healthy on the basis of their previous medical history, physical examination and routine laboratory tests. None of the subjects used alcohol or tobacco. All subjects were free from drugs 15 days before and during the study. They were randomly divided into 2 groups of 6 subjects each. The subjects were fasted over night at least 10h prior to dose. After collecting the zero hour blood sample (blank). A standardized high fat-breakfast approximately 900KCal was given in the morning half-an-hour before administration. Group A received Formulated Quetiapine fumarate and group B received commercial formulation was administered with 200ml of water. All the subjects were given a glass of water for every 2h (approximately 200 ml). Standardized lunch, snacks and dinner was provided to all the subjects respectively at 4, 8 and 12h after the administration of formulations, Blood samples (2ml) were collected by the intravenous route using heparinized disposable syringes at the following times: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 20 and 24 hrs. The blood samples were collected in vacutainers containing EDTA as anticoagulant and immediately centrifuged at 3000rpm for 15min. The separated plasma samples were stored at -200 C until analysed.

Determination of Quetiapine fumarate in Human plasma by HPLC method17

Determination of Quetiapine fumarate using internal standard lamotrogine by high performance liquid chromatography with a RP-C18 chromatographic column, Phenomenex Kinetex (150 mm × 4.6 mm i.d) and a mobile phase consisting of 0.1% ortho phosphoric acid with triethyl amine as modifier buffer: acetonitrile (50:50 % v/v) at a flow rate 0.6ml/min and the wavelength detection was 294 nm.

Preparation of Plasma Samples for HPLC Analysis

Human plasma (0.5ml) was prepared for chromatography by precipitating proteins with 2.5ml of ice-cold absolute ethanol for each 0.5ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was resuspended with 1 ml of acetonitrile by vortexing for 1min. After centrifugation (5000 – 6000 rpm for 10min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200μ1 of 50% of acetonitrile and 50% 0.1% orthophosphoric acid was injected for HPLC analysis.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (Cmax) and time to reach peak concentration (tmax) were directly obtained from concentration time data. In the present study, AUC0-t refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and AUC0-α refers to the AUC from time at zero hours to infinity.

Calculated using the formula AUC0-t + [Clast/K] where C last is the concentration in μg/ml at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life (t½). Volume of distribution (Vd), total clearance (CIT) and mean residence time for each subject using a non compartmental pharmacokinetic program. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

Results and discussion

Twelve formulations were prepared and evaluated for in vitro buoyancy lag time and total floating time. The time required for the tablet to rise to the surface (when the tablets were placed in a beaker containing 0.1 N HCl) for floating was described as the buoyancy lag time. $NaHCO_3$ induces CO_2 generation in the presence of HCl. All the formulations had buoyancy lag time in the range of 32 to 45 sec. The total floating time was found to be more than 12 hrs, which indicates a stable gel layer formation by all polymers and that $NaHCO_3$ remains for a longer time. The results of floating lag time and total floating time was depicted in Table 2 & Figure 1.

Table 2: Buoyancy lag time and total floating period of Quetiapine fumarate floating tablets

Formula code	Buoyancy lag time(sec)	Total floating time(hrs)
F1	42	>12
F2	35	>12
F3	40	>12
F4	42	>12
F5	37	>12
F6	40	>12
F7	43	>12
F8	37	>12
F9	35	>12
F10	45	>12
F11	36	>12
F12	32	>12

At time 0 **after 32 sec**

Figure 1: *In vitro* buoyancy lag time of the optimized formulation (F12)

All the formulations (F1-F12) were prepared with different grades of polymers like HPMC with different grades, POLYOX WSR 301 and a lipid excipient Gelucire 43/01. F1, F2 and F3 are having Quetiapine fumarate, HPMC K100M and WSR301 in different proportions shown the drug release was 76.3%, 80.0% and 86.5% in 12h respectively. The formulations F4 to F6 were developed using WSR301 and a combination of HPMC K15M& HPMC K100M and the % drug release of 77.5%, 84.2% and 91.7% respectively indicating comparatively better release rates than formulations F1to F3 (Table 3 & Figure 2). The formulation F7 was developed using WSR 301, Gelucire43/01 and HPMC K100M and the %drug release was 93%. The formulations F8 and F9 were developed using WSR 301, Gelucire 43/01 and HPMC K15M and the %drug release was found to be 95.6 % and 97.0% in 12h. The formulations F10, F11 and F12 were developed using WSR 301 and HPMC K15M and the % drug release was found to be 94.7 %, 96.8 % and 98.6% in 12hrs respectively. The results are summarized in Table 4& Figure 3. Formulation F12 selected as optimized formulation based on the better drug release, lag time and total floating time.

Table 3: **Cumulative percent drug release of formulations F1-F6**

Time (h)	F1	F2	F3	F4	F5	F6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	11.3±0.34	12.6±0.55	13.0±0.26	11.7±0.14	12.9±0.43	13.1±0.43
2	17.7±0.14	19.0±0.28	24.6±0.7	18.1±0.1	23.4±0.34	22.0±0.52
4	28.3±0.43	33.2±0.5	38.6±0.52	28.7±0.43	37.6±0.34	40.0±0.5
6	40.8±0.52	43.6±0.43	48.0±0.52	41.2±0.4	46.0±0.52	52.2±0.52
8	52.3±0.21	53.9±0.26	61.7±0.14	53.6±0.52	59.7±0.14	69.9±0.43
10	60.5±0.4	65.4±0.34	72.6±0.34	62.0±0.52	72.3±0.2	79.8±0.26
12	76.3±0.3	80.0±0.52	86.5±0.1	77.5±0.34	84.2±0.43	91.7±0.14

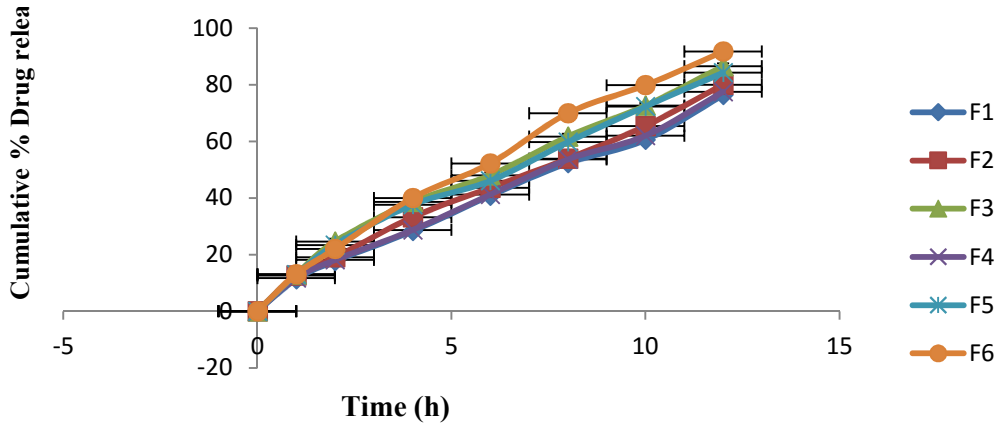


Figure 2: **Drug release profile from formulations F1, F2, F3, F4, F5 and F6**

Table 4: Cumulative percent drug release of formulations F7-F12

Time (h)	F7	F8	F9	F10	F11	F12	innovator
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	13.0±0.43	13.4±0.34	13.6±0.2	13.6±0.26	13.8±0.52	14.0±0.34	94.9±0.45
2	22.6±0.52	23.0±0.43	23.9±0.1	22.0±0.52	23.4±0.34	24.2±0.60	-
4	40.5±0.5	41.1±0.43	42.0±0.52	41.0±0.14	41.2±0.26	42.6±0.1	-
6	51.0±0.52	51.8±0.52	53.1±0.43	50.2±0.52	52.6±0.43	54.0±0.43	-
8	70.2±0.43	71.0±0.28	73.2±0.26	70.7±0.14	72.2±0.14	73.5±0.7	-
10	81.2±0.26	85.5±0.1	88.5±0.43	81.8±0.43	86.5±0.1	89.2±0.52	-
12	93.0±0.14	95.6±0.26	97.0±0.52	94.7±0.14	96.8±0.26	98.6±0.69	-

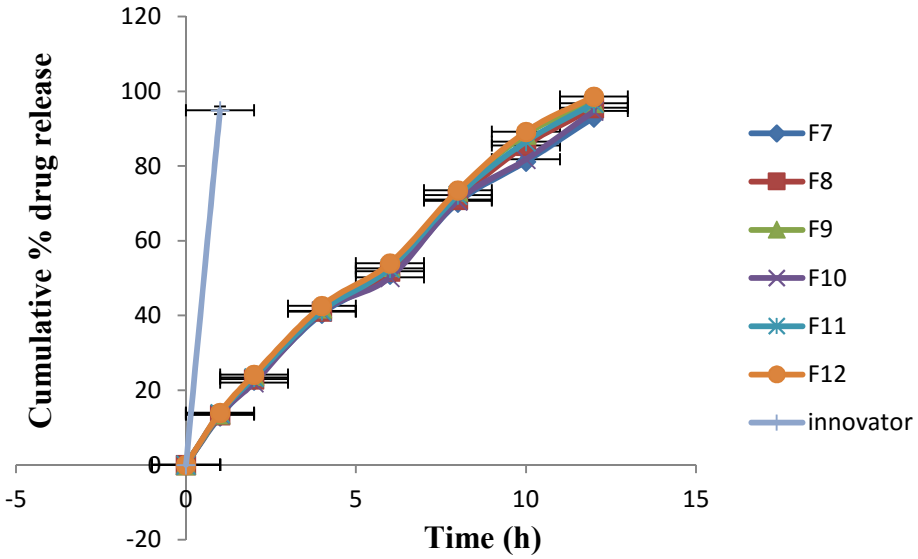


Figure 3: **Drug release profile from formulations F7-F12 and innovator**

Mathematical modeling of floating tablets

To explore the mechanism of drug release from QF floating tablets, various kinetic models like zero order, first order, Higuchi and Korsmeyer-Peppas equations were applied to the different formulations. The release order kinetics of optimized formulation (F12) was shown in **Table 5.** From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.979 indicates that the drug release follows a zero order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data into various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. The mass transfer with respect to square root of time has been plotted, revealed a linear graph with regression value close to one i.e. 0.986 stating that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.790 suggest that the drug release from floating tablet was anomalous non-fickian diffusion.

Table 5: Release order kinetics of optimized formulation (F12)

Formula code	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F12	0.979	8.821	0.832	0.141	0.986	35.06	0.998	0.790

Drug -excipient compatibility studies

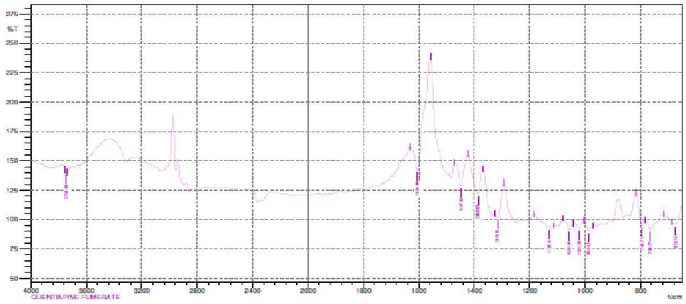


Figure 4: FTIR spectrum Quetiapine fumarate

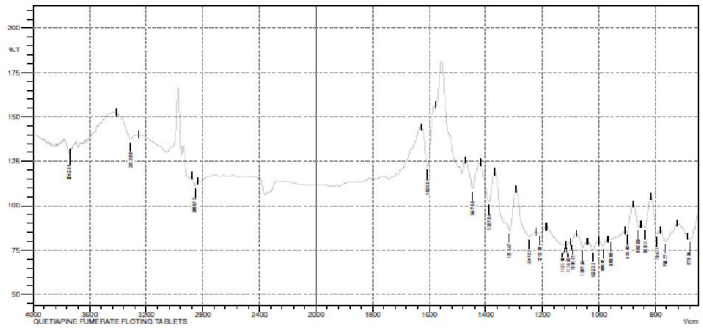


Figure 5: FTIR spectrum of optimized formulation (F12)

The FT-IR spectra of pure drug QF (Figure 4) and optimized formulation F12 (Figure 5) were found to be identical. The FTIR spectra of the optimized formulation displayed the characteristic peaks of both drug and polymers. Overall there was no alteration in the characteristic peaks of Quetiapine fumarate suggesting that there was no interaction between the drug and polymer.

Stability studies

The stability of optimized formulation (F12) of quetiapine fumarate floating tablets were tested for stability at 40°C/75%RH in properly closed HDPE bottles along with 1 gm desiccant for 3 months. The quetiapine fumarate release rate (Table 6) from the floating tablets (F22) showed no significant change during storage for 3 months, there is no significant change in floating lag time, total floating time and also in vitro drug release profile. The formulation stored in both conditions for 3 months floated on the surface of the media (0.1N HCl) for 12h.

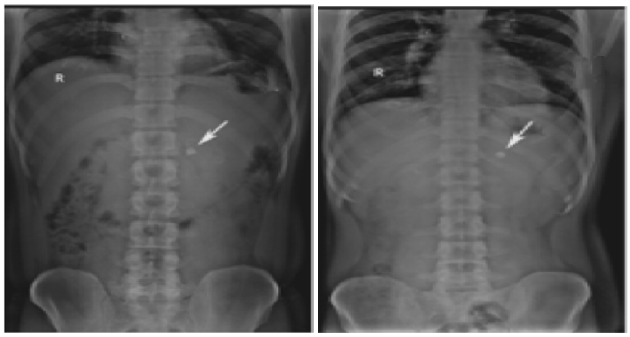
Table 6: Physico-chemical characteristics of optimized formulation (F12) stored at 40 ±2ºC /75 ±5%RH for 90 days

Retest Time For F12	Floating lag time(sec)*	Total Floating time (h)*	*In-vitro* drug release profile (%)*
0 days	32±2.6	>12hrs	98.6±0.69
30 days	33±2.4	>12hrs	98.2±0.25
60 days	33±1.2	>12hrs	97.6±0.83
90 days	34±3.5	>12hrs	97.0±0.19

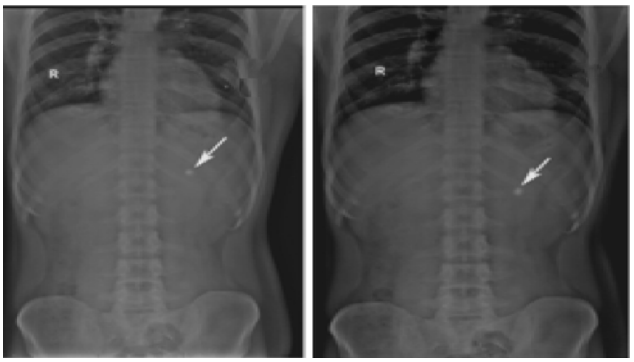
*Mean ± S.D (n=3)

Intragastric behavior of Quetiapine fumarate floating tablets

The radiographic images were taken at different periods post administration of the barium sulfate-loaded tablet in three human volunteers (Figure 6). It is clear that the tablet appears more or less at the same position for the initial 4h. This could be related to its floating ability. Later on, the tablet was slightly moved downwards, yet, remained within the stomach till the end of 6h. The increased gastric residence time favours increase in the bioavailability of drugs.



0.5 hours **2 hours**



4 hours **6 hours**

Figure 6: Radiographic images of optimized Quetiapine fumarate floating tablet (F12) in the stomach at different time intervals

***In vivo* bioavailability studies:**

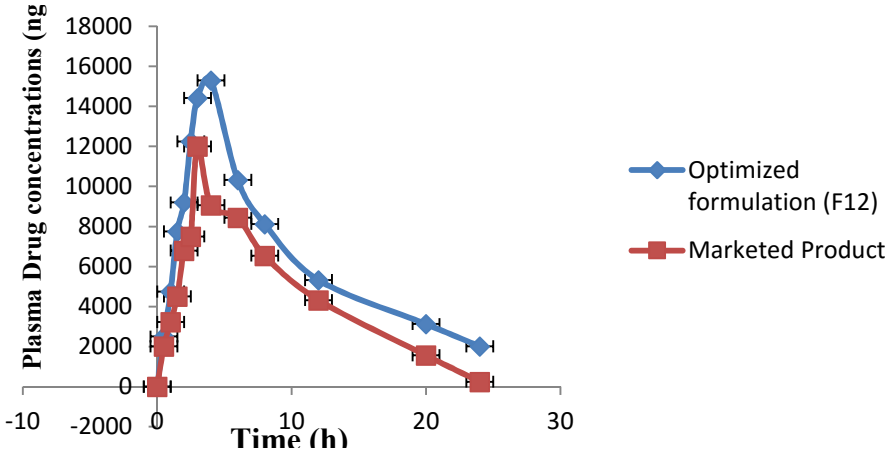


Figure 7: Plasma concentrations at different time intervals for Quetiapine fumarate optimized formulation and Marketed Product

Table 7: Comparison of pharmacokinetic parameters of Quetiapine fumarate optimized formulation and Marketed Product

Parameters	Quetiapine fumarate Optimized formulation (F12)	Marketed Product
C_{max}(ng/ml)	454±30.21	385±91.25
AUC_{0-t}(ng. h/ml)	3176±56.44	2597±44.26
$AUC_{0-\infty}$ (ng. h/ml)	3325±28.14	2826±38.12
T_{max} (h)	4.00±1.23	3.50±0.24
$t_{1/2}$ (h)	9.053 ± 0.519	8.164 ± 0.01
K_{el} (h^{-1})	0.051 ± 0.016	0.084 ± 0.018

Bioavailability parameters

Mean plasma concentration profiles of prepared Quetiapine fumarate optimized formulation and marketed product are presented in Figure 7. Quetiapine fumarate optimized formulation exhibited as sustained release *in vivo* when compared with marketed tablet. All the pharmacokinetics parameters displayed in Table 7. In this study in human subjects, prolonged drug absorption was achieved with the test formulation. The average peak concentration of the test formulation was significantly higher than that of the reference (454±30.21ng/ml for the test formulation versus 385±91.25ng/ml for the reference). In order to estimate the amount of drug absorbed from the test formulation, the relative bioavailability was calculated from the AUC of the reference and test formulations (2826±38.12ng. h/ml for the reference product versus 3325±28.14ng. h/ml for the test formulation). The results indicated that the test formulation could increase the bioavailability of Quetiapine fumarate in humans effectively. In this study, the Quetiapine fumarate floating tablet produce higher bioavailability than that of a marketed product, this overall increase in bioavailability and increased gastric residence time, caused by flotation of dosage form in the stomach.

Summary and conclusion

Present study aims in design of sustained release floating formulations of Quetiapine fumarate using different polymers like Gelucire 43/01, POLYOX WSR 301, HPMC K15M and HPMC K100M etc polymers to control the drug release and a lipid excipient to decrease the gastric irritation and to enhance the penetration of drug. Based on the evaluation parameters for F12 was found to be optimized formulation upon its floating lag time, buoyancy period and in vitro drug release was better than other formulations. The kinetic data revealed that the regression coefficient value of optimized formulation F12 closer to unity in case of zero order plot i.e. 0.979 indicates that the drug release follows a zero order mechanism. The mass transfer with respect to square root of time has been plotted, revealed a linear graph with regression value close to one i.e. 0.986 stating that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.790 suggest that the drug release from floating tablet was anomalous non fickian diffusion. The comparison plot of the In vitro drug release profiles of optimized formulation and innovator indicating the better drug release in F12 than innovator. The drug excipient compatibility studies were carried out to rule out any interactions between the drug and the polymers/excipients by FTIR and differential scanning calorimetric analysis. From the above results can conclude that the drug release from the optimized formulation F12 was in sustained manner for 12h by increasing the gastric residence time. The best formulation (F12) was selected based on in vitro characteristics and was used in vivo radiographic studies by incorporating BaSO4. These studies revealed that the tablets remained in the stomach for 6h in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. Studies to evaluate the pharmacokinetics in vivo showed better bioavailability, area under the concentration–time curve, elimination rate constant and half-life than marketed product.

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