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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLET OF QUETIAPINE FUMARATE

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Abstract:

The present research work is on gastro retentive floating matrix tablet of Quetiapine fumarate by using various hydrophilic polymers The formulation was developed by using different concentrations of polymers of various grades of HPMC and guar gum. Then Gas generating agent sodium bicarbonate concentration was optimized The formulation blend was subjected to various preformualation studies, and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Guar gum were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K 15 M retarded the drug release up to 12 hours in the concentration of 120 mg (F6).The formulations prepared with HPMC K100M (F8) were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Keywords: *Quetiapine fumarate , HPMC polymers , Floating tablets. Gastro retentive*

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INTRODUCTION

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action [1,2]

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed [3].

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS) [4,5].

Role of GI tract:

Stomach

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

From the discussion of the physiological factors in stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems [4, 5].

Types of Floating Drug Delivery Systems (FDDS) [6]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and
B. Non- Effervescent System.

1 Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating systems
II. Volatile Liquid/Vacuum Containing Systems.

2. Non-Effervescent Systems:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Bilayered Floating Tablets:

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

The atypical antipsychotic Quetiapine improves the affective symptoms of schizophrenia. More recently, two double-blind, randomized, phase placebo-controlled studies demonstrated that Quetiapine mono therapy was effective in the acute treatment of patients with bipolar I or II depression, and the efficacy of Quetiapine mono therapy in bipolar depression has since been confirmed by two additional maintenance studies. Furthermore, in a maintenance treatment study in patients with bipolar I disorder, Quetiapine monotherapy significantly reduced the risk of either a manic or mood event either as much as or more effectively than lithium for mania, and more effectively than lithium for depression [7,8,9].

In this study an initiative was taken to formulate Quetiapine Fumarate as a floating drug delivery system in order to improve absorption. It will remain in gastric region for longer duration causing increase in gastric residence time which may cause improved bioavailability & reduces drug waste. We used two hydrophilic cellulose derivatives: HPMC K 15 M, HPMC K 100 M, and guar gum. Sodium bicarbonate was incorporated in the formulation as gas generating agents.

MATERIALS AND METHODS:

Quetiapine Fumarate was a generous gift from Aurabindo Pharma Pvt Ltd Hyderabad India, Hydroxy Propyl Methyl Cellulose K100M, Guar gum, Sodium bicarbonate, Magnesium stearate, Micro crystalline cellulose, and Talc from Merck Specialities Pvt Ltd, Mumbai, India

Determination of λ max (UV-Spectroscopy)

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation Calibration Curve:

100mg of Quetiapine Fumarate pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50,60,70,80,90 and 100µg/ml of Quetiapine Fumarate per ml of solution. The absorbance of the above dilutions was measured at 271 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Preparation of Quetiapine fumarate gastro retentive floating tablets [10]

All the formulations were prepared by direct compression. The composition of different formulations is given in Table 1. The total weight of the tablet was considered as 300mg. Quetiapine Fumarate and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Drug: Polymer Interactions

Fourier Transform Infrared Spectroscopy [11]

The physical mixtures were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Pre-compression Characters of Powder Blend [12]:

Angle of Repose:

The frictional force in a loose powder can be measured by the angle of repose It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Tan θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Bulk Density:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, V0, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula,

Bulk Density = M / V0,

Where **M** – weight of sample,

V0 - apparent volume of powder

Tapped Density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of Powder Compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Optimization of Sodium bicarbonate Concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimized. As shown in table 2.

Evaluation of post compression parameters for prepared Tablets [13]

The designed formulation compression coated tablets were subjected for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation Test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table 3 and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Friability Test:

Weighed amount of 20 de-dusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The apparatus was operated for 4 minutes and reweighed the tablets. Friability was calculated by the following formula.

F =100 (W0-W)/W0

Where **W0** = Initial weight, **W** = Final weight

Hardness Test:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of tablets was carried out in Monsanto hardness tester. The result was complies with IP specification.

Thickness Test:

Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Determination of Drug Content:

Ten tablets were finely powdered and accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug

concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies:**

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* Drug Release Studies [14]**

Apparatus --USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl
RPM -- 75
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature-- 37°c ± 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 75 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data [15]:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixson-Crowell release model and Korsmeyer-Peppas release model.

Stability studies of optimized formulation [16]

According to ICH guidelines, 45 days stability study at 40C ±20C, 270C ±20C and 450C ±20C for 45 days at RH 75±5% of optimized formulation (F6) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 40C ±20C, 270C ±20C and 450C ±20C for 45 days at RH 75±5% for 45 days shown in table 8

RESULTS AND DISCUSSION:

The drug exhibited the **λ max** at 271 nm in 0.1 N Hydrochloric acid and has good reproducibility shown in Figure: 1

Drug – Excipient Compatibility Studies

Fourier Transform-Infrared Spectroscopy:

The different peaks of drug, polymer and their physical mixture indicate all groups and characteristics of the drug were not altered. There is no significant interaction in drug and polymer given in table 3. Physical mixture of drug and polymer was characterized by FTIR spectral analysis (figures 2,3) for any physical as well as chemical alteration of drug characteristics. Drug and polymers were found to be compatible.

Optimization of Sodium bicarbonate Concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 75mg concentration showed less floating lag time of 4 min and the tablets containing 50mg showing floating condition for more than 12 hours.(table No:2)

Pre-compression characters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties as shown in table No: 3.

Post compression parameters

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits, given in table No: 4

***In-Vitro* Drug Release Studies**

From the dissolution data it was evident that the formulations prepared with Guar gum as polymer formulation F1, F2, F3 were unable to retard the drug release up to desired time period i.e., 12 hours as

given in table: 5 and release was found that not following linearity (Fig. 4)

Whereas the formulations prepared with HPMC K15M F4, F5, F6 retarded the drug release in the concentration of 120 mg (F6) showed required release pattern table No:6 i.e., retarded the drug release up to 12 hours (Fig.5) and showed maximum of 96.33 % in 12 hours in linear pattern with good floating lag time and floating buoyancy time.

The formulations prepared with HPMC K 100M F7, F8, F9 showed more retardation even after 12 hours data is given table no: 7 they were not shown total drug release. Hence they were not considered. (Fig 6)

Release Rate Kinetics to Dissolution Data for F6 Formulation:

Various models were tested for explaining the kinetics of drug release.To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order (Fig 7), Higuchi (Fig 8), and Korsmeyer-Peppas (Fig 9), first order (FIg10), release model. From the above graphs it was evident that the formulation F6 was followed Higuchi mechanism and hence considered as optimized formulation.

Stability studies optimized formulation F6:

From stability studies it is clearly indicates that the optimized formulation found to be stable for expected time period as given in table No: 8

CONCLUSION:

Among all the formulations the formulations prepared by using Guar gum were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. As the concentration of polymer increased, the rate of drug release was found to be decreased. The formulations prepared with HPMC K 15 M retarded the drug release up to 12 hours in the concentration of 120 mg (F6).The formulations prepared with HPMC K100M (F8)were also retarded the drug release for more than 12 hours. from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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TABLES AND FIGURES:

Table 1: The Composition of Different Formulations

Formulation No.	Quetiapine fumarate	Guar gum	HPMC K15M	HPMC K100M	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102
F1	75	60	-----	-----	50	5	5	QS
F2	75	90	-----	-----	50	5	5	QS
F3	75	120	-----	-----	50	5	5	QS
F4	75	-----	60	-----	50	5	5	QS
F5	75	-----	90	-----	50	5	5	QS
F6	75	-----	120	-----	50	5	5	QS
F7	75	-----	-----	60	50	5	5	QS
F8	75	-----	-----	90	50	5	5	QS
F9	75	-----	-----	120	50	5	5	QS

All the quantities were in mg total weight is 300 mg.

Table 2: Optimization of Sodium bicarbonate Concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Quetiapine fumarate	75	75	75
2	HPMC K 100M	100	100	100
4	$NaHCO_3$	25	50	75
5	Mg.Stearate	5	5	5
5	Talc	5	5	5
7	MCC pH 102	Q.S	Q.S	Q.S

All the quantities are in mg

Table 3: Pre-Formulation Parameters Of Blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table 4: Post Compression Parameter

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	312.5	4.5	0.52	4.8	99.76	4.0
F2	305.4	4.2	0.54	4.9	99.45	4.2
F3	298.6	4.4	0.51	4.9	99.34	4.5
F4	310.6	4.5	0.55	4.9	99.87	4.1
F5	309.4	4.4	0.56	4.7	99.14	4.0
F6	310.7	4.2	0.45	4.5	98.56	4.4
F7	302.3	4.1	0.51	4.4	98.42	4.5
F8	301.2	4.3	0.49	4.7	99.65	4.6
F9	298.3	4.5	0.55	4.6	99.12	4.7

Table 5: Dissolution Data of Tablets Prepared With Guar gum

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	F2	F3
0.5	21.73	18.52	19.53
1	59.23	37.47	28.97
2	84.9	59.93	35.89
3	94.873	65.85	45.7
4	94.873	77.54	54.38
5		89.55	61.2
6		96.6	67.06
7			72.52
8			77.88
9			86.6
10			89.09
11			94.52

Table 6: Dissolution Data of Tablets Prepared With HPMCK15M

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F4	F5	F6
0.5	18.45	18.42	19.62
1	36.26	27.73	27.86
2	52.16	35.63	36.35
3	70.01	42.04	41.45
4	87.26	57.25	47.80
5	93.10	64.33	55.25
6		75.41	60.24
7		83.84	66.73
8		92.80	71.34
9			78.52
10			80.17
11			88.75

Table: 7 Dissolution Data of Tablets Prepared With HPMC K100M

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F7	F8	F9
0.5	18.81	19.89	14.21
1	29.02	28.04	18.87
2	35.70	35.43	27.19
3	43.32	41.65	35.66
4	49.25	47.18	43.32
5	55.28	53.81	51.06
6	60.92	58.89	57.13
7	66.08	64.53	63.63
8	70.44	69.43	69.71
9	77.22	72.83	73.34
10	80.90	79.98	79.27
11	87.83	83.52	82.86
12	91.90	88.65	85.97

Table 8: Stability Studies Of Optimized Formulation F6

Parameters	Physical appearance	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Drug content (%/ tablet)	Friability (%)
After 15 days	No change	404±3.36	3.51±1.84	6.4±0.23	100.25±0.35	0.51±0.06
After 30 days	No change	402±2.56	3.53±2.85	6.3±0.62	99.81±0.23	0.53±0.06
After 45 days	No change	402±4.25	3.54±3.96	6.2±0.95	99.01±0.83	0.53±0.05

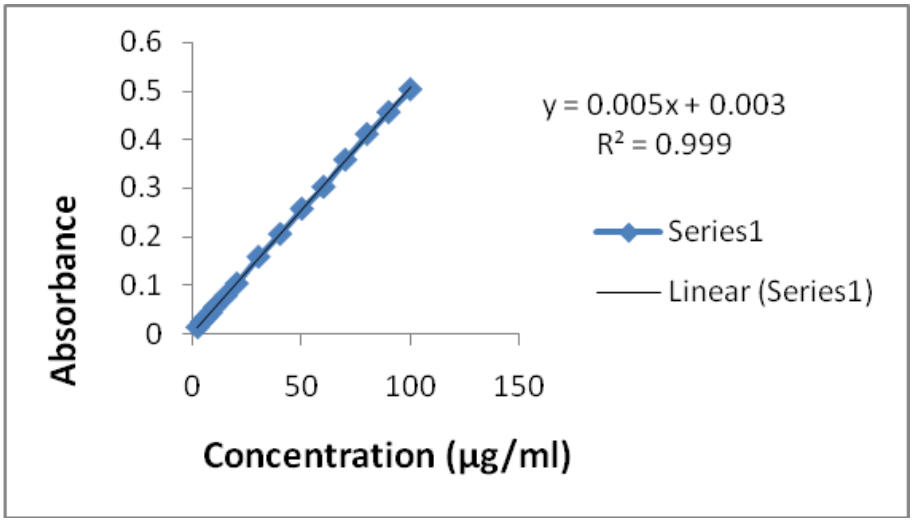

Fig 1: Standard graph of Quetiapine fumarate in 0.1N HCl

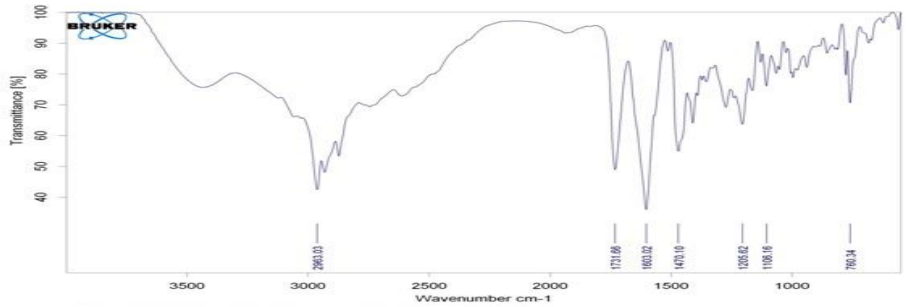

Fig 2: FT-IR Spectrum of Quetiapine Fumarate pure drug.

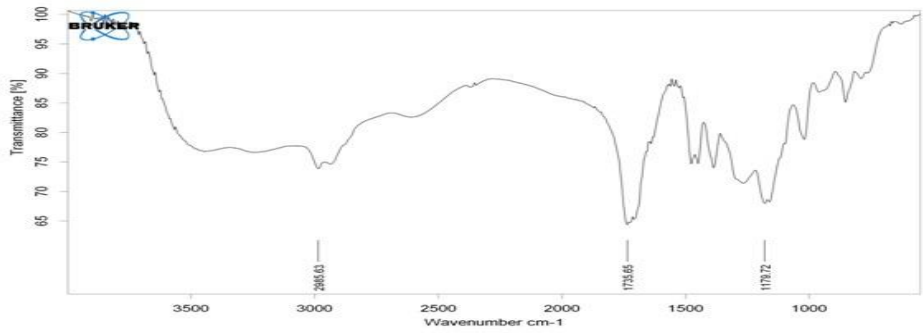

Fig 3: FT-IR Spectrum of Optimized Formulation

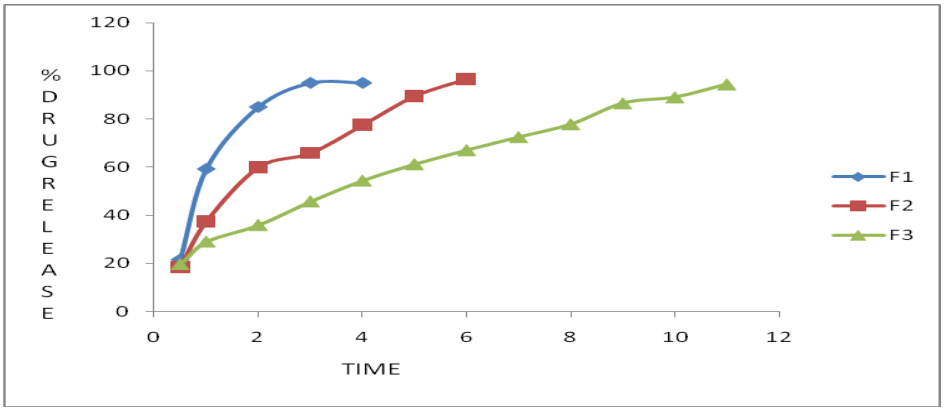

Fig 4: Dissolution profile of QUETIAPINE FUMARATE HCl floating tablets (F1, F2, F3 formulations).

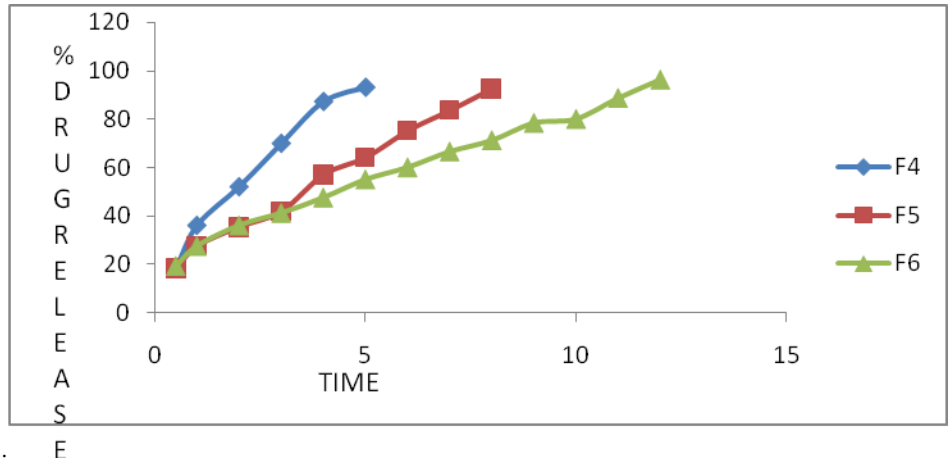

Fig: 5 Dissolution profile of Quetiapine fumarate HCl floating tablets (F4, F5and F6 Formulations

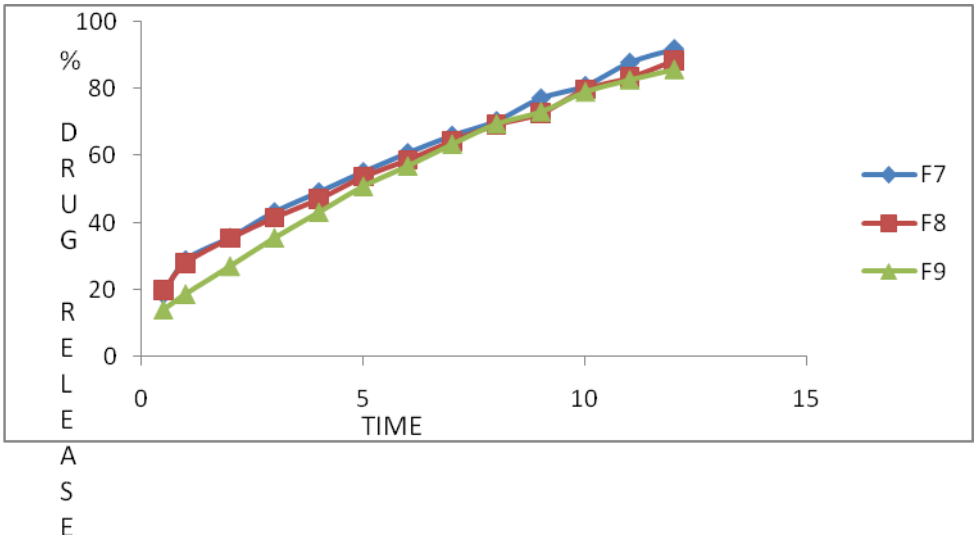

Fig 6: Dissolution profile of Quetiapine fumarate HCl floating tablets (F7, F8, F9 formulations)

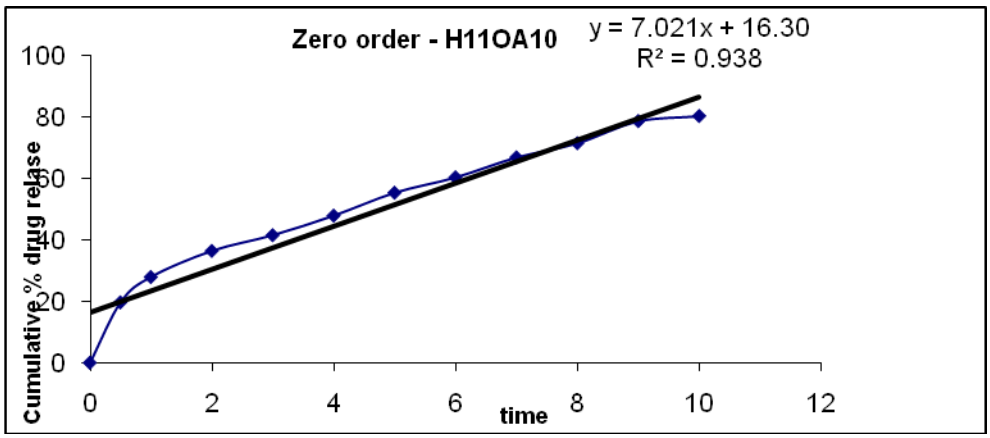

Fig 7 : Zero order release kinetics graph for F6 formulation

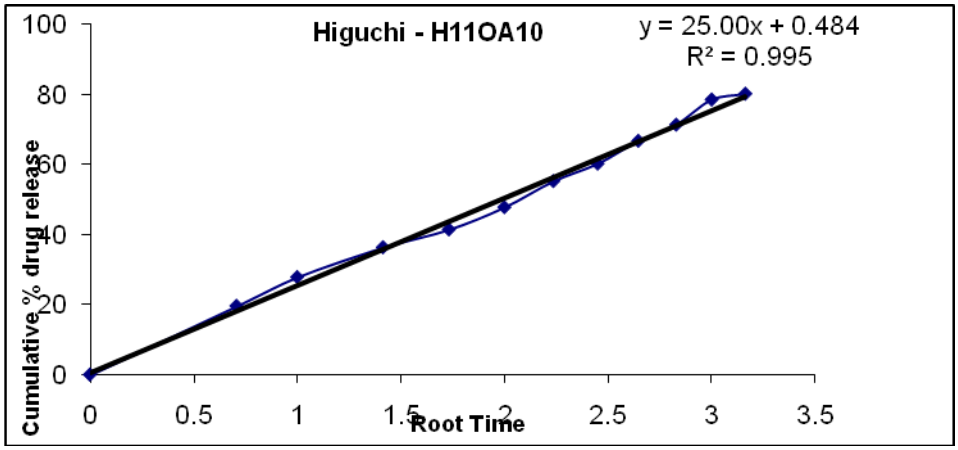

Fig 8 : Higuchi release kinetics graph F6 formulation

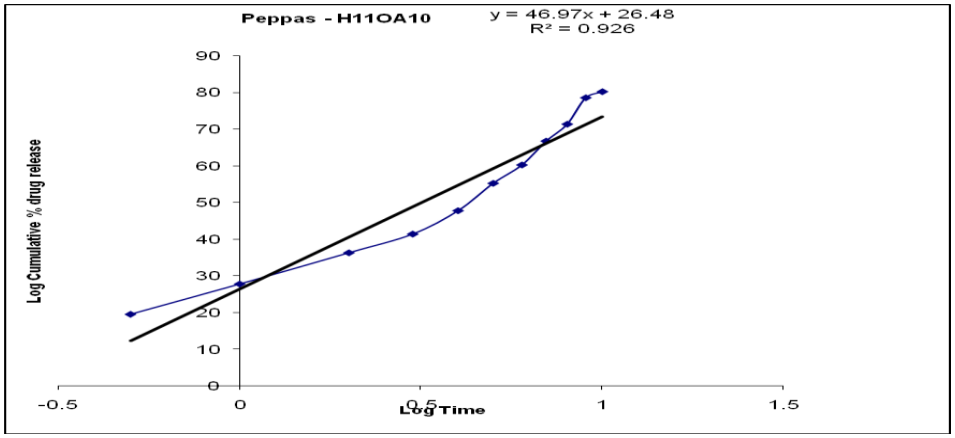

Fig 9: Korsmeyer peppas graph F6 formulation

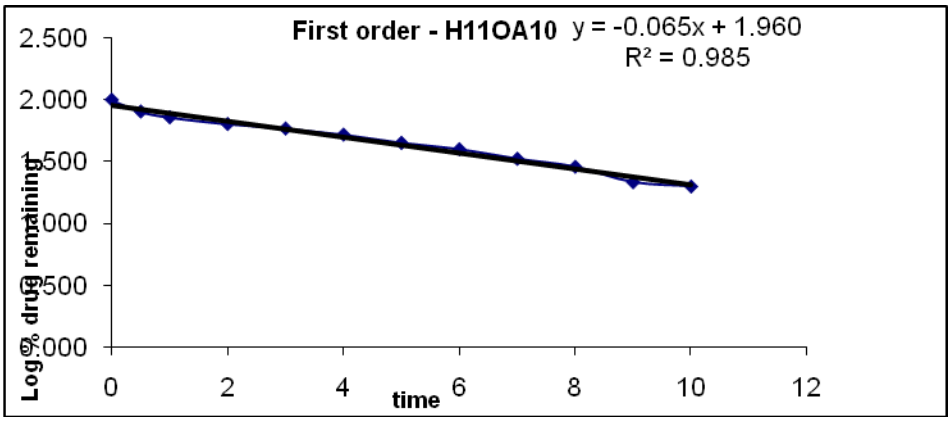

Fig 10: First order release kinetics graph F6 formulation