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Research

Formulation And *In Vitro* Evaluation Of Floating Tablets Of Quetiapine Fumerate

Dindigala Suresh*[1], Shivasri Krishna[1], Vandana[1], D. Radhika[1],

Department Of Pharmaceutics, Samskruti College Of Pharmacy In Ghatkesar, Telangana. 501301.

*Author for Correspondence: Dindigala Suresh
Email: dindigalasuresh@gmail.com

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Abstract

In the present research work floating matrix tablet formulation of Quetiapine Fumarate was prepared by using different polymers. Initially analytical method development was done for the drug molecule. And absorption maximum was determined based on the calibration curve developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of Hydroxyl Ethyl Cellulose (HEC), Chitosan, Sodium Alginate as polymeric substances. The formulations blend was subjected to various preformulations studies, flow properties. Among all the formulations, the formulation prepared with hydroxyl ethyl cellulose released the drug up to 24 hours (F3=99.84). The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Kors Mayer peppas mechanism of drug release.

Keywords: Quetiapine Fumarate, Hydroxy Ethyl cellulose(HEC), Chitosan, Sodium alginate, Floating tablets.

INTRODUCTION

Oral delivery of drugs is the preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration , patient compliance and flexibility in the formulation and cost effective manufacturing process.[1] Many of the drug delivery systems , available in the market are oral drug delivery type systems . Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life require frequent administration , which increases chances of missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration –time profile is obtained which makes attainment of steady state condition difficult.
3. The unavoidable fluctuations in the drug concentrations may lead to under medication or overmedication as the C max values fall or rise beyond the therapeutic range

4. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index , whenever overmedication occurs.[2]

   In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controllingthe rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue.[4]

Controlled drug delivery or modified drug delivery systems are divided into 4 categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, controlled delivery can be defined as:

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release adjacent to or in the diseased tissue.
3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically therapeutically based drug release system. In other words , the amount and the rate of drug release determined by the physiological therapeutic needs of the body.[5]

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. (fig.1).[6]Controlled drug deliveries usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

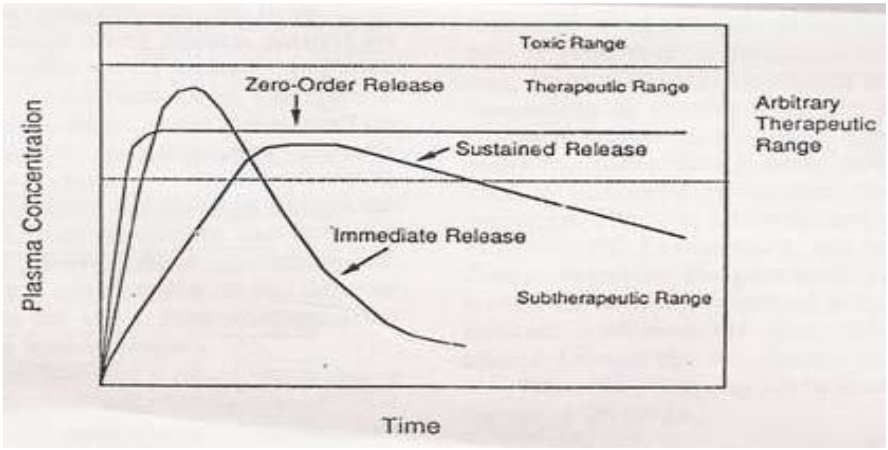

Fig 1: Drug level versus time profile shoeing differences between zero order , controlled release , slow first order sustained release and release from conventional tablet

Oral delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.[7]

Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Attempts to develop a single dose therapy for the whole duration of treatment have focused attention on controlled or sustained release drug delivery systems. Attention has been focused particularly on orally administered sustained drug delivery systems because of the ease of the administration via the oral route as well as the ease and economy of manufacture of oral dosage form. Sustained release describes the delivery of drug from the dosage forms over an extended period of time. It also implies delayed therapeutic action and sustained duration of therapeutic effect. Sustained release means not only prolonged duration of drug delivery and prolonged release, but also implies predictability and reproducibility of the drug release kinetics. A number of different oral sustained drug delivery systems are based on different modes of operation and have been variously

named, for example, as dissolution controlled systems, diffusion controlled systems, ion-exchange resins, osmotically controlled systems, erodible matrix systems, pH independent formulations, swelling controlled systems and the like.

An orally administered controlled drug delivery systems encounters a wide range of highly variable conditions, such as pH, agitation intensity and composition of the GI fluids as it passes down the GIT. Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the GIT and highly variable nature of the Gastric emptying process. An important factor, which may adversely affect the performance of an oral controlled drug delivery system is the G.I transit time. The time for absorption in the G,I transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation. G.I transit time vary widely between individuals, and depend up on the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to predictable bioavailability and times to achieve peak plasma levels. One of the important determinants of G.I transit is the residence time in the stomach

Majority of the drugs are well absorbed from all the regions of the G.I.T while some are absorbed from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Therefore, in instances where the drug is not absorbed uniformly over the GIT, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids. More particularly, in instances where a drug has a clear cut absorption window i.e., the drug is absorbed only from specific region of the stomach or upper parts of the small intestine, it may not be completely absorbed when administered in the form of a typical oral controlled drug delivery system. It is due to the relative brief gastric emptying in humans, which normally averages 2-3 h through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose, It is apparent that for a drug having such an absorption window, an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.

It is suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phased of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the dug there in a controlled and prolonged manner, So that the drug could be supplied continuously to its absorption sites in the upper GIT. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled dosage form for these drugs.

Incorporation f the drug in a controlled release gastroretentive dosage form (CRGRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharnacodynamic factors.

Controlled release or extended release dosage forms with prolonged residence times in the stomach are highly desirable for drugs. [8] which are

1. Administered one or more times a day
2. Only absorbed in the upper GI regions.
3. Insoluble in water
4. Targeted at sites in the upper GIT
5. Bioavailable through active transport mechanisms
6. Irritating to the mucosa
7. Misbalancing, irritating, or unsafe in the lower GI region.
8. More effective when plasma levels are more constant
9. That is locally active in the stomach
10. That is unstable in the intestinal or colonic environment or degrades in colon.
11. Have low solubility at high values.

MATERIALS

Quetiapine Fumarate-Procured From Ranbaxy Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Hydroxyl Ethyl Cellulose-Merck Specialities Pvt Ltd, Mumbai, India, Chitosan-Merck Specialities Pvt Ltd, Mumbai, India, Sodium alginate-Merck Specialities Pvt Ltd, Mumbai, India, Citric acid-Merck Specialities Pvt Ltd, Mumbai, India, Sodium bicarbonate-Merck Specialities Pvt Ltd, Mumbai, India, PVP K 30-Merck Specialities Pvt Ltd, Mumbai, India, Aerosil -Merck Specialities Pvt Ltd,

Mumbai, India, Sodium stearyl fumerate - Merck Specialities Pvt Ltd, Mumbai, India, Mannitol-Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY

Analytical method devlopment

a) Determination of absorption maxima

A solution containing the concentration 10µg/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 200-400nm.

b) Preparation calibration curve

10mg quetiapine Fumarate pure drug was dissolved in 10ml of methanol (stock solution 1) from stock solution 1ml of solution was taken and made up with 10ml of 0.1N Hcl (100µg/ml). from this 1ml was taken and made up with 10ml of 0.1N Hcl(10µg/ml). The above solution was subsequently diluted with 0.1N Hcl to obtain series of dilutions containing 2,4,6,8,10 µg/ml of per ml of solution. The absorbance of the above dilutions was measured at 254nm by using UV-Spetrophototmeter 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 coeeficient ($R^{2)}$ Which determined by least-square linear regression analysis.

Drug – excipients compatibility studies

Fourier transform infrared (FTIR) Spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR Spectra obtained on Bruker FTIR Germany (alpha T). The solid powder directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wavenumber of 4000cm^{-1} to 550cm^{-1}.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all theses can affect the characteristics of blends produced. The various characteristics of blends tested as per pharmacopoeia.

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 orizontal plame. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height(h), above a graph paper that is place 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:

Tan θ= h/r, Tan θ=Angle of repose, h= Height of the cone, r= radius of the cone base

Table 1: Angle of repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10gm powder blend was sieved and introduced into a dry 20ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apartment volume, Vo, was read.

The bulk density was calculated using the formula:
Bulk density= M/Vo
Where,
M= Weight of sample,
Vo=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 interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle 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

Table 2: Carr's index value(as per USP)

Carr's index	Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
2-35	Poor
33-38	Very Poor
>40	Very Very Poor

Formulation development of floating tablets

For optimization of sodium bicarbonate concentration, granules were prepared by direct compression method.

Procedure of direct compression method

1. Drug and all other ingredients were individually passed through sieve no ≠ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15min.
3. The powder mixture was lubricated with talc.
4. The tablets were prepared by using direct compression method by using 12mm punch.

Optimization of sodium bicarbonate

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 concentration of sodium bicarbonate was finalized and proceeded for further formulations.

Table 3: Optimisation sodium bicarbonate concentration

Ingredients	DO1	DO2	DO3
Quetiapine Fumarate	25	25	25
Hydroxy Ethyl Cellulose (HEC)	50	50	50
PVP K 30	5	5	5
$NaHCO_3$	15	30	45
Citric Acid	15	15	15
Aerosol	3	3	3
SSF	3	3	3
Mannitol	84	84	84
Total weight	200	200	200

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

FORMUALTION OF TABLETS

Table 4: Formulation composition for floating tablets

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Quetiapine Fumarate	25	25	25	25	25	25	25	25	25
Hydroxy Ethyl Cellulose (HEC)	12.5	25	50	-	-	-	-	-	-
Chitosan	-	-	-	12.5	25	50	-	-	-
Sodium alginate	-	-	-	-	-	-	12.5	25	50
Citric acid	15	15	15	15	15	15	15	15	15
NaHCO3	15	15	15	15	15	15	15	15	15
PVP k30	5	5	5	5	5	5	5	5	5
Aerosol	3	3	3	3	3	3	3	3	3
Sodium Stearyl Fumerate (SSF)	3	3	3	3	3	3	3	3	3
Mannitol	121.5	109	84	121.5	109	84	121.5	109	84
Total tablet weight	200	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSION

Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 294nm.

b. calibration curve

Graphs of quetiapine Fumarate was taken in 0.1N HCL(pH 1.2)

Table 5: Observations for graph of Quetiapine Fumarate in 0.1N Hcl

Concentration(µg/ml)	Absorbance
0	0
5	0.202
10	0.331
15	0.515
20	0.717
25	0.826

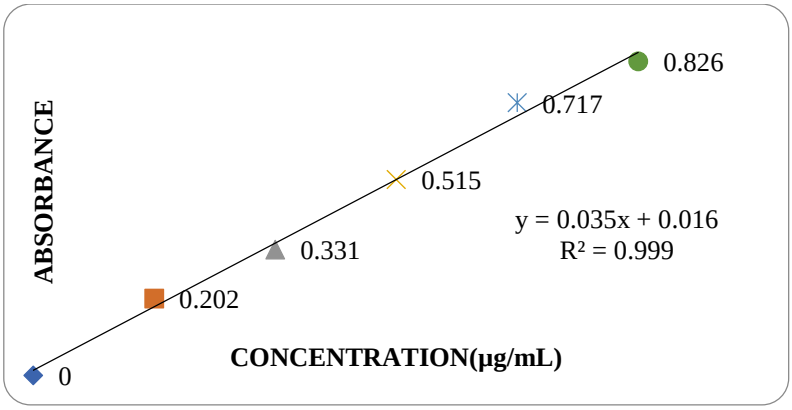

Fig 2: Standard graph of quetiapine Fumarate in 0.1N HCL

Standard graph of quetiapinr Fumarate was plotted as per the procedure in experimental method and its linearity is shown in table and fig. the standard graph of quetiapine Fumarate showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer-Lamberts" law.

Drug – Excipient compatibility studies
Fourier Transform – Infrared Spectroscopy

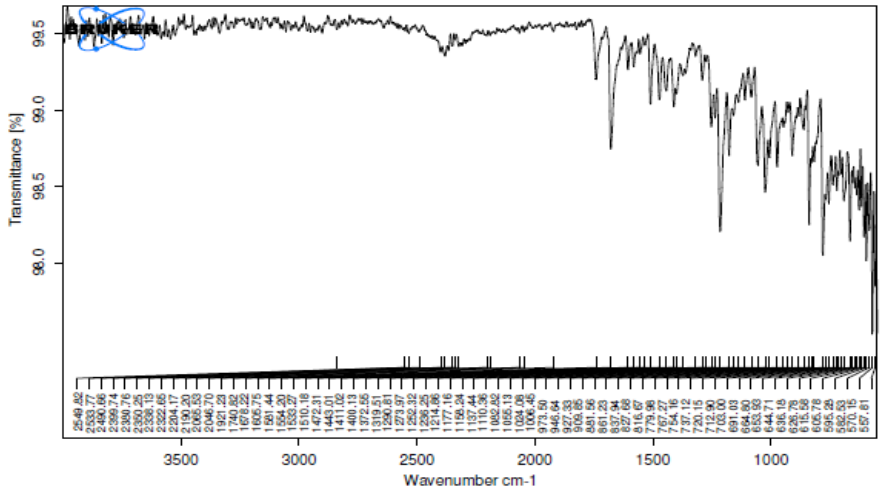

Fig 3: FTIR Spectrum of pure drug

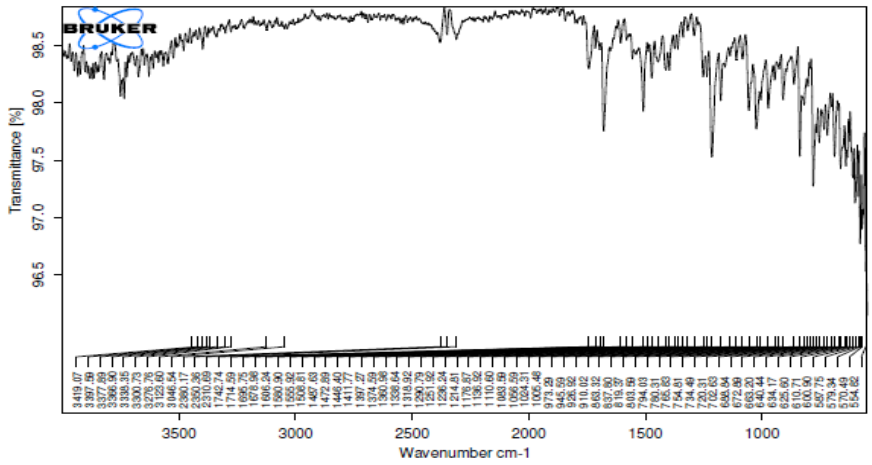

Fig 4: FTIR Spectrum of optimized formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Quetiapine Fumarate are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

Preformulaion parameters of powder blend

Table 6: 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	24.23	0.55	0.61	9.8	1.10
F2	25.17	0.47	0.58	18.96	0.23
F3	24.89	0.49	0.55	10.90	0.12
F4	26.41	0.52	0.63	17.46	1.21
F5	25.98	0.50	0.59	15.25	1.18
F6	26.22	0.53	0.64	17.18	1.20
F7	23.31	0.46	0.56	17.85	1.21
F8	25.48	0.48	0.54	11.11	1.12
F9	24.87	0.47	0.57	17.54	1.21

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 0.46 to 0.55(gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 to 0.64 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 19 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.21 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration

Three formulations were prepared with varying concentrations of sodium bicarbonate by direct compression method and three more formulations were prepared by wet granulation method to compare the floating buoyancy in between direct and wet granulation methods. The formulation containing sodium bicarbonate in 15mg concentration showed less floating lag time in wet granulation method and the tablet was in flowetating condition for more than 12 hours.

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, drug content and drug release studies were performed for floating tablets.

Table 7: *In vitro* quality control parameters

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Total Floating Time(Hrs)
F1	201.2	5.3	0.67	3.1	98.54	5.7	9
F2	200	5.1	0.58	3.5	99.26	5.2	11
F3	199.8	5.0	0.55	3.3	99.85	4.1	12
F4	201.7	5.5	0.59	3.4	98.78	5.5	10
F5	198.6	5.4	0.61	3.6	99.12	4.5	12
F6	200.3	5.7	0.57	3.8	99.29	5.9	7
F7	201.4	5.1	0.62	3.4	98.47	4.9	12
F8	201.9	4.9	0.64	3.7	98.19	5.8	9
F9	200.8	5.2	0.57	3.2	98.23	6.0	7

All the parameters such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

In Vitro drug release studies

Table 8: Dissolution data of floating tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	10.3	14.14	18.64	12.64	16.84	8.34	13.87	10.45	5.39
2	26.5	28.59	30.17	24.37	37.21	22.44	29.94	22.45	19.84
4	36.8	40.86	49.56	38.75	46.74	33.96	45.97	38.89	28.53
6	49.65	54.78	57.31	49.24	54.23	41.77	51.34	47.56	35.61
8	58.9	60.85	66.97	58.97	69.81	55.13	63.67	55.74	47.43
10	65.72	71.32	76.84	65.64	75.36	62.52	77.55	68.67	59.43
12	77.26	81.27	88.79	72.12	86.99	71.35	85.88	79.98	67.76
24	84.69	90.32	99.84	89.27	99.75	78.31	91.57	85.39	72.84

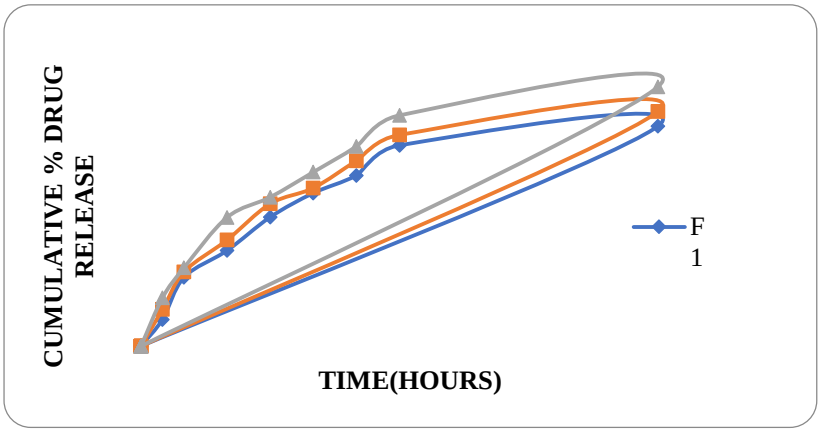

Fig 5: Dissolution data of Quetiapine Fumarate floating tablets containing Hydroxy ethyl cellulose (HEC)

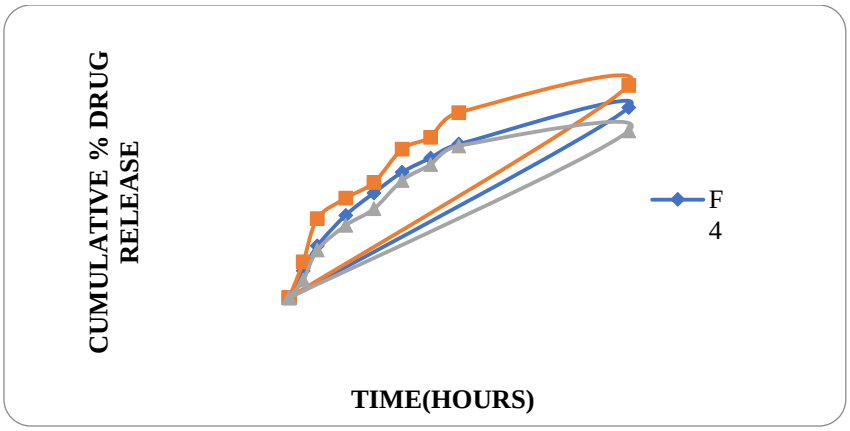

Fig 6: Dissolution data of Quetiapine Fumarate floating tablets containing chitosan

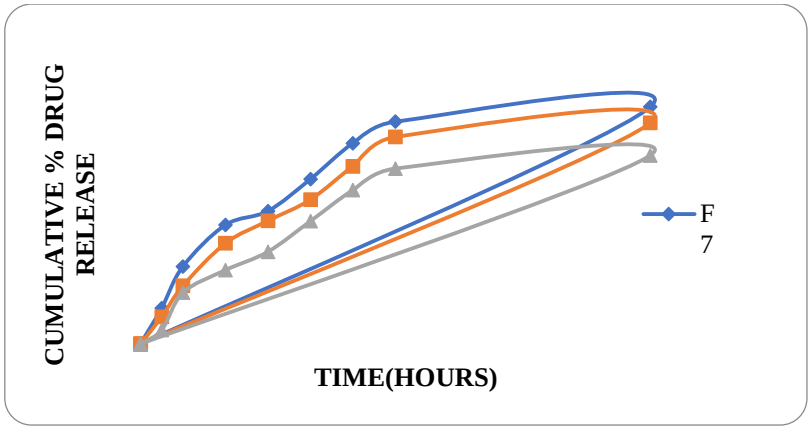

Fig 7: Dissolution data of Quetiapine Fumarate floating tablets containing sodium alginate

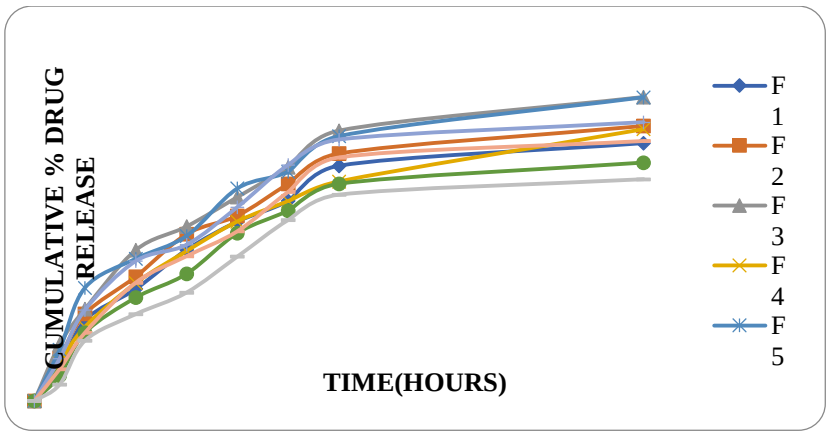

Fig 8: Dissolution data of quetiapine Fumarate floating tablets containing all formualations (Hydroxy ethyl cellulose(HEC),Chitosan and Sodium alginate)

From the dissolution data it was evident that the formulation prepared with HEC polymer showed better drug release in increasing order. The formulation F3 prepared with HEC shows good drug release more than 12hours in the concentration 50mg. The formulations F5 prepared with chitosan as polymer releases the drug upto 12hrs. But F4 and F6 formulations retards the drug release. The formulations F7,F8,F9 prepared with sodium alginate polymer showed drug release in decreasing order. Hence from the above dissolution data it was concluded that F3 formulation was considered as optimized formulation because good drug release (99.84%) in 24hours.

Application of release rate kinetics to dissolution data for optimised formulation

Table 9: Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.64	1	1.000	1.270	0.000	1.910	18.640	0.0536	-0.730	81.36	4.642	4.333	0.308
30.17	2	1.414	1.480	0.301	1.844	15.085	0.0331	-0.520	69.83	4.642	4.118	0.524
49.56	4	2.000	1.695	0.602	1.703	12.390	0.0202	-0.305	50.44	4.642	3.695	0.947
57.31	6	2.449	1.758	0.778	1.630	9.552	0.0174	-0.242	42.69	4.642	3.495	1.147

66.97	8	2.828	1.826	0.903	1.519	8.371	0.0149	-0.174	33.03	4.642	3.209	1.433
76.84	10	3.162	1.886	1.000	1.365	7.684	0.0130	-0.114	23.16	4.642	2.850	1.791
88.79	12	3.464	1.948	1.079	1.050	7.399	0.0113	-0.052	11.21	4.642	2.238	2.404
99.84	24	4.899	1.999	1.380	-0.796	4.160	0.0100	-0.001	0.16	4.642	0.543	4.099

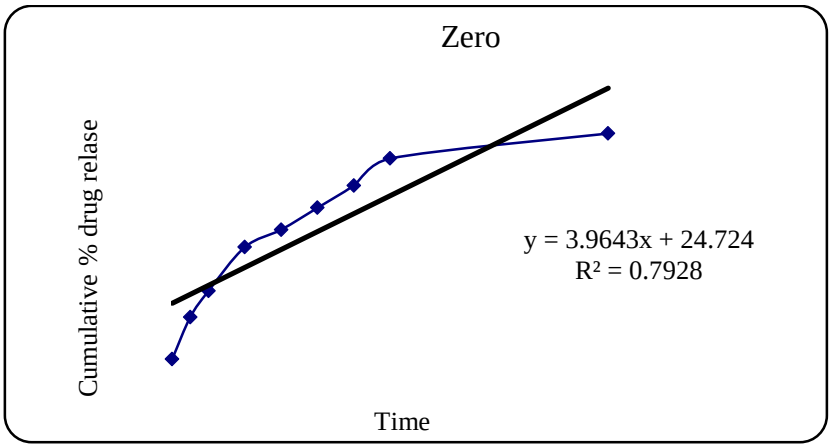

Fig 9 : Zero order release kinetics

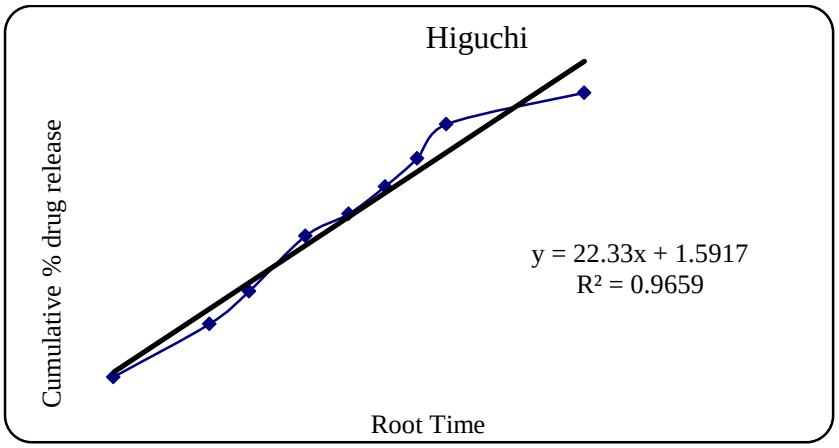

Fig 10: Higuchi release kinetics

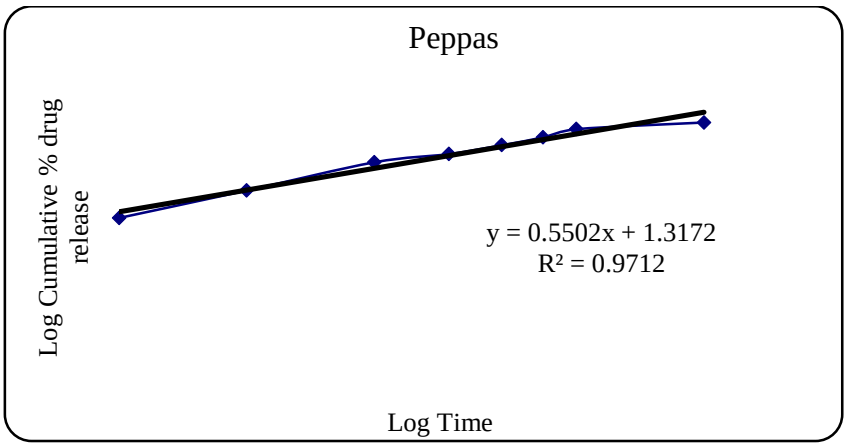

Fig 11: Kors mayer peppas release kinetics

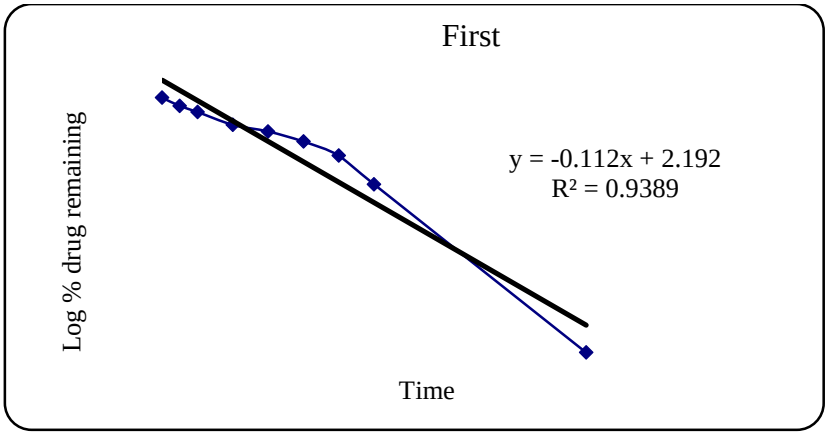

Fig 12: First order release kinetics

Optimised formulation F3 was kept for release kinetics studies. From the above graphs it was evident that the formulation F3 was followed Kors mayer peppas release kinetics.

CONCLUSION

Development of floating drug delivery of quetiapine Fumarate tablets is to provide the drug action up to 24hours.Floating tablets were prepared by direct compression method using various polymers like hydroxyl ethyl cellulose (HEC), chitosan, sodium alginate. The formulated floating tablets were evaluated for different parameters such as drug excipients compatablity studies, weight variation, sthickness, hardness, content uniformity, in vitro buoyancy studies, in vitro drug release studies performed in 0.1N HCL for 24 hours and the data was subjected to zero order, first order, higuchi release kinetics and karsmayer peppas graph.

The following conclusions could be drawn from the results of various experiments

- FTIR studies concluded that there was no interaction between drug and excipients.
- The physic-chemical properties of all the formulations prepared with different polymers hydroxyl ethyl cellulose (HEC), chitosan, sodium alginate were shown to be within limits.
- Quality control parameters for tablets such as weight variation, hardness, friability, thickness, drug content and floating lag time were found to be within limits.
- In vitro drug release studies were carried out for all prepared formulation and from that Concluded F3 formulation has sown good results.
- Finally concluded release kinetics to optimized formulation (F3) has followed kors mayer peppas kinetics.
- Present study concludes that floating system may be a suitable method for quetiapine Fumarate administration.

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