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Research

Formulation Development And *Invitro* Evaluation Of Quetiapine Fumarate Controlled Release Matrix Tablets

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Abstract

The present investigation concerns the development of controlled release matrix tablet of Quetiapine Fumarate. Matrix tablet of Quetiapine Fumarate was formulated by using Eudragit S 100 and HPMC grades as a polymeric matrix forming materials in various concentrations to study their ability to retard the release. All the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.73 % in 24 hours hence it is considered as optimized formulation F5 which contains HPMC K4 M. It followed Zero order release mechanism.

Keywords: Quetiapine

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. 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.[1,2,3]

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.[6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

A controlled release drug delivery system is capable of achieving the following benefits over conventional dosage forms:

- ✓ Total dose is low.
- ✓ Reduced GI side effects and other toxic effects.
- ✓ Reduced dosing frequency.
- ✓ Better patient acceptance and compliance.
- ✓ Less fluctuation in plasma drug levels.
- ✓ More uniform drug effect.
- ✓ Better stability of drug.[7,]

Advantages of Controlled Release Drug Delivery System

1] Therapeutic advantage: Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance: Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration. Avoid night time dosing: It also good for patients to avoid the at night time.[8,9,10]

Disadvantages

1] Dose dumping: Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment: In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3] Poor In-vitro In-vivo correlation: In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.

4] Increased potential for first pass clearance: Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating anenzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

5] Patient variation: The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in

gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.
6] Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, can not be accommodated.
7] There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.
8] Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make te product very difficult or sometimes impossible to prepare.
9] Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.
10] Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms.[11]

Factor Influencing the Formulation of Oral Controlled Release Drug Delivery System
Physicochemical Factors
Solubility

Low aqueous solubility drugs have low oral bioavailability. Drugs having good solubility in stomach are poor choice for controlled/sustained oral dosage forms. The water solubility limits the loading efficiency of drug into a variety of carrier systems such as liposome and micro particles, where highly water-soluble drug tend to leach fast from the carrier. The pH dependent solubility particularly in the physiological pH rangewould be another problem for controlled release formulation because of the variation in pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system allow to estimate contribution of three major factors Solubility, Dissolution and Intestinal Permeability which affect oral absorption. Class III (High solubility-Low permeability) and Class IV (Low solubility-Low permeability) drugs is poor candidate for controlled release dosage form.

Drug Stability

A drug in a solid state undergoes degradation at a much slower rate than a drug in suspension or solution6,. Drugs that are unstable in gastric pH can be developed as slow release dosage form and the drugs can be delayed till the dosage form reaches the intestine. Drugs that undergo gut-wall metabolism and show instability in small intestine are not suitable for oral controlled drug delivery systems.

Molecular Size and Diffusivity

Diffusivity defined as the ability of a drug to diffuse through membrane, is inversely related to molecular size. Diffusivity depends on size and shape of the cavities of the membrane. More than 95% of drugs are absorbed by passive diffusion. The upper limit of drug molecular size for passive diffusion is 600 Dalton. The examples of the drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

Partition coefficients

Partition coefficient id defined as the fraction of drug in an oil phase to that of an aqueous phase. It governs the permeation of drug particles through biological membrane. Drugs with high partition coefficient value easily permeate through biological membrane. The diffusion of drug molecules across rate controlling membrane or through the matrix system essentially relies on partition coefficient. Drugs that have lower partition coefficient are not suitable for oral controlled release drug delivery system and drugs that have higher partition coefficient are also not suitable for oral controlled drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidate for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption.

Biological factors
Absorption

The aim of formulating controlled release product is to place a control on delivery system. The desirable quality of oral controlled delivery system is that it should release complete drug and the release drug should be completely absorbed. The fraction of drug absorbed from the system can be lower than the expected

due to degradation of drug, protein binding, site-specific, dose-dependent absorption, poor water solubility and small partition coefficient.

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of drug, are poor candidate for oral drug delivery system. The apparent volume of distribution is one of the important parameter of drugs that describes the magnitude of distribution as well as protein binding within the body. The distribution of drug can be determined by the volume of distribution at steady state and T/P ratio.

$$T/P=K12/ (K21-b)$$

T=Amount of drug in peripheral compartment,
P=Amount of drug in central compartment,
K12=Constant for distribution of drug from central to peripheral compartment,
K21=Constant for distribution of drug from peripheral to central compartment,
b=Slow disposition constant.

Metabolism

Metabolism of a drug is either an inactivation, of an active drug or conversion of an inactive drug to an active metabolite. There are two factors related to metabolism of drug which restrict the design of sustained/controlled drug delivery. For chronic administration, drugs that are capable of either inducing or inhibiting enzyme synthesis, they are poor candidates for controlled delivery systems due to difficulty in maintaining uniform blood levels. Drugs possessing variations in bioavailability due to first-pass effect or intestinal metabolism are not suitable for sustained/controlled drug delivery.

Half- life

The duration of action is dependent on the biological half- life. Drugs with short half-life (greater than 2 hrs) are most suitable for controlled drug delivery system. Factors influencing the half-life of a drug are elimination, metabolism, and distribution.

Therapeutic index

Margin of safety can be described by considering therapeutics index, which is the ratio of median toxic dose and median effective dose.Therapeutic index = TD50/ED50. Drugs with low therapeutics index are unsuitable for drug incorporation in controlled release formulation.The side effects can be minimized by controlling the concentration within therapeutic range.

Size of dose

If the dose of a drug in conventional dosage form is high, then it is less suitable candidate for CRDDS. This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty.

Absorption window

Certain drugs when administered orally are absorbed only from a specific part of GI tract. This part is known as ‘absorptionwindow’. These kinds of drugs are not suitable for CRDDS

Plasma concentration response relationship

Plasma drug concentration is more responsible for pharmacological response than dose. But the drugs having pharmacological activity independent of plasma concentration are poor candidate for oral CR drug delivery system.

Concentration dependency on transfer of drug

If transfer of drug from one compartment to other follows zero order kinetic process then such drugs are poor candidate for oral CR delivery system. It should be first order kinetics. The following figure represents various formulation strategies for oral CR drug delivery system.

MATERIALS

Quetiapine Fumarate-Procured from Dr. Reddy’s Pharmaceuticals Hyderabad. Provided by SURA LABS, Dilsukhnagar, Eudragit S-100-Merck Specialities Pvt Ltd, Mumbai, India, HPMC K4 M-Yarrow Chem. Products, Mumbai, India, HPMC K15 M- Yarrow Chem. Products, Mumbai, India, MCC-Merck Specialities Pvt Ltd,

Mumbai, India, PVP K30-SD Fine Chemicals, Mumbai, India, Magnesium stearate-SD Fine Chemicals, Mumbai, India, Talc-Loba Chem, Mumbai, India

METHODOLOGY

Analytical method development

Determination of absorption maxima

100mg of Quetiapine Fumarate pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Quetiapine Fumarate pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20 and 25µg/ml of Quetiapine Fumarate per ml of solution. The absorbance of the above dilutions was measured at 290 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 (R2)which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

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

Angle of repos

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. 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 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:

$\tan \theta = h / r$ $\tan \theta$ = 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

ulk density

Density is defined as weight per unit volume. Bulk density, is defined as themass 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 the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where,M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk densitythe 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 and 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:

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

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
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Quetiapine Fumarate Total weight of the tablet was considered as 200mg.

Procedure:

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

Table 3: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Quetiapine Fumarate	25	25	25	25	25	25	25	25	25	25	25	25
Eudragit S 100	15	30	45	60	-	-	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	15	30	45	60	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	15	30	45	60
MCC	141	126	111	96	141	126	111	96	141	126	111	96
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSION

Standard Calibration curve of Quetiapine Fumarate

Table 4: Concentration and absorbance obtained for calibration curve of Quetiapine Fumarate in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 290 nm)
1	0	0
2	5	0.129
3	10	0.249
4	15	0.365
5	20	0.471
6	25	0.591

It was found that the estimation of Quetiapine Fumarate by UV spectrophotometric method at λ_{max}290 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml.

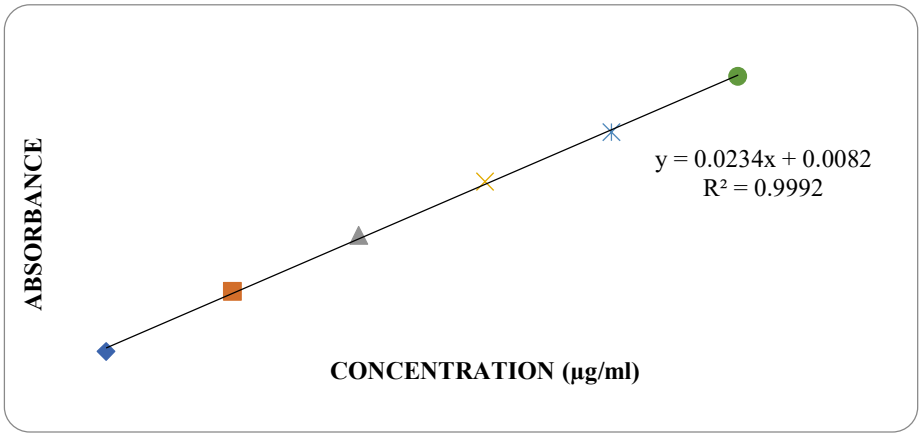

Fig 1: Standard graph of Quetiapine Fumarate in 0.1 N HCl

Table 5: Concentration and absorbance obtained for calibration curve of Quetiapine Fumarate in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 294 nm)
1	0	0
2	5	0.157
3	10	0.301
4	15	0.434
5	20	0.561
6	25	0.692

It was found that the estimation of Quetiapine Fumarate by UV spectrophotometric method at λ_{max}294 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml.

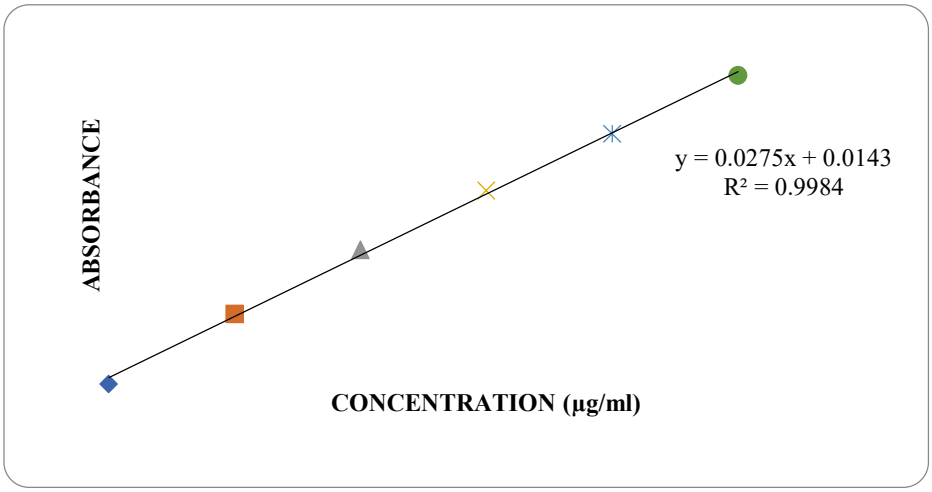

Fig 2: Standard graph of Quetiapine Fumarate in pH 6.8 Phosphate buffer

Evaluation Parameters for sustained release tablets of Quetiapine Fumarate

Pre-compression parameters

The data's were shown in Table 8.3.The values for angle of repose were found in the range of 16.26°-26.57°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.362±0.29to 0.433±0.16 (gm/cc) and 0.509±0.24to 0.530±0.52 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 16.26 % to 28.30 %. The Hausner ration fall in range of 1.19±0.16to 1.39±0.25. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 6: Pre-compression parameters

Formulations	Bulk Density(gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.380±0.45	0.530±0.52	28.30	1.39±0.25	26.57
F_2	0.362±0.29	0.485±0.25	25.36	1.33±0.52	27.09
F_3	0.384±0.23	0.545±0.11	31.25	1.41±0.22	27.06
F_4	0.411±0.28	0.509±0.29	18.44	1.24±0.22	18.44
F_5	0.419±0.30	0.515±0.28	19.08	1.28±0.23	19.08
F_6	0.423±0.50	0.519±0.30	18.32	1.20±0.25	18.32
F_7	0.433±0.16	0.509±0.24	16.26	1.20±0.21	16.26
F_8	0.417±0.37	0.515±0.28	18.71	1.22±0.26	18.71
F_9	0.413±0.16	0.512±0.21	17.60	1.25±0.16	17.60
F_{10}	0.429±0.22	0.521±0.29	18.46	1.28±0.22	18.46
F_{11}	0.428±0.35	0.514±0.27	17.37	1.20±0.30	17.37
F_{12}	0.425±0.15	0.527±0.25	16.75	1.19±0.16	16.75

Post compression Parameters

Average weight test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 97.18 to 100.2 mg, so the perissible limit is ±5% (.220 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 3.0 to3.9 kg/cm^2,which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-8.4 The result showed that thickness of the tablet is raging from 4.12 to 4.99 mm.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.4. The average friability of all the formulations lies in the range of 0.26 to 0.69 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.16-99.75%.

Table 7: post compression parameter

FD	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	198.32	5.3	4.15	0.25	98.14
F_2	199.62	5.1	4.36	0.69	97.68
F_3	197.59	5.6	4.15	0.54	99.10
F_4	198.45	5.9	4.61	0.15	98.64
F_5	200.01	5.1	4.25	0.67	96.58
F_6	198.44	5.5	4.45	0.52	98.71
F_7	198.67	5.7	4.35	0.47	99.01
F_8	197.53	5.9	4.19	0.28	96.37
F_9	196.72	5.8	4.28	0.56	99.45
F_{10}	198.12	5.4	4.31	0.38	98.26
F_{11}	199.24	5.6	4.11	0.49	99.78
F_{12}	198.75	5.1	4.52	0.18	98.43

***In-Vitro* Dissolution studies**

In-Vitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours.The samples were withdrawn at regular time intervals of 30 min,1 hour,2 ,3,4,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 8.

Table 8: *In -vitro* dissolution data

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	5.18	7.04	9.10	12.54	18.95	15.50	20.49	14.82	23.87	13.85	12.57	8.15
1	8.95	14.07	13.56	17.36	21.78	23.62	26.87	17.52	32.58	18.91	18.59	15.67
2	15.69	18.31	17.89	22.19	25.87	28.66	31.95	23.92	48.27	21.82	22.79	20.86
3	19.87	22.00	26.57	28.73	28.49	36.48	36.72	27.49	52.25	26.76	28.64	25.97
4	24.35	28.75	34.94	32.76	32.58	41.25	41.83	31.72	58.25	31.82	35.44	28.71
5	28.61	30.42	39.46	37.92	37.52	47.39	48.92	38.96	62.68	34.71	39.23	33.29
6	33.87	36.57	43.29	44.38	48.27	53.22	55.67	43.58	69.24	38.52	40.94	37.83
7	38.58	42.77	48.34	51.97	52.25	59.78	62.18	46.71	75.48	43.56	47.46	43.12
8	43.72	48.77	53.12	56.86	58.25	63.49	67.11	54.75	80.12	47.69	56.81	47.92
9	49.12	53.49	57.98	60.14	62.68	67.11	71.92	57.14	86.91	53.11	59.22	53.89
10	56.14	56.42	64.35	65.87	69.24	72.49	76.83	61.79	92.33	58.94	62.99	57.12
11	61.33	60.38	67.54	71.98	75.48	76.38	80.17	68.81	96.87	63.15	66.98	64.91

12	65.83	67.82	72.11	74.52	80.12	81.63	83.41	72.96	98.14	67.48	73.17	68.19
16	69.71	75.86	78.42	80.47	86.14	85.96	87.34	76.12		73.15	77.25	73.89
20	75.15	81.92	83.57	86.99	91.78	91.18	96.42	79.27		80.12	81.68	78.12
24	79.28	86.19	91.45	97.16	98.73	95.31		84.17		89.27	83.42	80.91

From the tabular column 8.5 it was evident that the formulations prepared with Eudragit S 100 as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. Eudragit S 100in the concentration of 60 mg showed good % drug release i.e., 97.16 in 24 hours. Where as in case of formulations prepared with HPMC K4 M as retarding polymer, the formulations with 15 mg concentration of polymer showed complete drug release in 24 hours only, whereas the concentration of polymer increases the retarding nature decreased. The Formulation Containing HPMC K4 M in 15 Mg Concentration Showed good retarding nature with required drug release in 24 hours i.e., 98.73%.

Where as in case formulations prepared with HPMC K15 M as retarding polymer, as the concentration of polymer increases the retarding nature was decreased. When compared with HPMC K4 polymer it was failed to produce desired drug release pattern.

From the above results it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 24 hours.

Application of Release Rate Kinetics to Dissolution Data

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, and Korsmeyer-Peppas release mode.

Table 9: Release kinetics data 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
18.95	0.5	0.707	1.278	-0.301	1.909	37.900	0.0528	-0.722	81.05	4.642	4.328	0.314
21.78	1	1.000	1.338	0.000	1.893	21.780	0.0459	-0.662	78.22	4.642	4.277	0.365
25.87	2	1.414	1.413	0.301	1.870	12.935	0.0387	-0.587	74.13	4.642	4.201	0.441
28.49	3	1.732	1.455	0.477	1.854	9.497	0.0351	-0.545	71.51	4.642	4.151	0.491
32.58	4	2.000	1.513	0.602	1.829	8.145	0.0307	-0.487	67.42	4.642	4.070	0.572
37.52	5	2.236	1.574	0.699	1.796	7.504	0.0267	-0.426	62.48	4.642	3.968	0.674
48.27	6	2.449	1.684	0.778	1.714	8.045	0.0207	-0.316	51.73	4.642	3.726	0.916
52.25	7	2.646	1.718	0.845	1.679	7.464	0.0191	-0.282	47.75	4.642	3.628	1.014
58.25	8	2.828	1.765	0.903	1.621	7.281	0.0172	-0.235	41.75	4.642	3.469	1.172
62.68	9	3.000	1.797	0.954	1.572	6.964	0.0160	-0.203	37.32	4.642	3.342	1.300
69.24	10	3.162	1.840	1.000	1.488	6.924	0.0144	-0.160	30.76	4.642	3.133	1.508
75.48	11	3.317	1.878	1.041	1.390	6.862	0.0132	-0.122	24.52	4.642	2.905	1.736
80.12	12	3.464	1.904	1.079	1.298	6.677	0.0125	-0.096	19.88	4.642	2.709	1.933
86.14	16	4.000	1.935	1.204	1.142	5.384	0.0116	-0.065	13.86	4.642	2.402	2.240
91.78	20	4.472	1.963	1.301	0.915	4.589	0.0109	-0.037	8.22	4.642	2.018	2.623
98.73	24	4.899	1.994	1.380	0.104	4.114	0.0101	-0.006	1.27	4.642	1.083	3.559

From the above graphs it was evident that the formulation F5 was followed Zero order release mechanism.

FTIR

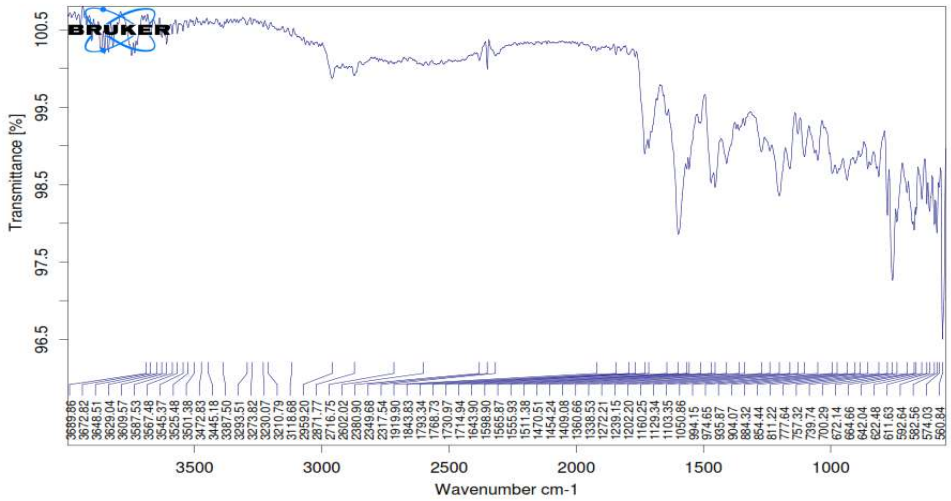

Fig 3: FT-TR Spectrum of Quetiapine Fumarate pure drug

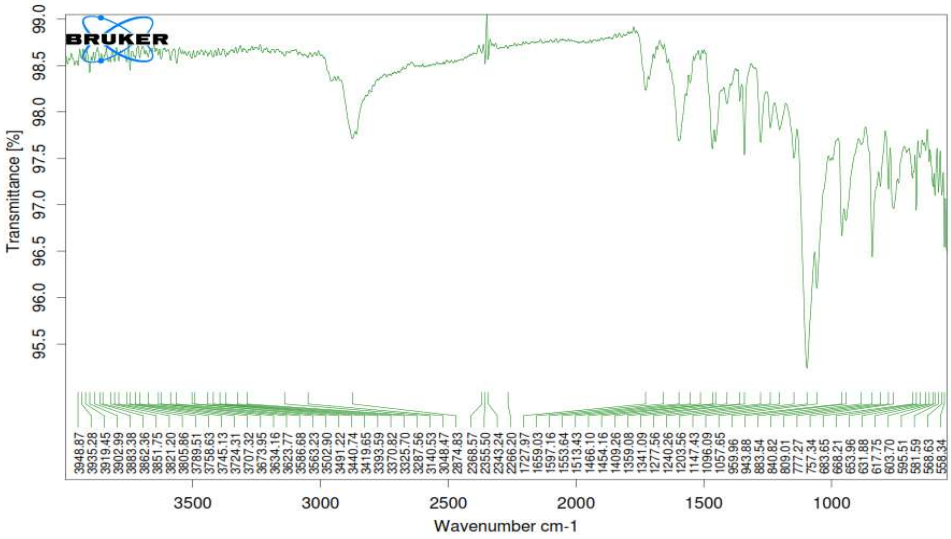

Fig 4: FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

Matrix tablets were prepared by Direct compression methodusing Eudragit S 100, HPMC K4 Mand HPMC K15 M as a matrix forming materials in different proportion. Study indicates that Eudragit S 100, HPMC K4 Mand HPMC K15 M (1:1; 1:2 and 1:3) ratio were found suitable for theuse as pharmaceutical excipients in the formulation and manufacturing of controlled release matrix tablets of Quetiapine Fumarate. FTIR studies concluded that there was no interaction between drug and excipients.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 F5 formulation has shown good results. It is evident from overall studies that HPMC K4 M possess potential for Controlled Release Matrix Tablets of Quetiapine Fumarate from the matrix tablet.

REFERENCES

1. 1.Sathish Ummadi, B. Shravani, N. G. Raghavendra Rao, M. Srikanth Reddy, B. Sanjeev Nayak. Overview on Controlled Release Dosage Form. International Journal of Pharma Sciences Vol. 3, No. 4 (2013): 258-269.
2. Brahmankar D.M. and Jaiswal S.B. (1995): "Biopharmaceutics and Pharmacokinetics" a Treatise. Vallabh Prakashan, First Edition; 336-337.
3. Lachman Leon, Lieberman Herbert A., Kanig Joseph L. (1996) "The theory and practice of industrial pharmacy" Second edition, Varghese publishing house; Bombay, 171-196.
4. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. Vallabh Prakashan, Delhi: 2009; 399-401.
5. John C, Morten C, The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone. 2002; 290-300.
6. Ali Nokhodchi, Shaista Raja, Pryia Patel, and Kofi Asare-Addo. The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems. Bioimpacts. 2012; 2(4): 175–187.
7. John C, Morten C, The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone. 2002; 290-300.
8. Sathish Ummadi, B. Shravani, N. G. Raghavendra Rao, M. Srikanth Reddy, B. Sanjeev Nayak. Overview on Controlled Release Dosage Form. International Journal of Pharma Sciences. 3(4): (2013): 258-269.
9. Vyas S,P, Khar RK.Controlled Drug delivery: Concepts and Advances .Concepts and Advances.1st ed.vallabh prakashan,2002,p,156-189.
10. Shargel L,Yu ABC. Modified release drug products. In:Applied Biopharmaceutics and Pharmacokinetics.4th ed.McGraw Hill.1999;169-171.
11. Welling P. G. and Dobrinska M. R., Dosing consideration and bioavailability assessment of controlled drug delivery system, Chapter 7, Controlled drug delivery; fundamentals and applications, 2nd edition, Robinson J.R. and Lee V. H. L. (Eds.), Marcel Dekker Inc., New York, 1978, 29,p. 254, 373.
12. Manisha Gahlyan, Saroj Jain. Oral Controlled Release Drug Delivery System- A Review.
13. Mamidala R, Ramana V, Lingam M, Gannu R, Rao MY. Review article factors influencing the design and performance of oral sustained/controlled release dosage form. Int. journal of pharmaceutical science and nanotechnology. 2009; 2:583.
14. Patel Nidh, Chaudhary Anamika, Soni Twinkle, Sambyal Mehul, Jain Hitesh,Upadhyay Umesh. Controlled Drug Delivery System: A Review. IAJPS 2016, 3 (3), 227-233.
15. Crank, J. (1975). The Mathematics of Diffusion. New York: Oxford Press.