Int J Pharm Bio Sci 2013 Oct; 4(4): (P) 578 - 595

Research Article **Pharmaceutics**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

DESIGN, *IN VITRO* AND *IN VIVO* EVALUATION OF QUETIAPINE FUMARATE EXTENDED RELEASE TABLETS

KOTHAMASU SOMA SEKHAR*[1,2], MADDI VENKATA NAGABHUSHANAM[1], PROF. K.R.S.SAMBASIVA RAO[2] AND D.V.R.N.BHIKSHAPATHI[3]

[1]Department of Pharmaceutics, D.C.R.M. Pharmacy College, Inkollu–523167, Andhra Pradesh, India.
[2]Department of Biotechnology, Acharya Nagarjuna University, Guntur – 522510.
[3]Vijaya College of Pharmacy, Hayath Nagar, Hyderabad- 501511.

ABSTRACT

The present investigation reports the design and evaluation of extended release film-coated matrix tablets of Quetiapine Fumarate to treat schizophrenia using different polymers mainly Carboxy methyl ethyl cellulose and Ethyl cellulose in combination by wet granulation method. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, *in vitro and in vivo* release studies. The film coated tablet formulations of various batches (50 mg, 150mg, 200 mg, 300mg and 400 mg) showed acceptable physicochemical properties. Optimized formulations were selected from each batch was based on the evaluation parameters and drug release kinetics. The FTIR & DSC studies indicated absence of any interaction between Quetiapine Fumarate and polymers. The optimized formulations follows zero order release kinetics and showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.45 < n < 0.89$. The innovator product Seroquel XR tablets in different strengths shown to be followed first order release kinetics. From the release kinetic study it can be concluded that the drug release pattern of optimized formulations was controlled manner for 24 hours. The optimized formulation of C6 (200mg) was evaluated for its bioavailability compared with pure drug as reference standard. *In vivo* studies were carried out for 200mg tablets and the values of C_{max} and t_{max} clearly indicated that the drug release was controlled and maintained constant plasma concentration upto 24 hours after oral administration in comparison with pure drug. The results suggest that the developed extended-release tablets of Quetiapine Fumerate could perform therapeutically better than available dosage forms in the market.

KEYWORDS: Quetiapine Fumerate, wet granulation, *in vivo* studies, carboxy methyl ethyl cellulose, ethyl cellulose

KOTHAMASU SOMA SEKHAR
Department of Pharmaceutics, D.C.R.M. Pharmacy College, Inkollu–523167, Andhra Pradesh, India.

Corresponding author

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Extended-release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance[1]. By incorporating the dose for 24 h into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented[2]. This helps to avoid the side-effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy[3]. Controlled and sustained release products provide an immediate release of drug that promptly reduces the desired therapeutic effect, followed by a gradual release of additional amounts of drug to maintain this effect over a pre-determined period. Such a dosage form leads to the better management of the acute or chronic disease condition[4]. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing[5]. Cellulose derivatives, Eudragit and Carbopol are used as polymers in formulating controlled release matrix systems. There are various methods for preparing matrix tablets, namely direct compression, wet granulation, melt granulation, response surface methodology etc[6]. Schizophrenia is a chronic and disabling brain disease. It is a state of mental impairment marked by hallucinations. It is characterized by distorted perceptions of reality, hallucinations and illusions, delusions, disorder thinking, emotional expression. The main types of schizophrenia are Paranoid schizophrenia, disorganized schizophrenia (hebephrenic schizophrenia), Catatonic schizophrenia, Residual schizophrenia, schizoaffective disorder and undifferentiated schizophrenia[7,8]. Quetiapine fumarate (2-(2-(4-dibenzo [b, f] [1, 4] thiazepine-11-yl-1-piperzinyl) ethoxy)-ethanol) is an antagonist at serotonin 5-HT 1 and 5-HT 2, dopamine D 1 and D 2, histamine H1, and adrenergic alpha1 and alpha2 receptors. It is prescribed for the treatment of schizophrenia. It is a second generation antipsychotic[9]. To reduce the frequency of administration and to improve patient compliance, extended-release formulation of Quetiapine fumarate is desirable. In the present work, an attempt was made to develop extended-release matrix tablets of Quetiapine fumarate using hydrophilic matrix materials such as carboxy methyl ethyl cellulose and microcrystalline cellulose. The main objective of the study was to investigate the performance of several hydrophilic matrix systems prepared by CMEC and ethyl cellulose, controlling the release of Quetiapine fumarate for 24h.

MATERIALS AND METHODS

Materials

Quetiapine fumarate was generous gift from Matrix laboratories, Hyderabad. Ethyl cellulose, Carboxy methyl ethyl cellulose, Microcrystalline cellulose (MCC), Dibasic Calcium Phosphate, Magnesium stearate, Lactose Monohydrate were obtained free of charge from Hetero Labs Ltd, Hyderabad, India.

Methods

Formulation of tablets

Matrix tablets containing of different weight batches i.e.50mg, 150 mg, 200mg, 300 mg and 400mg of Quetiapine fumarate tablets were prepared by wet granulation technique. The composition of each batch was shown in Table 1, 2, 3, 4 & 5 respectively**.** All the components were screened and then thoroughly mixed in a bottle using tumbling method for a period of 15 min. The powder mix was granulated with 5% w/w alcoholic solution. The wet mass was passed through # 16 and the granules were dried at 50°C for 2 hrs in a hot air oven. The dried granules were passed through # 20 and lubricated with magnesium stearate by further blending for 3 min. Compression was done on 27 stations Rimek tablet compression machine using 8 mm punches. Film coating was done for the tablets which can modify the drug release profile.

Table 1
Composition of Quetiapine fumarate (50mg) extended release tablets

S. No	INGREDIENTS (mg)	A1	A2	A3	A4	A5	A6
	I) Dry Mix						
1	Quetiapine fumarate	57.60	57.60	57.60	57.60	57.60	57.60
2	Dibasic Calcium Phosphate	33.10	31.35	23.35	26.35	24.35	24.35
3	Lactose Monohydrate	21.75	19.00	17.00	15.00	15.00	13.00
4	Carboxy Methyl Ethyl cellulose	2.00	4.25	6.25	8.75	9.75	10.75
5	Ethyl Cellulose	2.00	4.25	6.25	8.75	9.75	10.75
	II) Granulation:						
6	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s
	III) Extra granulation						
7	Microcrystalline Cellulose	2.50	2.50	2.50	2.50	2.50	2.50
8	Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25
	Total weight of the tablet	**125.00**	**125.00**	**125.00**	**125.00**	**125.00**	**125.00**
	IV) Coating						
9	Carboxy Methyl Ethyl cellulose	1.92	1.92	1.92	1.92	1.92	1.92
10	Opadry	2.88	2.88	2.88	2.88	2.88	2.88
11	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s

Table 2
Composition of Quetiapine fumarate (150mg) extended release tablets

S.No	INGREDIENTS (mg)	B1	B2	B3	B4	B5	B6
	I) Dry mix						
1	Quetiapine fumarate	172.80	172.80	172.80	172.80	172.80	172.80
2	Dibasic Calcium Phosphate	89.05	89.05	84.05	79.05	75.05	71.05
3	Lactose Monohydrate	74.00	60.00	50.50	45.00	40.00	35.00
4	Carboxy Methyl Ethyl cellulose	6.75	13.50	20.25	26.25	30.75	35.25
5	Ethyl Cellulose	6.75	13.50	20.25	26.25	30.75	35.25
	II) Granulation						
6	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s
	III) Extra granulation						
7	Microcrystalline Cellulose	7.50	7.50	7.50	7.50	7.50	7.50
8	Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75
	Total weight of the tablet	**375.00**	**375.00**	**375.00**	**375.00**	**375.00**	**375.00**
	IV) Coating						
9	Carboxy Methyl Ethyl cellulose	5.76	5.76	5.76	5.76	5.76	5.76
10	Opadry	8.64	8.64	8.64	8.64	8.64	8.64
11	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s

Table 3
Composition of Quetiapine fumarate (200mg) extended release tablets

S.No	INGREDIENTS (mg)	C1	C2	C3	C4	C5	C6
	I) Dry Mix						
1	Quetiapine fumarate	230.40	230.40	230.40	230.40	230.40	230.40
2	Dibasic Calcium Phosphate	127.40	119.40	111.40	105.40	101.40	71.05
3	Lactose Monohydrate	90.10	80.00	70.00	60.00	55.00	50.00
4	Carboxy Methyl Ethyl cellulose	9.00	18.00	27.00	35.00	39.50	44.00
5	Ethyl Cellulose	9.00	18.00	27.00	35.00	39.50	44.00
	II) Granulation						
6	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s
	III) Extra granulation						
7	Microcrystalline Cellulose	10.00	10.00	10.00	10.00	10.00	10.00
8	Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00
	Total weight of the tablet	**500.00**	**500.00**	**500.00**	**500.00**	**500.00**	**500.00**
	IV) Coating						
9	Carboxy Methyl Ethyl cellulose	7.68	7.68	7.68	7.68	7.68	7.68
10	Opadry	11.52	11.52	11.52	11.52	11.52	11.52
11	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s

Table 4
Composition of Quetiapine fumarate (300mg) extended release tablets

S.No	INGREDIENTS (mg)	D1	D2	D3	D4	D5	D6
	I) Dry mix						
1	Quetiapine fumarate	345.60	345.60	345.60	345.60	345.60	345.60
2	Dibasic Calcium Phosphate	188.10	178.10	168.10	158.10	148.10	143.10
3	Lactose Monohydrate	130.0	115.00	95.00	90.00	90.00	80.00
4	Carboxy Methyl Ethyl cellulose	15.00	30.00	45.00	52.50	57.50	62.50
5	Ethyl Cellulose	15.00	30.00	45.00	52.50	57.50	62.50
	II) Granulation						
5	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s
	III) Extra granulation						
6	Microcrystalline Cellulose	15.00	15.00	15.00	15.00	15.00	15.00
7	Magnesium stearate	7.50	7.50	7.50	7.50	7.50	7.50
	Total weight of the tablet	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**	**750.00**
	IV) Coating						
8	Carboxy Methyl Ethyl cellulose	11.52	11.52	11.52	11.52	11.52	11.52
9	Opadry	17.28	17.28	17.28	17.28	17.28	17.28
10	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s

Table 5
Composition of Quetiapine Fumerate (400mg) extended release tablets

S. No	INGREDIENTS (mg)	E1	E2	E3	E4	E5	E6
	I) Dry Mix						
1	Quetiapine fumarate	460.80	460.80	460.80	460.80	460.80	460.80
2	Dibasic Calcium Phosphate	270.80	240.80	230.80	210.80	190.80	180.80
3	Lactose Monohydrate	140.00	140.00	130.00	120.00	120.00	110.00
4	Carboxy Methyl Ethyl cellulose	30.00	45.00	60.00	70.00	80.00	90.00
5	Ethyl Cellulose	30.00	45.00	60.00	70.00	80.00	90.00
	II) Granulation						
6	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s
	III) Extra granulation						
7	Microcrystalline Cellulose	20.00	20.00	20.00	20.00	20.00	20.00
8	Magnesium stearate	10.00	10.00	10.00	10.00	10.00	10.00
	Total weight of the tablet	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**
	IV) Coating						
9	Carboxy Methyl Ethyl cellulose	15.36	15.36	15.36	15.36	15.36	15.36
10	Opadry	23.04	23.04	23.04	23.04	23.04	23.04
11	IPA + water	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of Quetiapine fumarate extended release tablets

The following physical parameters were evaluated

Thickness

The thickness of a tablet was the only dimensional variable related to the process.10 tablets were measured for their thickness and diameter with vernier calipers. Average thickness and diameter were calculated[10].

Weight variation

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weighs to the average. The tablets met the UP test that there were no more than 2 tablets were outside the percentage limit and no tablet differed by more than 2 times the percentage limit[10].

Hardness

Hardness of the tablets was determined by breaking it between the second and third fingers with thumb being as a fulcrum. There was “sharp” snap, the tablet was deemed to have acceptable strength. Hardness of the tablets is also determined by Stokes Monsanto hardness tester and the hardness should found within the range of 3-15 kg/cm² [11]. The friability of tablets is determined by Roche fribilator, 20 tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and

subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets from a distance of six inches with each revolution. After operation the tablets were dedusted and reweighed.

Friability is determined by
F=100 (1-W0/Wt)
Where,
W0 = Wt of tablets before friability test.
Wt = Wt of tablets after friability test[11].

Content uniformity

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 20, 25, 30 and 40 mg drug (100 mg) was extracted with 100 mL of 0.1 N Hydrochloric acid and sonicated for 15 minutes. The solution was filtered through a 0.22 µm PVDF syringe filter SLGV Millipore, properly diluted with 0.1 M hydrochloric acid, and then the drug content was measured.

Dissolution studies

The *in vitro* dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 750 ml of 0.1N HCl (pH 1.2) for first 2 hours and then 900 ml of phosphate buffer (pH 6.2) from 3 to 24 h. The dissolution medium was kept in thethermostatically controlled water bath, maintained at 37±0.5 ^{0}C. Basket rotation was adjusted to 100 rpm. At definite intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 276 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

Kinetic modeling of drug release

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

$Mt = M0 + k0t$ (1)

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

$Mt = M0 – kHt1/2$ (3)

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

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

DRUG EXCIPIENT COMPATABILITY STUDIES

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, HPMC E15, Maltodextrin, Drug and HPMC mixture and optimized formulation. Accurately weighed samples were placed on aluminum plate, sealed with aluminum lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

Stability studies

The stability of Quetiapine fumarate extended release tablets of various strengths (50, 150, 200, 300 & 400 mg) to assess their stability with respect to their physical appearance, drug content and release characteristics after storing at 25°C/60% RH and 40°C/75% RH in properly

closed HDPE bottles along with 1 g desiccant for 6 months[14].

Pharmacokinetic Studies of Quetiapine fumarate

Animal Preparation

The extended release tablet of Quetiapine fumarate 200mg strength was chosen for the bioavailability study. Six male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25^0C, Relative Humidity 45% and 12 h alternate light and dark cycle] with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee

(IAECNO: P8/VCP/IAEC/2012/03/DBP/AE5/RABBITS/M9). The rabbits were fasted overnight before the administration of formulation (ER tablet contain Quetiapine fumarate 0.1mg) and reference standard (Quetiapine fumarate). The rabbits were randomly divided into two groups each group contains three animals. The group A rabbits were received Quetiapine fumarate ER tablets and group B received pure drug administered orally. Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24hrs after dosing. Blood samples were collected in heparinized tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) was prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was resuspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200 μ1 of 70 % of acetonitrile and 30% water was injected for HPLC analysis.

Table 6
Chromatographic conditions

Column	C18
Mobile Phase	Acetonitrile: water (40:60)
Flow rate	1mi/min
Injection volume	20μl
Retention time	2.817
Temperature	Ambient

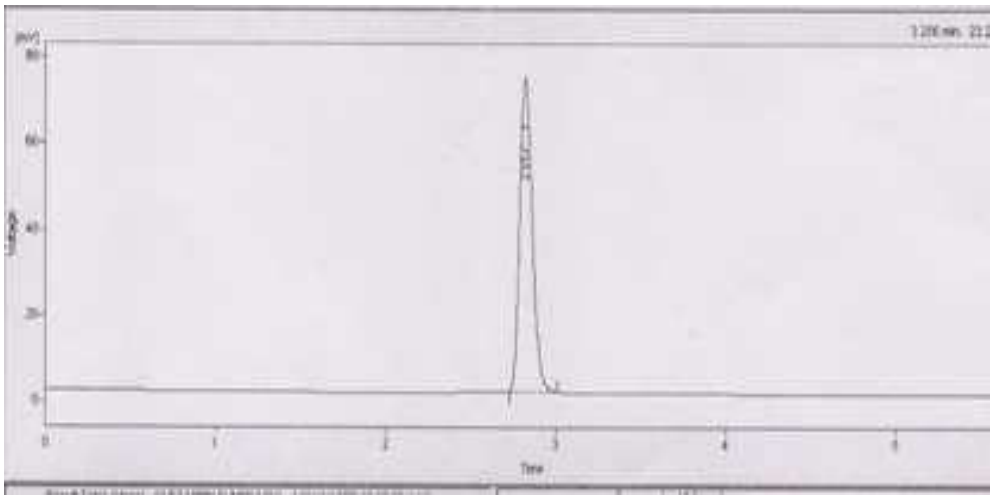

Figure 1
Standard chromatogram of Quetiapine fumarate

Table 7
Standard calibration curve of Quetiapine fumarate

S. No	Concentration(µg)	Area
1	10	186.972
2	20	375.944
3	30	560.916
4	40	795.888
5	50	926.86
6	60	1121.832

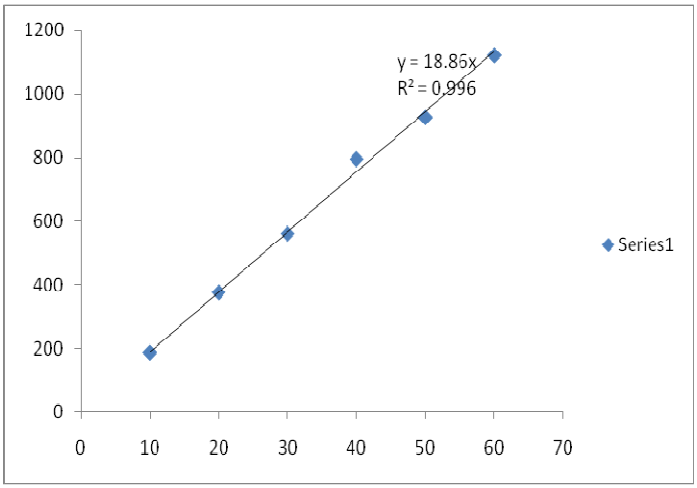

Figure 2
Standard calibration curve of Quetiapine fumarate in rabbit plasma by HPLC

RESULTS AND DISCUSSION

Evaluation of Tablets

The data of physical parameters such as hardness, thickness, weight variation, friability, content uniformity of all the optimized formulations are included in the Table 8**.** All the parameters lie within the limits.

Table 8
Physical parameters of extended release tablets of Quetiapine fumarate optimized formulations (50, 150, 200, 300 & 400mg)

Formulation	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content Uniformity (mg/tab)
A6	124±0.7	9.2±0.13	3.3±0.02	0.54±0.01	99.69±0.45
B6	375±0.5	9.4±0.15	3.4±0.03	0.58±0.02	98.76±0.41
C6	500±0.6	9.6±0.13	3.9±0.02	0.57±0.01	99.90±0.38
D6	750±0.8	10±0.14	4.2±0.04	0.65±0.03	99.80±0.42
E6	1000±0.7	9.8±0.16	4.3±0.03	0.68±0.01	99.79±0.39

In vitro Dissolution study

The dissolution study on optimized Formulations No.A6, B6, C6, D6 and E6 were carried out using 0.1N HCl (pH 1.2) for first 2 hours and then phosphate buffer (pH 6.2) was used from 3 to 24 h. The dissolution graphs for all the formulations with different strengths like 50, 150, 200, 300 & 400mg are shown in Fig. No. 3-7 respectively, From this study, an important conclusion can be drawn that by using hydrophilic polymers like CMEC & EC in combination in increasing quantity, it extended release pattern of drug to sufficient level results are shown in Table 9, which helps to shown maximum therapeutic effect.

Table 9
Dissolution profile of optimized Quetiapine fumarate extended release tablets (50, 150, 200, 300 & 400mg)

	Cumulative % of drug release				
TIME (hrs)	**A6**	**B6**	**C6**	**D6**	**E6**
0	0	0	0	0	0
1	18.80	25.81	27.00	28.01	29.80
2	28.42	32.15	32.50	33.85	34.10
4	33.71	37.84	41.10	41.28	42.80
6	38.31	45.78	47.80	48.41	50.40
8	45.80	53.21	53.80	54.29	57.80
12	54.31	60.89	64.51	61.88	65.90
16	64.31	76.12	75.42	74.81	82.31
20	75.21	83.45	85.30	85.85	91.55
24	94.96	95.50	96.53	97.80	95.80

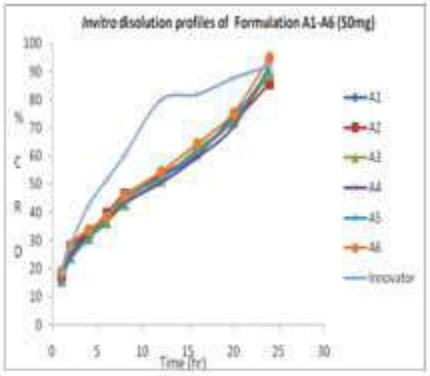

Figure 3: Drug release profiles formulation A1-A6 with Seroquel 50mg XR tablet

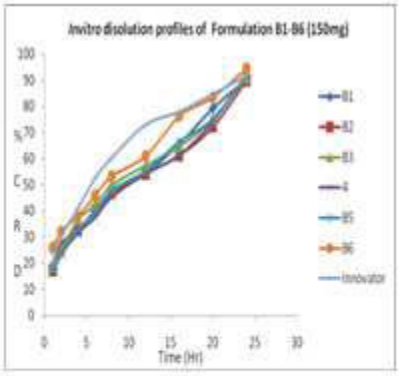

Figure 4: Drug release of profiles formulationB1-B6 Seroquel 150mg XR tablet.

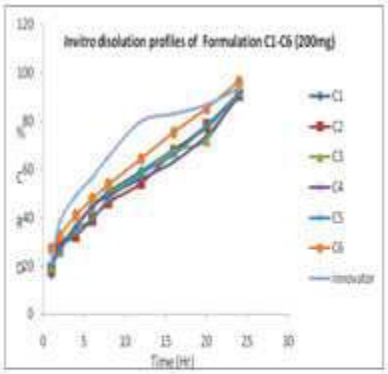

Figure 5: Drug release profiles of formulation C1-C6 with Seroquel 200mg XR tablet.

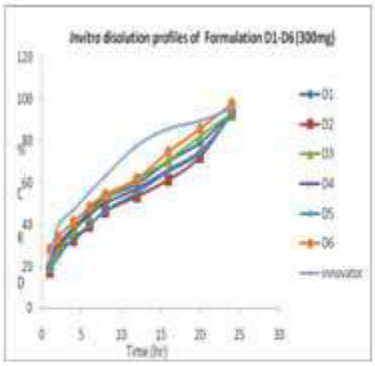

Figure 6: Drug release profiles of formulation D1-D6 with Seroquel 300mg XR tablet.

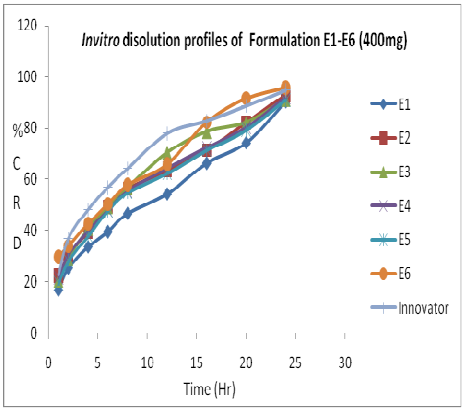

Figure 7
Drug release profiles of formulation E1-E6 with Seroquel 400mg XR tablet

Kinetic modeling of drug release

To study the release kinetics of Quetiapine fumarate extended release tablets, the goodness-of-fit method was applied and different kinetic equations were applied to interpret the release rate from the matrices. In the present study, The best formulations A6, B6, C6, D6 and E6 were achieved by using polymers such as CMEC & EC in the different ratios was able to prolong the drug release for about 24hrs. Percent release of drug at the end of twenty four hour for A-6, B-6, C-6, D-6 and E-6 were 94.96%, 95.50, 96.53, 97.89 and 95.80 respectively (Table 9). These values clearly indicated the decrease of drug release as a consequence of increase of polymer. The linear nature of the curves obtained for zero-order, first order, Higuchi model and Hixon - Crowel model as demonstrated by very close and higher R^2 values suggests that the release from the formulations may follow any one of these models. When the higher correlation coefficient values are considered, the release data seem to best fit with the Higuchi model and first order kinetics. R^2 values obtained from zero order equation for A-6, B-6, C-6, D-6 and E-6 were 0.990, 0.990, 0.992, 0.993 and 0.980 respectively (Table 10 & Figure 8-32). The best linearity was found in Higuchi's equation plot 0.975, 0.985, 0.990, 0980 and 0.988 (Table 10 & Figure 8-32) respectively indicating the release of drug from matrix as a square root of time dependent process based on diffusion. The n values for korsmeyer and peppas equation for A-6, B-6, C-6, D-6 and E-6 were found to be 0.463, 0.503, 0.474, 0.467 and 0.468 respectively (Table 10 & Figure 8-32).. The prepared hydrophilic tablet formulations showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.45 < n < 0.89$ (Table 10 & Figure 8-32). Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion. The kinetic parameters of innovator product SEROQUEL in different strengths was studied and found to follow by first order release kinetics (Table 11).

Table 10

Kinetic parameters of Quetiapine fumarate extended release tablets (A6,)

Formulation	Zero Order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope
A6	0.990	2.796	0.927	-0.034	0.975	16.70	0.960	0.463	0.952	0.086
B6	0.990	2.910	0.932	-0.045	0.985	17.46	0.987	0.503	0.963	0.105
C6	0.992	2.915	0.898	-0.059	0.990	17.52	0.994	0.474	0.954	0.112
D6	0.993	2.895	0.848	-0.056	0.980	17.30	0.977	0.467	0.933	0.117
E6	0.9880	2.955	0.964	-0.054	0.988	17.84	0.988	0.468	0.974	0.118

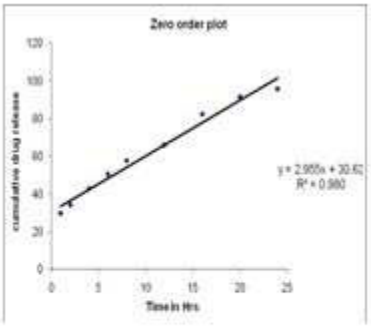

Figure 8: Zero- order release model of Quetiapine fumarate ER formulation (A6)

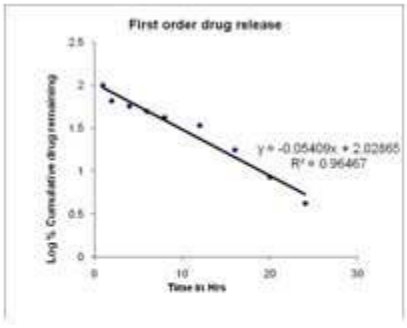

Figure 9: First-order release model of Quetiapine fumarate ER formulation(A6)

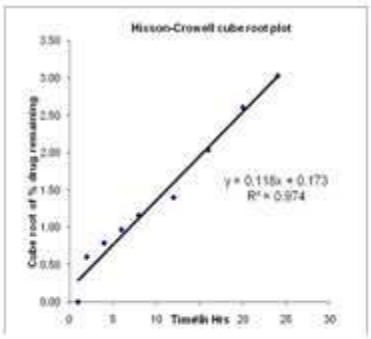

Figure 10: Hixson-Crowell cube root plot model of extended Quetiapine fumarate ER formulation (A6)

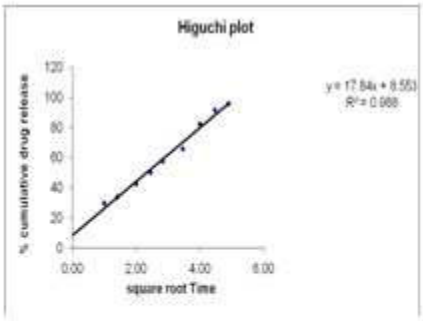

Figure 11: Higuchi plot of Quetiapine Fumarate ER formulation (A6)

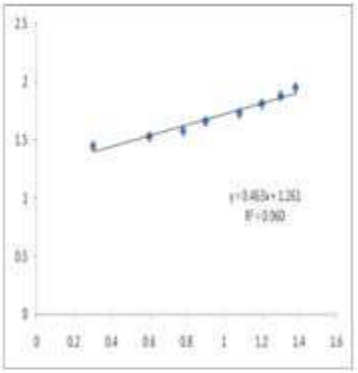

Figure12: Korsmeyer-peppas plot of Quetiapine fumarate ER formulation (A6)

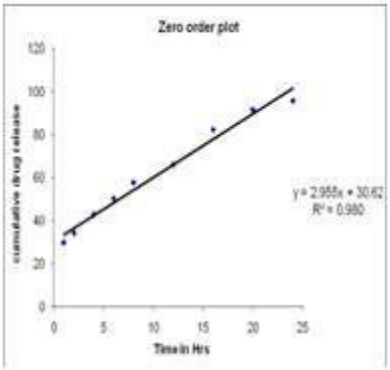

Figure13: Zero-order release model of Quetiapine fumarate ER formulation (B6)

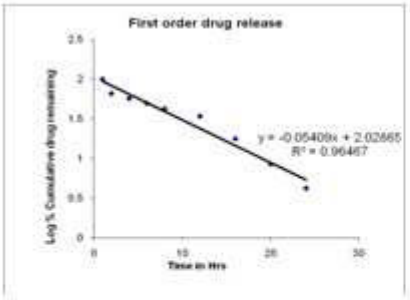

Figure14: First-order release model of Quetiapine fumarate ER formulation (B6)

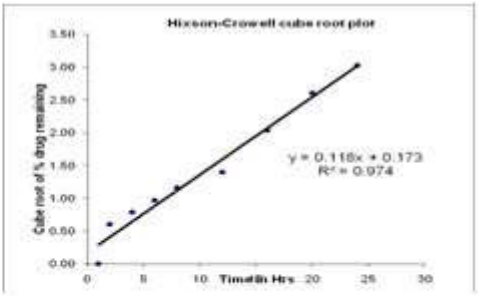

Figure 15: Hixson-Crowell cube root plot model of Quetiapine fumarate ER formulation (B6)

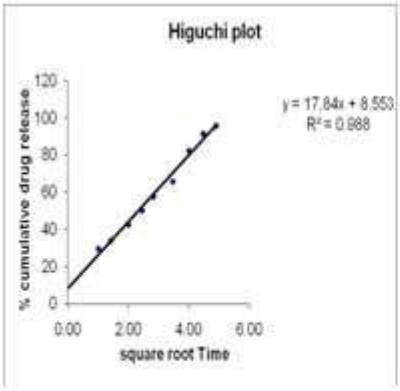

Figure 16: Higuchi plot of Quetiapine fumarate ER formulation (B6)

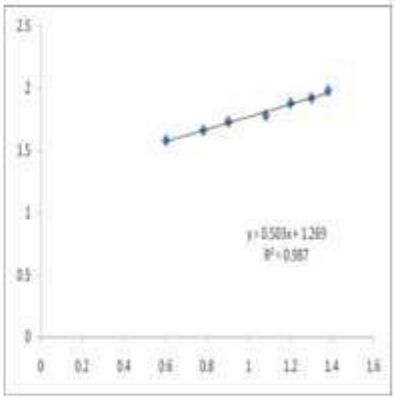

Figure17: Korsmeyer-peppas plot of Quetiapine fumarate ER formulation (B6)

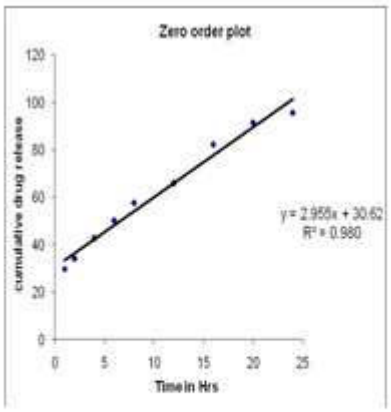

Figure 18: Zero-order release model of Quetiapine fumarate ER formulation (C6)

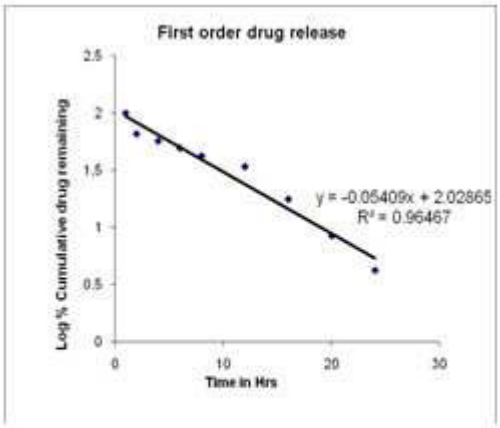

Figure 19: First order release model of Quetiapine fumarate ER formulation (C6)

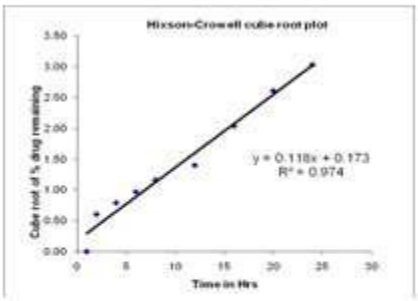

Figure 20: Hixson-Crowell cube root plot model of Quetiapine Fumarate ER formulation (C6)

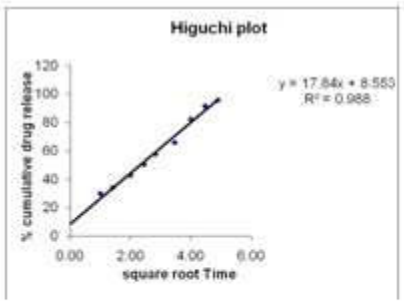

Figure 21: Higuchi plot of Quetiapine Fumarate ER formulation (C6)

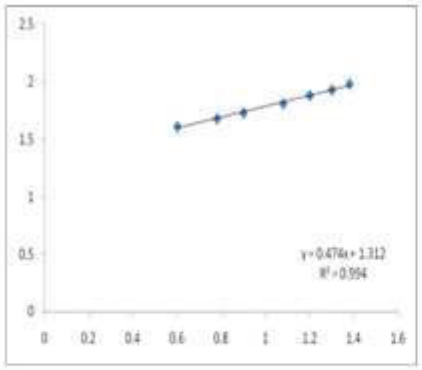

Figure 22: Korsmeyer-peppas plot of Quetiapine fumarate ER formulation (C6)

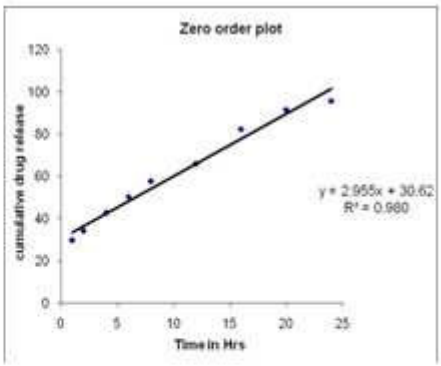

Figure 23: Zero-order release model of Quetiapine fumarate ER formulation (D6)

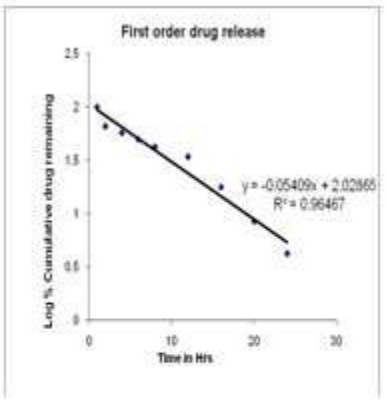

Figure 24: First-order release model of Quetiapine fumarate ER formulation (D6)

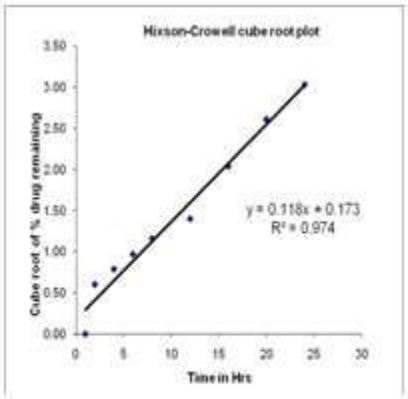

Figure 25: Hixson-Crowell cube root plot model of Quetiapine fumarate ER formulation (D6)

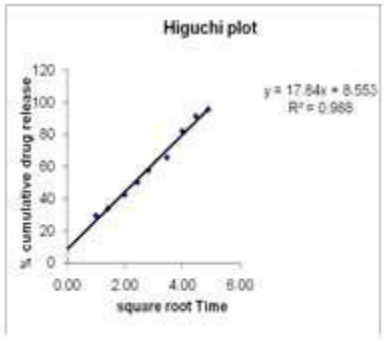

Figure 26: Higuchi plot of Quetiapine fumarate ER formulation (D6)

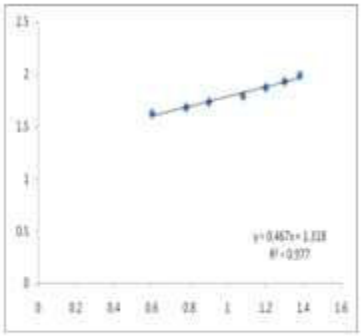

Figure 27: Korsmeyer-peppas plot of Quetiapine fumarate ER formulation (D6)

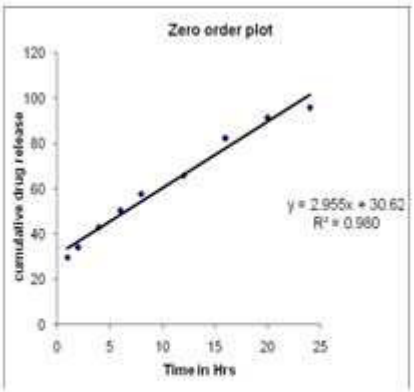

Figure 28: Zero-order release model of Quetiapine fumarate ER formulation (E6)

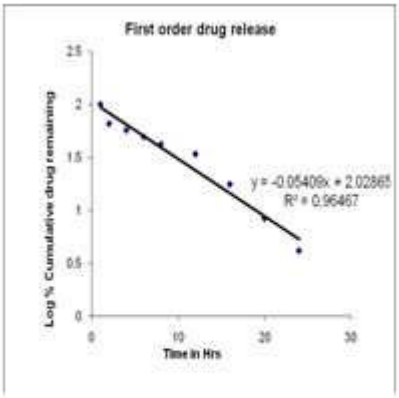

Figure 29: First-order release model of Quetiapine fumarate ER formulation (E6)

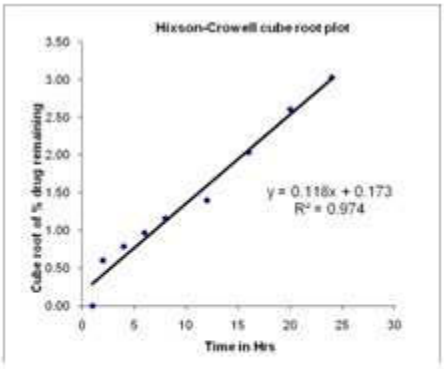

Figure 30: Hixson-Crowell cube root plot model of Quetiapine fumarate ER formulation (E6)

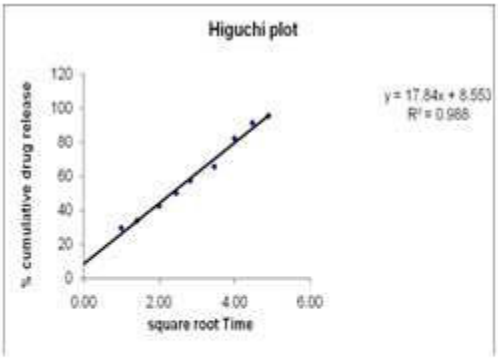

Figure 31: Higuchi plot of Quetiapine fumarate ER formulation (E6)

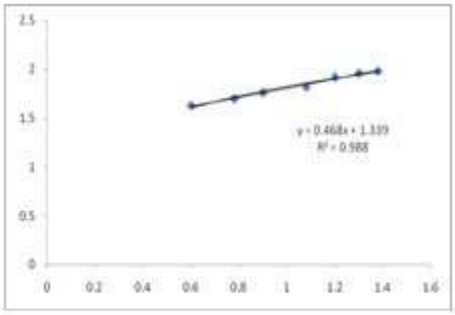

Figure 32: Korsmeyer-peppas plot of Quetiapine fumarate ER formulation (E6)

Table 11
Kinetic parameters for innovator product SEROQUEL 50, 150, 200, 300 & 400 mg XR tablets

Formulation	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Korsmayer-Peppas model	
				r^2	"n" value
SEROQUEL 50 XR	0.891	0.980	0.971	0.970	0.464
SEROQUEL 150 XR	0.920	0.980	0.987	0.983	0.447
SEROQUEL 200 XR	0.874	0.966	0.963	0.978	0.378
SEROQUEL 300 XR	0.915	0.981	0.982	0.989	0.406
SEROQUEL 400 XR	0.902	0.976	0.979	0.992	0.406

DRUG EXCIPIENT COMPATABILITY STUDIES
FT-IR studies

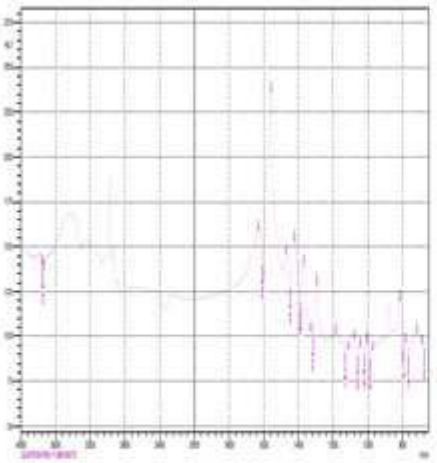

Figure 33: FTIR spectrum Quetiapine Fumarate

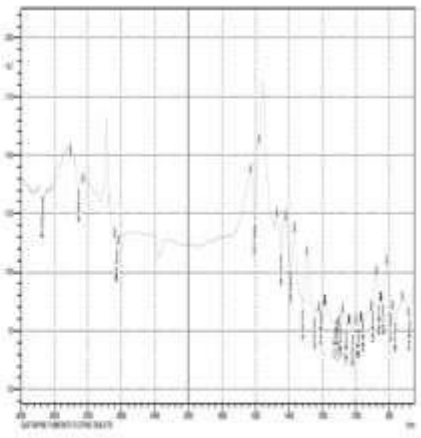

Figure 34: FTIR spectrum of optimized formulation

In order to get evidence on the possible interactions of drug with excipients, FTIR analysis was used. The FTIR spectrum of the pure drug was shown in Figure 33 and the FTIR spectra of optimized formulation (Figure 34) displayed the characteristic peaks of both drug and polymers. Overall there

was no alteration in the characteristic peaks of Quetiapine fumarate suggesting that there was no interaction between the drug and polymer.

Differential Scanning Calorimetry (DSC)

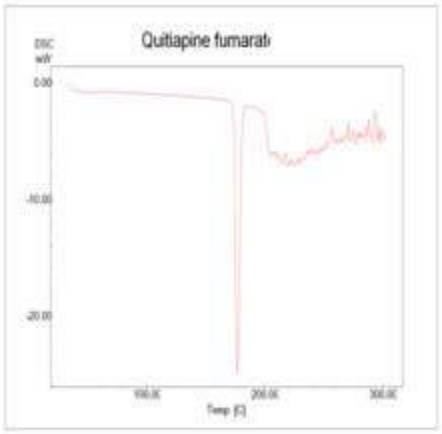

Figure 35: DSC Thermo gram of Quetiapine Fumarate

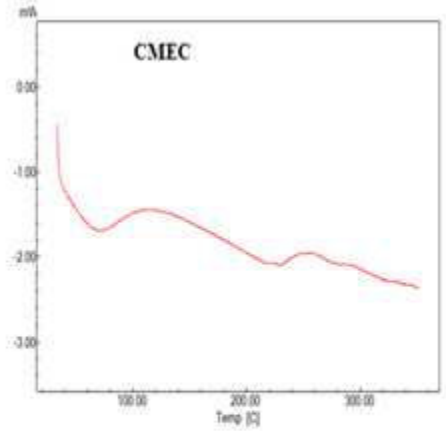

Figure 36: DSC Thermo gram of Carboxy Methyl Ethyl Cellulose

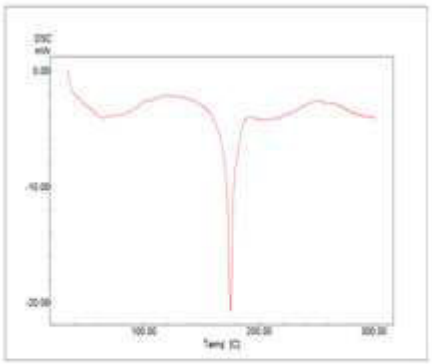

Figure37: DSC Thermo gram of optimized formulation

DSC was used to detect interactions between Quetiapine fumarate and other excipients. DSC results revealed that the melting point of the pure drug Quetiapine fumarate was 173.94, CMEC 50^{o}C and optimized formulation 170.3^{o}. There is no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there is no interaction between drug and other excipients used in the formulation.

Stability Studies for optimized formulations of Quetiapine Fumarate with various strengths

The formulations after storing at 25°C/60% RH and 40°C/75% RH for 6 months, no significant change was observed in physical parameters like hardness, friability, drug content and in vitro dissolution profile. The results indicated that all the optimized formulations were stable.

Bioavailability studies

Table 12
Plasma levels of Quetiapine fumarate ER Tablets and pure drug at different time intervals (Mean ± SD, n = 3)

Time (min)	Quetiapine fumarate ER Tablets	
	Quetiapine fumarate ER Tablets	Pure drug (Standard)
1	100±11.2	170±15.8
2	230±18.3	314±10.4
4	350±24.2	380±22.5
6	400±16.2	264±16.3
8	500±23.5	174±14.8
12	430±16.3	22±17.6
16	350±18.3	12.4±15.3
20	300±15.2	0
24	170±16.3	0

Table 13
Comparison of pharmacokinetic parameters of Quetiapine Fumarate ER Tablets and reference standard (oral solution of the pure drug) in Rabbits (Mean ± SD, n = 3)

Parameters	Quetiapine fumarate ER Tablets	Pure drug (Reference)
Dose (mg/kg)	0.1	0.1
Cmax (ng/ml)	920±13.5	750±23.5
AUC 0-t (µg.hr/ml)	6708.24±400.44	5098.26±368.24
AUC 0-inf (µg.hr/ml)	9236.84±468.22	7022.14±3396.23
Tmax (h-1)	8	4
t 1/2 (h)	12.5±3.124	6.25±2.665
K el (h-1)	0.68±0.05	0.5168±0.002
MRT(h)	33.6±544	24.76±264

Bioavailability Parameters

The mean Quetiapine fumarate plasma concentrations - time profiles for the prepared Quetiapine fumarate ER Tablets and the pure drug Quetiapine fumarate are shown in Table 12. The bioavailability parameters for the both formulations are summarized in Table 13. The statistical comparison of C_{max}, t_{max}, AUC0–∞ and AUC0–t indicated a significant difference between the two treatments, there is a significant difference for the period effect was observed in this study. Based on the statistical inferences it was concluded that the two formulations exhibited significantly different plasma level-time profiles. *In vivo* study indicated significance difference between ER tablet and pure drug, both exhibited significantly different drug plasma level - time profiles. Therefore, the present Quetiapine fumarate containing ER tablet is considered to be potentially useful for the treatment of antipsychotic effect where improved patient compliance and convenience is expected.

CONCLUSION

Systematic studies were conducted on Quetiapine fumarate extended release tablets with various strengths like 50, 150, 200, 300 & 400 mg. All the formulations were evaluated for different properties. The best formulations A6, B6, C6, D6 and E6 was achieved by using polymers such as CMEC and Ethyl cellulose in 1:1 ratio by wet granulation method was able to prolong the drug release for about 24hrs. The drug release pattern from the optimized formulations of A-6 (50mg), B-6(50mg), C-6(50mg), D-6 (50mg) and E-6(50mg) were found to be 94.96%, 94.50%, 96.53%, 97.89% and 95.80% respectively. The optimized formulations follows zero order release kinetics and showed non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation, $0.45 < n < 0.89$. Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion. The

innovator product Seroquel XR tablets in different strengths shown to be followed first order release kinetics. From the release kinetic study it can be concluded that the drug release pattern of optimized formulations was controlled manner for 24 hours. *In vivo* studies were performed in rabbits and the values of C_{max} and t_{max} clearly indicated that the drug release was controlled and maintained constant plasma concentration upto 24 hours after oral administration in comparison with pure drug.

REFERENCES

1. Pogula M, Nazeer S Extended release formulation. Int J Pharm Tech, 2: 625–84, (2010).
2. Fyhr P, Downie K, Extended release drug delivery technology. Innov Pharm Tech, 3: 80–86, (2003).
3. Vijay J, Sahadevan JT and Mehra Gilhotra R, Formulation and Evaluation of Cephalexin Extended-release Matrix Tablets Using Hydroxy Propyl Methyl Cellulose as Rate-controlling Polymer. J Young Pharm, 4(1): 3–12, (2012).
4. Harinatha Reddy P, Pragati Kumar B, Duraivel S, Formulation And Evaluation Of Sustained Release Tablets Of Quetiapine Fumarate. Journal of Chemical and Pharmaceutical sciences, JCPS 5 (4): 181-184, (2012).
5. Leon lachman, Joseph L. Kanig: The theory and practice of industrial pharmacy. 3rd edn, 1990, 71, 88, 183, 299, 316, 430-456,386-392.
6. Udaya S. Toti, Tejraj M. Aminabhavi, Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride. Journal of Controlled Release, 95(3): 567-577, (2004).
7. Arvanitis LA, Miller BG, Seroquel Trial 13 Study Group. Multiple fixed doses of 'Seroquel' (Quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biological Psychiatry, 42(4): 233-46, (1997).
8. Borison RL, Arvanitis LA, Miller BG, Study-Group. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol, 16(2): 158-69, (1996).
9. Hamner MB, Arvanitis LA, Miller BG, Link CGG, Hong WW, Plasma prolactin in schizophrenia subjects treated with Seroquel TM (ICI 204,636). Psychopharmacology Bull, 32(1): 107-110, (1996).
10. Rippe E, Compression of solid and compressed dosage forms. In: Encyclopedia of pharmaceutical technology. Swarhrick, J.Marcel Dekker. Inc., 149-166, (1990)
11. Pharmacopoeia of India. Ministry of health and family welfare. Govt. of India, Controller of publications, vol.II., 736; A-80-83, 147 and 169, (1996)
12. Higuchi, T., Mechanism of Sustained Action Medication: Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices. J. Pharm. Sci, 52: 1145-1149, (1963).
13. Hamid A. Merchant, Harris M. Shoaib, Jaweria Tazeen and Rabia I. Yousuf. Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxy propyl methylcellulose: A technical note. AAPS PharmSciTech 7: E1 – E6, (2006).
14. S. B. Tiwari, T. K. Murthy, R. M. Pai, P. R. Mehta and P. B. Chowdary, “Controlled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix System,” *AAPS PharmSciTech*, Vol. 4, No. 3: 18-23, (2003).