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Development and *in vitro* evaluation of Quetiapine Fumarate Sustain release tablets

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Abstract: The main objective of the present work was to develop sustained release matrix tablets of quetiapine fumarate using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and PVP K30. Varying ratios of drug and polymer like were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of two different rate controlling material. After evaluation of physical properties of tablet, the in vitro release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Dissolution data was analysed by Higuchi expression. It was observed that matrix tablets contained polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs. Among all the formulations, formulation QFSRT/08 which contains 60% HPMC K15M and 06% of PVP K30 release the drug which follow Higuchi kinetics via, swelling, diffusion and erosion and the release profile of formulation QFSRT/08 was comparable with the prepared batch products. Stability studies (40±2ºC/75±5%RH) for 6 months indicated that quetiapine fumarate was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.
Keywords: Quetiapine Fumarate, HPMC K 15 M, PVP K30, Matrix tablets, Higuchi Model.

INTRODUCTION

In matrix devices, the drug is homogeneously dispersed in either a hydrophobic or hydrophilic polymer matrix. The release rate from matrix systems remains unaffected by thin spots, pinholes, and other similar defects, which can be a serious problem with reservoir systems[(1)]. Hydroxypropyl methylcellulose (HPMC), a semi synthetic derivative of cellulose, has its popularity for the formulation of sustained release (SR) dosage forms as a swellable and hydrophilic polymer[(2-3)]. Its non-toxic property, ease of handling, ease of compression, ability to accommodate a large percent of drug, negligible influence of the processing variables on drug release rates, and relatively simple tablet manufacturing technology make it an excellent carrier material. Various formulation factors influence the drug release form HPMC matrices, viz., polymer viscosity, polymer particle size, drug/polymer ratio, drug solubility, drug particle size, drug loading, compression force, tablet shape, formulation excipients, coatings, processing techniques, as well as the testing medium.

The goal of antipsychotic drug development efforts over the past 10 years has been to develop agents with increased efficacy and safety and fewer of the side effects commonly associated with the older

antipsychotic medications. The newer agents, often called atypical antipsychotics, are effective in treating both the positive and negative symptoms of schizophrenia and are associated with fewer neurological- and endocrine-related side effects compared to the older agents[4]. Quetiapine fumarate is the most recently introduced atypical antipsychotic and is indicated for the management of the manifestations of psychotic disorders and schizophrenia. Further, quetiapine's pharmacological effects appear selective for the mesolimbic and mesocortical dopamine systems, which are believed to be the areas of the brain responsible for the therapeutic effects of antipsychotics. In contrast to most standard antipsychotics and some atypical antipsychotics, quetiapine's effects on the nigrostriatal dopamine system, which is responsible for the extrapyramidal (or motor) side effects, are minimal. Quetiapine also has minimal activity on dopamine receptors in the tuberoinfundibular dopamine system, thereby avoiding the problem of hyperprolactinemia, common with the standard antipsychotics and some atypical antipsychotics. Because of these properties, quetiapine is an effective antipsychotic agent with a relatively benign side effect profile. Patients on long-term treatment report high compliance, good satisfaction, increased ability to function and improvements consistent with a better quality of life. Because of quetiapine's excellent tolerability profile, its use is particularly appropriate in patients especially sensitive to adverse effects, e.g., elderly patients with psychotic symptoms and other neurological disorders such as Parkinson's and Alzheimer's disease[4-8].

However, no literature was found on the use of HPMC polymer as a tablet matrix forming material for the development of sustained release formulations of quetiapine fumarate. In light of the above discussion, the objective of this study was to formulate sustained release oral tablet formulations of quetiapine fumarate by matrix embedding technique using HPMC polymer as a retardant material.

Table 1: Formulation of sustained release tablets of quetiapine fumarate

Ingredients (mg per Tablet)	QFSRT/ 01	QFSRT /02	QFSRT /03	QFSRT /04	QFSRT /05	QFSRT /06	QFSRT /07	QFSRT /08	QFSRT /09
Quetiapine Fumarate	236.524	236.524	236.524	236.524	236.524	236.524	236.524	236.524	236.524
Lactose	59.131	59.131	59.131	59.131	-	-	-	-	-
Microcrystalline Cellulose	-	-	-	-	47.305	59.131	59.131	59.131	59.131
PVP - K30	9.460	9.460	-	14.191	14.191	14.191	14.191	14.191	16.55
HPMC	-	-	70.957	70.957	70.957	70.957	82.7834	94.60	94.60
Silicon Dioxide	2.365	2.365	2.365	2.365	2.365	2.365	2.365	2.365	2.365
Talcum	4.730	4.730	4.730	4.730	4.730	4.730	7.095	7.095	7.095
Magnesium Stearate	1.182	1.182	1.182	1.182	1.182	2.3652	4.730	5.913	5.913
Iso Propyl Alcohol	-	Q.S.	-	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Water	-	-	Q.S.	-	-	-	-	-	-

MATERIALS AND METHODS

Materials:

Quetiapine Fumarate was donated by IPCA Laboratories, India, hydroxypropyl methylcellulose by Colorcon Asia, India, PVP K30 (Noveon, Inc., USA.) and Magnesium Stearate by Zydus Cadila, India. All other chemicals and reagents used were of analytical grade and purchased from Merck Ltd., India.

Methods

Formulation of matrix tablets Matrix tablet containing 100mg equivalent weight of Quetiapine Fumarate were prepared by wet granulation technique. The composition of each tablet is shown in table 1. All the components were screened and then thoroughly mixed in a bottle using tumbling method for a period of 15 mins. The powder mix was granulated with iso propyl alcohol. 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 mins and finally talc was added to the blend. Compression was done on 10 station Ratnakar tablet compression machine (M/s Ratnakar Engg. Ltd. Ahemadabad) using 10 mm punches.

Evaluation of tablets

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and stability studies. Pfizer hardness[9] tester was used for the determination of the hardness. In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 3 tablets was evaluated. The crown-to-crown thicknesses of twenty tablets from each batch were determined using vernier calipers. The Friability[9] of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W0 / W) \times 100$$

Where,

W_0 is the weight of the tablets before the test and

W is the weight of the tablet after the test.

For determination of drug content at least three tablets from each formulation were weighed individually, pulverized, and diluted to 250ml with sufficient amount of phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analysed spectrophotometrically at 242nm. In vitro drug release studies for the prepared matrix tablets were conducted for a period of 12 hrs using a 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at 37±0.5°C and at 100 rpm speed, the in vitro release study was performed in 0.1 N HCL pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. At every interval 10 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 242 nm for Quetiapine Fumarate by a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated.

Stability Studies

The stability study[10] of the tablets QFSRT/07 & QFSRT/08 were carried out according to ICH guidelines at 2±2°C, 25±2°C/60±5% RH, 30±2°C/65±5% RH, 40±2°C/75±5% RH, 55±2°C for one, three & six months by storing the samples in (Stablab, Mumbai) stability chamber.

FTIR Studies

IR spectra for Quetiapine fumarate[11] and formulation QFSRT/08 tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA.) with KBr pellets.

DSC Studies

DSC scans of about 5mg; using an automatic thermal analyser system performed accurately weighed Quetiapine Fumarate and tablet containing the same amount of drug. (DSC 60, Shimadzu, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C.

RESULTS AND DISCUSSION

Precompressional parameters of granules shows (Table 2), angle of repose (25.563 to 39.811), % compressibility (05.431 to 26.931%), and Hausner's ratio (1.057 to 1.369) are in the range given in official standards. Table 3 shows post compressional parameters i. e. hardness (5.06 to 6.52 kg/cm^2), friability (0.317 to 1.497 %), weight variation (0.128 to 0.540) and thickness (5.30 to 5.42 mm). Drug content was (99.189 to 99.649%) within the acceptable official limits.

Table 2 - Precompressional parameters of granules

Formulations Code	Angle of repose (Degrees)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner ratio	Compressibility Index (%)
QFSRT/01	30.452 ± 1.382	0.662 ± 0.004	0.906 ± 0.005	36.858 ± 0.460	1.369 ± 0.005	26.931 ± 0.246
QFSRT/02	32.113 ± 1.370	0.523 ± 0.004	0.572 ± 0.013	09.367 ± 2.343	1.094 ± 0.023	08.536 ± 1.981
QFSRT/03	28.307 ± 1.612	0.619 ± 0.004	0.735 ± 0.014	18.906 ± 2.682	1.187 ± 0.027	15.871 ± 1.922
QFSRT/04	26.740 ± 1.323	0.581 ± 0.003	0.677 ± 0.007	16.488 ± 1.561	1.165 ± 0.016	14.144 ± 1.156
QFSRT/05	33.808 ± 1.224	0.567 ± 0.002	0.673 ± 0.003	16.818 ± 0.731	1.168 ± 0.007	14.394 ± 0.535
QFSRT/06	39.811 ± 0.908	0.576 ± 0.002	0.656 ± 0.002	14.005 ± 0.408	1.140 ± 0.004	12.284 ± 0.314
QFSRT/07	25.563 ± 0.888	0.579 ± 0.002	0.630 ± 0.002	08.825 ± 0.659	1.088 ± 0..007	08.107 ± 0.556
QFSRT/08	26.229 ± 0.771	0.604 ± 0.002	0.638 ± 0.002	05.746 ± 0.657	1.057 ± 0.007	05.431 ± 0.588
QFSRT/09	30.781 ± 0.778	0.641 ± 0.004	0.708 ± 0.003	10.380 ± 1.119	1.104 ± 0.011	09.398 ± 0.921

Table 3 - Post compressional parameters

Formulations	Average Weight (mg.) (±SD), n=20	Diameter (cm.) (±SD), n=03	Thickness (mm.) (±SD), n=03	Hardness ($Kg./cm^2$) (±SD), n=03	Friability (%) (±SD), n=10	Weight variation (%) (±SD), n=20	Drug Content (%) (±SD), n=03
QFSRT/01	318.224 ± 0.842	1.1	5.30 ± 0.031	5.06 ± 0.02	3.02 ± 0.141	0.193 ± 0.176	99.369 ± 0.413
QFSRT/02	317.859 ± 0.541	1.1	5.31 ± 0.082	5.96 ± 0.06	1.379 ± 0.095	0.379 ± 0.289	98.649 ± 0.270
QFSRT/03	374.470 ± 2.195	1.1	5.34 ± 0.035	5.88 ± 0.05	1.497 ± 0.478	0.488 ± 0.306	99.198 ± 0.156
QFSRT/04	388.775 ± 2.472	1.1	5.35 ± 0.036	5.99 ± 0.04	1.395 ± 0.239	0.540 ± 0.313	99.189 ± 0.270
QFSRT/05	377.553 ± 0.973	1.1	5.39 ± 0.021	6.14 ± 0.02	1.241 ± 0.733	0.216 ± 0.132	98.649 ± 0.270
QFSRT/06	390.780 ± 0.801	1.1	5.40 ± 0.021	6.33 ± 0.04	0.667 ± 0.224	0.171 ± 0.107	99.468 ± 0.156
QFSRT/07	406.608 ± 1.117	1.1	5.41 ± 0.026	6.38 ± 0.01	0.323 ± 0.014	0.237 ± 0.128	99.369 ± 0.156
QFSRT/08	419.230 ± 0.712	1.1	5.42 ± 0.006	6.45 ± 0.01	0.317 ± 0.055	0.128 ± 0.108	99.640 ± 0.156
QFSRT/09	422.834 ± 0.955	1.1	5.42 ± 0.015	6.52 ± 0.01	0.347 ± 0.191	0.194 ± 0.107	99.550 ± 0.156

Table - 4 Release Kinetics Parameters for quetiapine fumarate SR Formulations

Batch No.	Zero Order		First order		Higuchi model		Kosymer-Peppas Model	
	m	r^2	m	r^2	m	r^2	m	r^2
QFSRT/01	11.290	0.909	0.302	0.766	35.220	0.995	0.520	0.983
QFSRT/02	10.900	0.771	0.269	0.971	36.140	0.954	0.393	0.929
QFSRT/03	11.690	0.920	0.277	0.851	37.620	0.987	0.589	0.979
QFSRT/04	9.078	0.919	0.198	0.794	31.820	0.998	0.530	0.997
QFSRT/05	8.968	0.931	0.198	0.767	29.370	0.988	0.493	0.981
QFSRT/06	6.974	0.816	0.214	0.816	27.610	0.968	0.329	0.957
QFSRT/07	7.510	0.903	0.173	0.832	28.640	0.994	0.504	0.987
QFSRT/08	7.272	0.769	0.165	0.979	29.530	0.959	0.399	0.961
QFSRT/09	8.264	0.806	0.189	0.887	30.510	0.970	0.346	0.992

Dissolution study of all the formulations was carried out using 0.1 N HCl pH 1.2 for 2 hrs. and in phosphate buffer pH 6.8 up to 12 hrs. Formulations QFSRT/01 to QFSRT/02 was prepared by using PVP K30 polymer. Figure 1 shows the release profile of formulations QFSRT/01 to QFSRT/02. Among those formulations, formulation prepared with PVP K30 shown faster drug release within 8 hrs than formulations prepared with other polymers, formulation QFSRT/03 with HPMC K15 M shown drug release in 7 hrs and formulation QFSRT/04 prepared with combinations of polymers HPMC K15 M & PVP K30 shown drug release in 10 hrs. With all four formulations, an initial burst release of the drug followed by a steady-state release was observed. The initial burst release can be accounted for the high concentration of highly soluble quetiapine fumarate at the surface that dissolves immediately. Figure 2 shows the release profile of formulations QFSRT/04 to QFSRT/08. These formulations were prepared by using combinations of polymer. With all four formulations, an initial burst release of the drug followed by a steady-state release was observed. Formulation QFSRT/08 which is prepared with HPMC K15M 40% with PVP K30 6 % has showed 99.20% release in 12 hrs. From the release study it was found that the polymer concentration in formulation QFSRT/05 to QFSRT/07 was sufficient to sustain the drug release up to 12 hrs. Among these three formulations, formulations with HPMC K15M along PVP K30 with show higher initial burst release due to hydration rate of this synthetic polymer relates to its hydroxy propyl substitutes percentage[6]. HPMC K15M contains the greatest amount of these groups and produces strongly viscous gel that plays an important role in drug release especially at the beginning of the release profile. Figure 3 shows the release profile of formulations QFSRT/03, QFSRT/04 & QFSRT/09. These formulations were prepared with polymer blend of HPMC K15M alone or combination with PVP K30 with different ratios was taken. From the release study it is observed that, from the formulations drug release will be controlled up to 10 hrs. In these formulations as the concentration of HPMC K15M increased, the release rate is decreased. From the release study it is observed that, from the formulations drug release will be controlled upto 12 hrs. In these formulations as the concentration of HPMC K15M increased, the release rate is decreased. This is possibly due to slower erosion of HPMC and/or may be due to the increased viscosity of PVP K30, which might have helped to keep the hydrated gel intact thus, releasing the drug for 12 hrs[7]. Among these formulations QFSRT/08 contain the ratio of 40:06 % of HPMC: PVP K30 showed 99.20% release in 12 hrs. From the release study it is clearly seen that there is synergism effect showed in the prepared formulations.

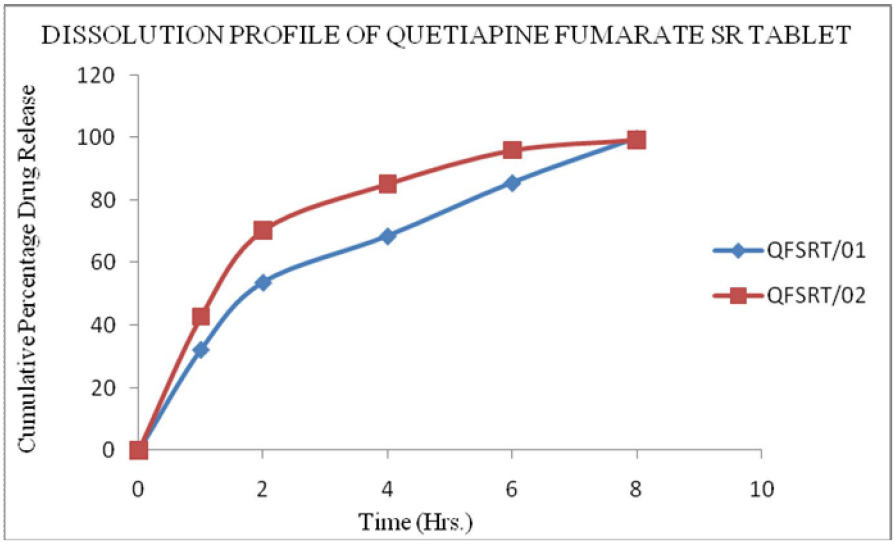

Figure 1. Dissolution release profiles of quetiapine fumarate formulations (each data point represents the average of six tablets with SD)

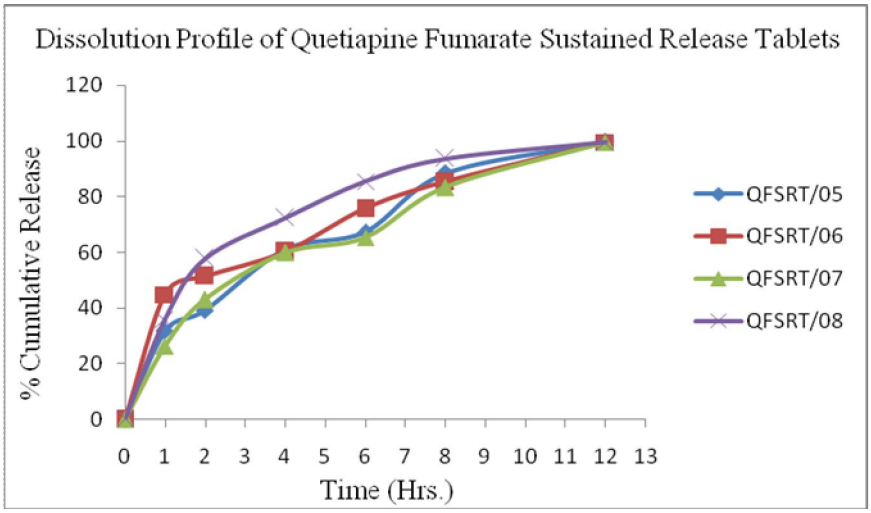

Figure 2. Comparative release profiles of quetiapine fumarate formulations (each data point represents the average of six tablets with SD)

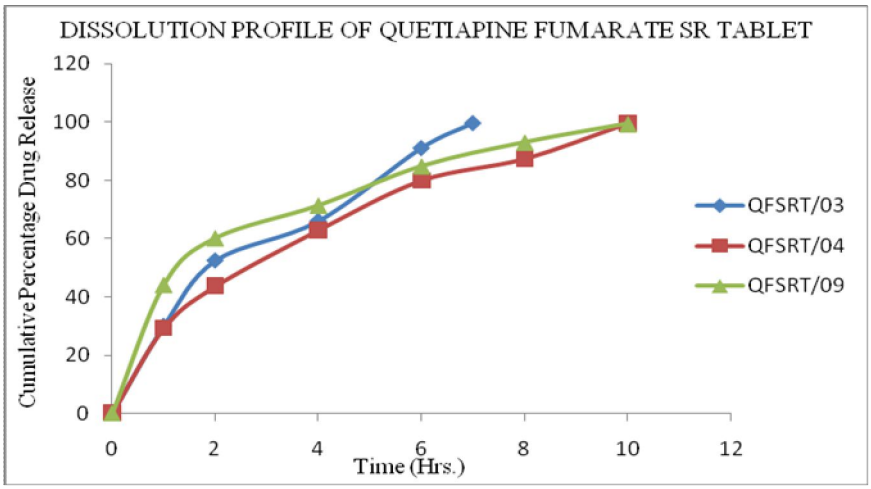

Figure 3. Comparative release profiles of quetiapine fumarate formulations (each data point represents the average of six tablets with SD)

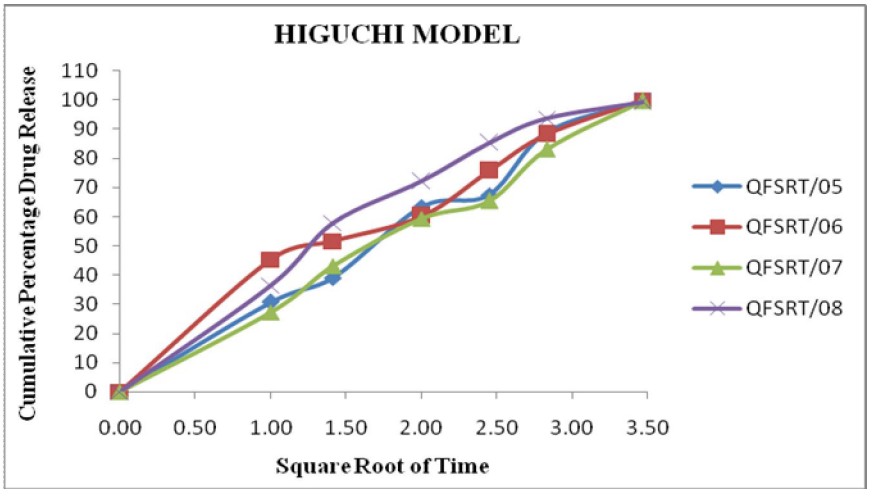

Figure 4. Comparative release profiles of quetiapine fumarate formulations in Higuchi model

Table 5 - Stability Study of Quetiapine fumarate SR Tablet

Formulation Code	Duration of Period (Months)	Assay (%)	Hardness (Kg./cm2)	Friability (%)
QFSRT / 08	1	98.459	6.42	0.467
	3	98.459	6.41	0.525
	6	98.189	6.41	0.525

Kinetics and mechanism of drug release

Kinetic results shown in table IV reveals that all formulations follows Higuchi kinetics (Fig. 4)[12-15] as correlation coefficient (r^2) values are higher than that of Zero order[16-18], first-order release[19] and Kosymer – Peppas kinetics[20]. The calculated n values from power law equation for drug release profiles were between 0.5119-0.7523 with a correlation coefficient (r^2) values >0.93, suggest that drug release mechanism from matrix tablets followed non- Fickian (anomalous) transport mechanism.

Stability Studies

The stability study of the prepared tablets were carried out according to ICH guidelines at 2±2°C, 25±2°C/60±5% RH, 30±2°C/65±5% RH, 40±2°C/75±5% RH, 55±2°C for one, three & six months[29-31] by storing the samples in (Stablab, Mumbai) stability chamber. The results from stability studies are shown in table 5.

FTIR Study

IR spectrum of quetiapine fumarate (Figure 5) shows a broad peak at 3750 cm^{-1} may be due to O-H stretching, 3080 cm^{-1} Ar-H stretching and 2880 cm^{-1} C-H stretching, 2380 cm^{-1} may be due to aromatic C=C stretching, 1600 cm^{-1} may be due to C-N, 1340 cm^{-1} maybe due to C-H bending. 1030 cm^{-1} may be due to –C-O-C group. 791 cm^{-1} may be due to substituted benzene ring. The IR spectrum of the best formulation obtained during the from the results, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the best formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains it's identity without going any chemical interaction with the polymers used.

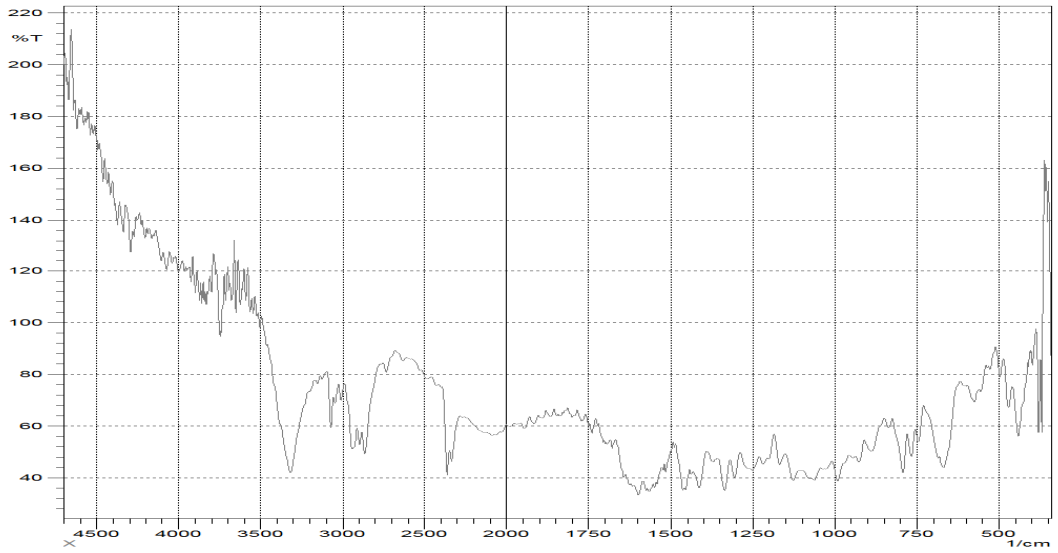

Figure 5. IR spectrum of quetiapine fumarate

DSC study

Figure 6 shows the DSC thermographs of pure drug (A1) and formulation F16 (H2C8) (A4). Thermographs obtained by DSC studies, revealed that the melting point of pure drug is 234°C and that of the drug in the formulation is 233°C as there is no much difference in the melting point of the drug in the thermographs of drug and that of in the formulation. It may be concluded that, the drug is in the same pure state even in the formulation without interacting with the polymers.

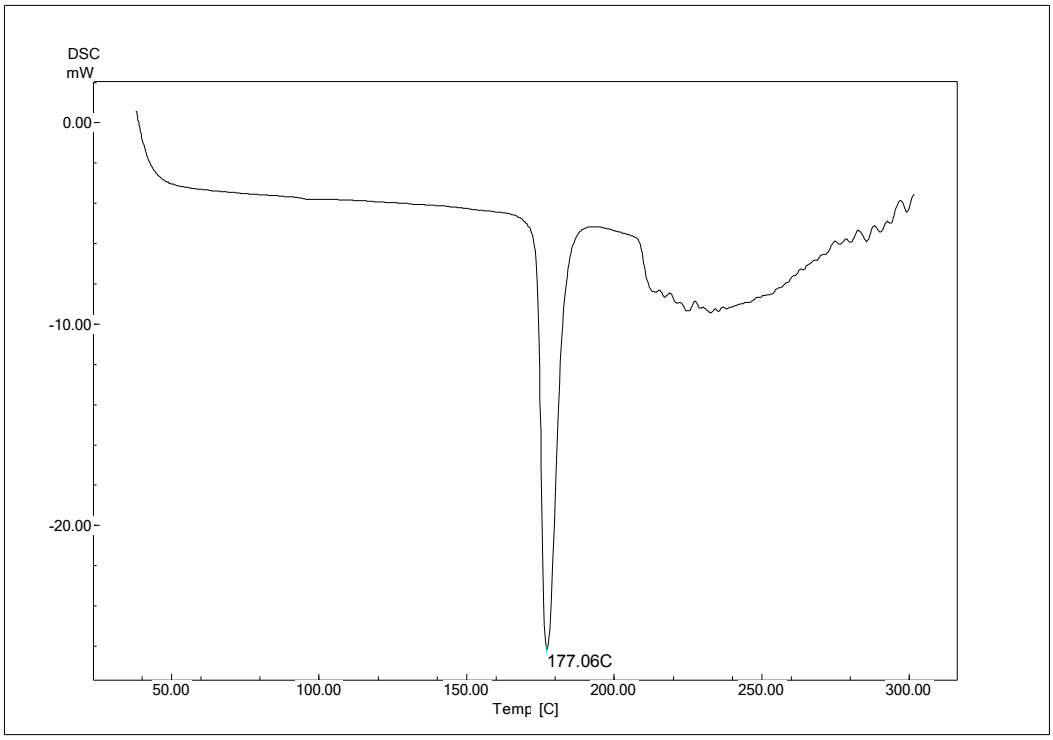

Figure 6 : DSC thermographs of pure drug

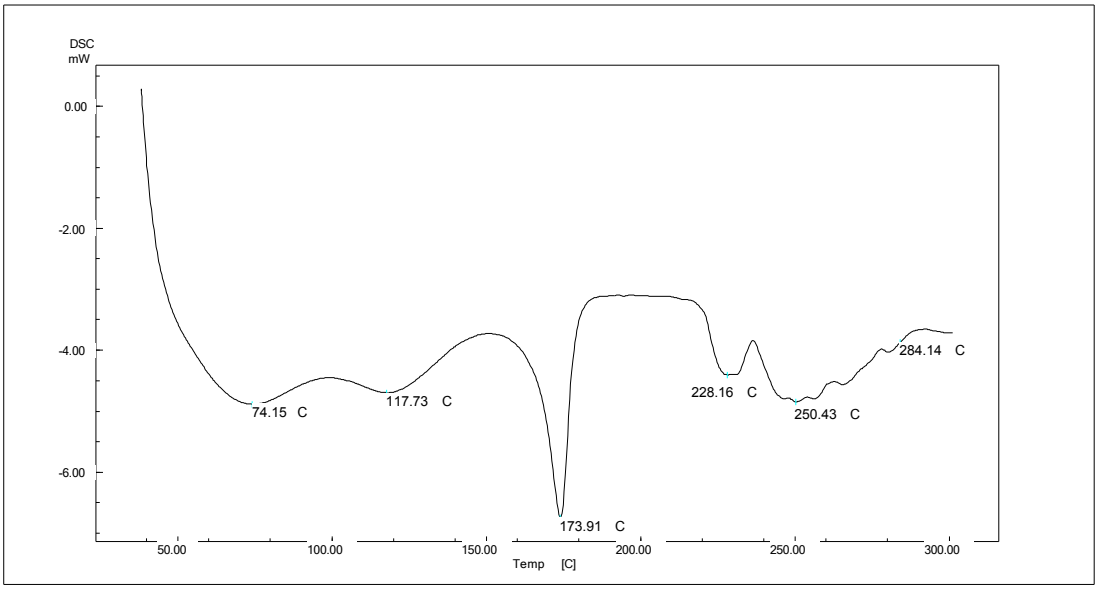

Figure 7 : DSC thermographs of quetiapine fumarate SR tablet

CONCLUSION

The formulations prepared with HPMC & PVP K30 polymer show 100% drug release in 12hrs and formulations could retard the drug release upto desired time period. The tablets containing polymer blend of HPMC K 15M and PVP K30 retard the drug release because both are swellable polymer. From the release study it is observed that as we increase the concentration of HPMC, the release of drug is decreased. This is possibly due to slower erosion of HPMC and may be due to the increased viscosity of PVP K30 which might have helped to keep the hydrated gel intact thus releasing the drug for 12 hrs. Among these formulations QFSRT/08 contain the ratio of 40:06 % of HPMC: PVP K30 showed 99.20% release in 12 hrs and the release profile follows higuchi kinetics. From the release study it is observed that as we increase the concentration of PVP K30, the release of drug is decreased due to higher swelling rate of PVP K30 which is observed from the data of swelling study. From the Korsmeyer Peppas study, the n value of the formulations show that the release profile obeys non-Fickian diffusion which shows that drug is released via, swelling, diffusion and erosion mechanism. Stability studies, FTIR, and DSC indicated that drug was stable in the tablets. In conclusion, PVP K30 and HPMC K 15M can be used as rate controlling polymers by appropriate selection of the level of polymers in the matrix.

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