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HPMC BASED EXTENDED-RELEASE MATRIX TABLETS OF AN ANTI-PSYCHOTIC DRUG BY DRY GRANULATION METHOD

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Key words:

Quetiapine Fumarate, HPMC K 4M, Matrix systems, Sustained release, Higuchi Model.

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ABSTRACT: The aim of the present study was to develop and characterize an oral sustain release drug delivery system for commonly prescribed antipsychotic Quetiapine fumarate. Hydrophilic matrix based tablets using different concentrations of hydroxypropyl methylcellulose (HPMC) viz. K4M CR was developed using dry granulation technique. The prepared tablets were of 400 mg dose and were designed for once- daily administration. The formulations prepared were evaluated for the release of Quetiapine fumarate over a period of 24 hrs. Using USP type I dissolution test apparatus. The prepared tablets were evaluated for physical properties. The in-vitro drug release studies revealed that the tablets containing 12% of HPMC K4M CR of the total tablet weight showed satisfactory results and was able to control the release over 20 hrs. The *in-vitro* release data of prepared formulations followed Korsmeyer- Peppas and Higuchi kinetics strongly. The selected formulation was compared with the marketed product for the drug release pattern and was matched using similarity factor (f2) above 50. The selected formulation was evaluated in comparison to Quetiapine Extended-release tablets formulation manufactured using wet granulation method. In conclusion, the dissolution profiles and the mathematical model fittings indicate that release of Quetiapine fumarate can be effectively controlled by use of hydrophilic matrix systems.

INTRODUCTION: Quetiapine fumarate (QF) (bis [2-(2-[4-(dibenzo[b,f][1,4] thiazepin – 11 - yl)] ethoxy) ethanol] fumarate, a dibenzothiazepine derivative, is a recent antipsychotic drug with an atypical neuropharmacological profile. Quetiapine is the antipsychotic that has the highest serotonin/dopamine binding ratio, being the serotonin type 2 (5-HT2)-receptor blocking effect about twice as strong as the dopamine D2-receptor blocking effect [1]. Due to this binding pattern, Quetiapine causes minimal extra pyramidal side effects.

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It is readily absorbed from the gastrointestinal track with oral bioavailability of about 83% and a plasma elimination half life ranging from 6-7 hours. Administration of QF in the sustain release dosage form as once daily would be more desirable as this formulation is intended to be given to schizophreniac patients. The sustain release form would also control the mood for longer period of time by maintaining the plasma concentration of drug well above the therapeutic concentration.

At a pH above 4, the water solubility is poor; towards pH 2, an increase in solubility is noticeable. However, below pH 2, solubility is decreasing owing to the ion effect [2]. Due to its poor solubility over the physiological pH range but its high permeability, Quetiapine is classified as a BCS class II drug [3]. It appears as effective as the older antipsychotics producing side effects no worse than those encountered with standard antipsychotics. This characteristic makes

Quetiapine well tolerated and effective in patients who are particularly susceptible to these severe side effects, including the elderly and adolescents and those with pre-existing dopaminergic pathologies, such as Alzheimer's disease and Parkinson's disease.

An effort was therefore made to develop simple and effective sustain release tablets of Quetiapine Fumarate using a polymer matrix system. Hydroxypropyl methyl cellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral sustains release drug delivery system [4]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels and finally dissolves slowly [5]. The gel becomes viscous acting as a protective barrier to both, the influx of water and the efflux of drug in solution [6]. As reported by Ford et al, [7] the proportion of polymer in the formulation increases the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix. Narasimhan and Peppas [8] showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of drug release form HPMC matrix is dependent on various factors such as type of polymers, drug, drug-polymer ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation.

The aim of the present study was to design and develop the sustain release matrix tablets of Quetiapine Fumarate, and to study the effect of different excipients on the drug release profiles. Further evaluation of the tablet against a wet granulation product and cost effective evaluation for dry granulation process as an alternative.

MATERIALS AND METHODS:

Materials Quetiapine fumarate was procured from Medichem. HPMC 2208 - Methocel K4M (colorcon), Lactose monohydrate (Foremost), Co-povidone - Plasdone S-630 (ISP Technologies), Colloidal Silicon dioxide(Evonik), Magnesium stearate (Peter Greven)

Preparation of tablets by dry granulation method:

Matrix tablets were prepared by dry granulation method. The composition of various formulations is given in **Table 1**. Quetiapine Fumarate and other excipients including HPMC K4M were initially passed through 40# sieve. The sifted material is blended for suitable time interval in a lab scale bin blender. The blended material is lubricated with Magnesium Stearate sifted through #40 sieve for 5 minutes.

The lubricated blend is compacted in vertical roller compactor at suitable parameters to arrive at desired granular material. The obtained granules were lubricated with extra granular Magnesium Stearate for 5 minutes and resulting granules were evaluated for the flow properties. Tablets were compressed on 21.58 x 8.6 mm capsule shaped punches on 10 station mini press tableting machine (Guoyao Longli). Six different formulas having different concentrations of HPMC K4M were prepared. These tablets were evaluated for drug release and to study the effect of polymer concentration on drug release.

TABLE 1: DIFFERENT TABLET COMPOSITIONS

	Quantity (mg) per Tablet[#]					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Quetiapine Fumarate	460.52	460.52	460.52	460.52	460.52	460.52
Lactose monohydrate	541.48	505.48	475.48	445.48	385.48	325.48
Co-povidone	30.00	30.00		30.00	30.00	30.00
HPMC (Methocel K4M)	144.00	180.00	240.00	240.00	300.00	360.00
Colloidal Silicon Dioxide	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium Stearate	18.00	18.00	18.00	18.00	18.00	18.00
Total	**1200.0**	**1200.0**	**1200.0**	**1200.0**	**1200.0**	**1200.0**

Formulation F1, F2, F4,F5 and F6 contains 12%, 15%, 20%, 25% and 30% of HPMC K4M respectively.
Formulation F3 contains 0% binder and 20% HPMC K4M

Preparation of tablets by wet granulation method:

Quetiapine ER tablets were prepared by wet granulation method. The composition of formulations is given in **Table 2**, manufacturing process of Quetiapine Granules involves 2 steps. Viz dry granulation and wet granulation. Magnesium Oxide light is compacted in roller compactor at pre determined parameters to obtain granules of required granulometry as per in-process specification. The compacted Magnesium oxide light granules and other excipients are introduced into wet granulation process. Methylene chloride containing PVP K-30 is used as a granulating agent. The obtained granules are dried in Fluid bed dryer and lubricated with extra granular magnesium stearate. The lubricated granule is compressed using suitable Tablet punches for a target tablet weight of 1200 mg.

TABLE 2: TABLET COMPOSITIONS

Material name	Quantity (mg) per Tablet[$]
	F7 – Wet granulation process
Quetiapine Fumarate	460.52
Magnesium Oxide Light Compacted	180.0
Microcrystalline cellulose	59.74
Lactose Monohydrate	59.74
Carrageenan Gum	300.0
Povidone K30	120.0
Methylene chloride	Quantity Sufficient
Magnesium Stearate	20
Total	**1200.0**

[$]: The above wet granulation is the optimised formulation designed during development activity in the laboratory. Here the Tablet composition is listed in **Table 2** and the tablet dissolution profile will be compared with the dry granulation tablets. Other critical parameters and quality attributes not executed as a scope of this research article.

Evaluation of Granules properties:

The lubricated granules were evaluated for granules parameter Viz., Bulk density, tapped density, compressibility index, and Hausner ratio and particle size distribution. Bulk density, tapped density, compressibility index and Hausner ratio was determined by using routine lab model. The particle size distribution was conducted using Sieve shaker apparatus.

Evaluation of tablets:

As mentioned in the preparation of tablet section, to study the effect of polymer concentration of drug release, 6 different formulas, having different concentrations of polymer HPMC were developed. **Fig.1** shows the drug release profiles of the 6 formulations studied. The prepared tablets were tested as per standard procedure for weight variation (n=10), hardness (n=10), thickness (n=10) and friability. Hardness of the tablets was determined by using Erweka tablet hardness tester, Friability test (n=10) was conducted using Roche friabilator (F. Hoffman-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier calipers (Aerospace).Further the similarity factor f2 for the release of Quetiapine Fumarate between the test product and that of the marketed formulation, Seroquel XR (AstraZeneca Pharmaceuticals, USA), was performed.

Study of Binder concentration:

Initial trials for extended release tablets were planned with 2.5% concentration of dry binder (Co-povidone). To evaluate the influence of Co-povidone concentration on drug release a feasibility trial was designed without binder and HPMC concentration at 20%.

Dissolution testing:

Dissolution studies were performed using the USP I, Basket-rotating method (Electrolab dissolution tester, TDT-08, India) at 37 °C ± 0.5 °C and 2000 rpm using 0.1 N HCl in the initial 5 hours with 900 ml and phosphate buffered solution, pH 6.8 (PBS) till the end of the study [9] at 1000 ml, as the dissolution media. The end of the study [9] at 1000 ml, as the dissolution media. A 2 ml aliquot of

sample was withdrawn at regular time intervals, filtered and then these samples were diluted 10 folds with distilled water and then assayed using High performance liquid chromatography. The cumulative % drug release was calculated for the formulations.

Mechanisms of drug release:
To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations [10, 11]:

Zero- order equation: $\mathbf{Q = k_0 t}$

Where, Q is the amount of drug released at time t, and k_0 is the release rate;

First- order equation: $\mathbf{\log (100\text{-}Q) = \log 100 - k_1 t}$

Where, Q is the percentage of drug release at time t, and k1 is the release rate constant;

Higuchi's equation: $\mathbf{Q = k_2 t^{1/2}}$

Where, Q is the percent of drug released at time t, and k2 is the diffusion rate constant;

Korsmeyer Peppas equation: $Mt/ M\infty = k t^{n}$

Where, $Mt/ M\infty$ is the fractional solute release, t is the release time, k is the kinetic constant and n is an exponential value.

Control of complete drug release:
After the evaluation of the initial prepared tablets containing 20-25% of HPMC composition for the drug release it was observed that there existed an incomplete drug release upto24 hrs, in which about 36 – 69 % of the drug was released. So to increase the drug release towards complete dissolution two more formulations were tried which containing HPMC K4M (12.0%, and 15%).

These formulations were then evaluated for physical parameters and also for dissolution profile. The reduced polymer concentration was compensated with increased lactose concentration. Increased Lactose concentration alleviated the drug release by acting as pore former.

Similarity factor (f2) Analysis:
In- vitro release profile of the marketed Quetiapine Fumarate sustain release tablets (SR) tablets, (SeroQuel XR, AstraZeneca, USA) was performed under similarity conditions as used for in- vitro release testing of the test product for the release of QF. The similarity factor between the two formulations was determined using the data obtained from the drug release pattern. The data was analyzed by the following formula shown in equation 1.[12]

$$f_2 = 50\ log\left\{\left[1 + \frac{1}{n}\sum_{n=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where, **n** = number of pull points, $\mathbf{R_t}$ = Reference profile at time point t and $\mathbf{T_t}$= Test profile at same time point.

RESULTS AND DISCUSSION: The ER tablets of Quetiapine Fumarate were prepared as there was no literature available on the prepared dosage form and Quetiapine Fumarate was a drug of choice in case of many psychotic patients. Dry granulation was the prepared technique for making SR formulations, as the other techniques did not give satisfactory flow properties due to the fluffiness of the drug.

Granules Properties: The lubricated granules were evaluated for granules parameter Viz., Bulk density, tapped density, compressibility index, and Hausner ratio and particle size distribution. The results are compiled in **Table 3**. The flow property indicated by empirical value of compressibility index shows that all the batches had satisfactory flow properties.

Particle size distribution of lubricated granules is found to be similar for all the manufactured batches without any significant in Granulometry. This the effect of formula composition is bound to have negligible effect on the granules properties.

TABLE 3: GRANULES PROPERTIES OF FORMULATIONS PREPARED

Granules Parameter	F1	F2	F3	F4	F5	F6
Bulk Density	0.610	0.607	0.610	0.590	0.579	0.579
Tapped Density	0.840	0.759	0.740	0.749	0.760	0.710
Compressibility Index	27.90	20.00	17.60	20.60	25.00	19.70
Hausner Ratio	1.37	1.25	1.21	1.25	1.33	1.24
Particle Size distribution						
% Retains on Sieve #60 ASTM	56.3	48.3	55.1	56.3	56.3	54.3
% Passed through Sieve #60 ASTM	44.8	51.2	45.2	42.5	42.4	44.6

Physical Properties

The results obtained for the weight variation, hardness, thickness and friability, and drug content are given in **Table 4**. All the prepared formulations were seen to be complying with the official requirements of uniformity of weight. The drug content was found to be close to 100% of the label claim for Quetiapine Fumarate in all the formulations. The hardness and friability, the measures of strength of the tablets were found to be >12 Kp and <1% respectively, these values were within limit. Thus all the physical parameters of the compressed matrices were found to be practically within controls.

TABLE 4: PHYSICAL PROPERTIES OF FORMULATIONS PREPARED

Test	F1	F2	F3	F4	F5	F6
Individual tablet weight (mg)	1192 – 1209	1196 – 1214	1195 – 1214	1182 – 1219	1190 - 1210	1198 – 1220
Thickness (mm)	6.94 – 7.06	6.85 – 7.01	6.88 – 6.93	7.0 – 7.2	7.00 – 7.14	6.96 – 7.03
Hardness (Kp)	14.2 – 17.9	12.8 – 18.7	16.2 – 19.6	12.3 – 17.4	13.0 – 18.6	15.0 – 18.3
Friability (%)	0.0	0.09	0.06	0.07	0.10	0.09
Drug Content (%)	99.6	98.3	98.8	99.0	98.2	98.4

In- vitro release studies and effect of binder concentration:

As the drug in study had a slight solubility in water moderate molecular weight HPMC is used as a rate controlling polymer (K4M) to retard the release of drug from a matrix at levels of 12 to 30% w/w in tablets prepared. The effect of polymer level on the release of the drug from matrix tablets was studied for tablets containing 12%, 15%, 20%, 25% and 30% of the polymer. (Formulations F1 to F6). **Fig. 1** shows that the amount of HPMC used affects the release rate of the drug.

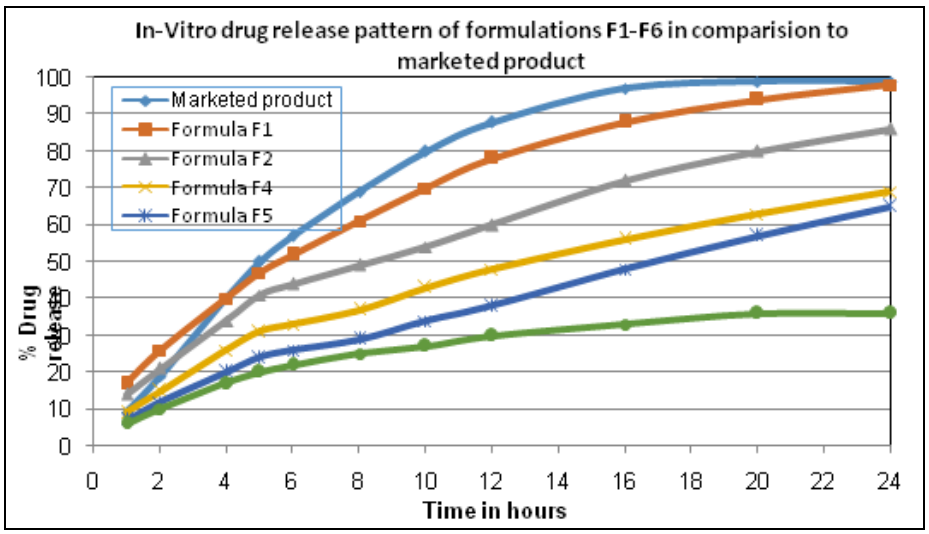

FIG. 1: *IN-VITRO* DRUG RELEASE PATTERN OF FORMULATIONS F1-F6 IN COMPARISON TO MARKETED PRODUCT

Tablets containing 12% and 15% of HPMC K4M showed >80% release in 20 hrs and the drug release was complete at 24 hours. Whereas tablets containing 20 – 30% of HPMC K4M showed a more retardation and incomplete rug release at 24 hours. On further evaluation of Tablets without dry binder and its dissolution profile pattern, there was no significant difference in Granulometry,

tablets physical property and dissolution pattern. Thus, evaluated batches indicating that higher the percentage of the polymer more is the drug release retardation and 12% HPMC K4M concentration showed similar release patterns to marketed product

There was no significant difference in formulation F3 and F4 manufactured with 0% and 2.5% of binder concentration respectively on Granules properties, Tablet physical properties. Furthermore there was no significant on drug release profile (**Fig. 2**), and effect of HPMC rate controlling polymer is found to be pre-dominant. The concluding choice for binder concentration to be based on further variation study after freezing polymer concentration.

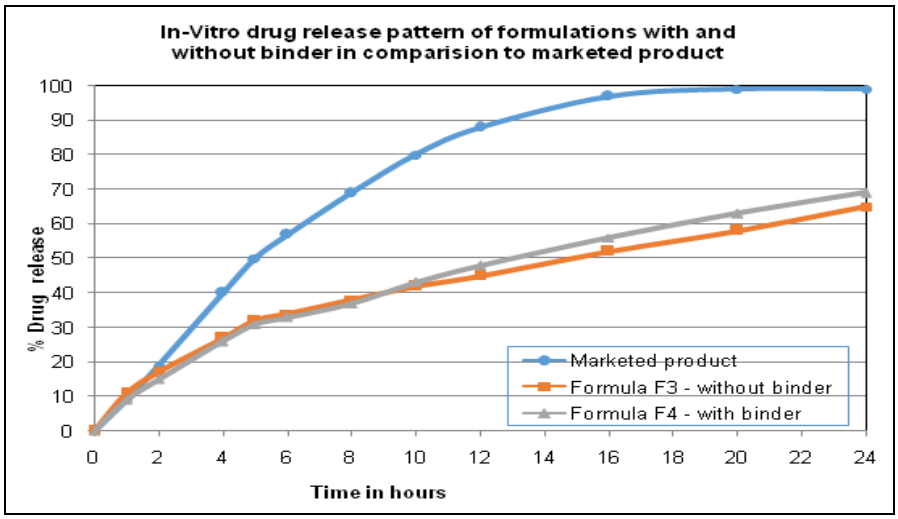

FIG.2: *IN-VITRO* DRUG RELEASE PATTERN OF FORMULATIONS WITH AND WITHOUT BINDER IN COMPARISON TO MARKETED PRODUCT

Similarity Factor for formulation selection and comparison with wet granulation tablet dosage:

The principles purposes of dissolution testing are 3-fold: (1) for quality control, to ensure the uniformity of product from batch to batch; (2) to help to predict bioavailability for formulation development; and (3) as a measure of change when formulation changes are made to an existing formulation. So, to compare the release pattern from two different formulations of the same drug f2 factor can be used. Similarity factor analysis between the prepared tablets and Seroquel SR tablets (marketed) for the release of Quetiapine Fumarate showed an f2 factor (f2 = 60) greater than 50. As shown in **Fig. 3**, the f2 factor confirms that the release of QF from the prepared tablets was similar to that of the marketed tablet.

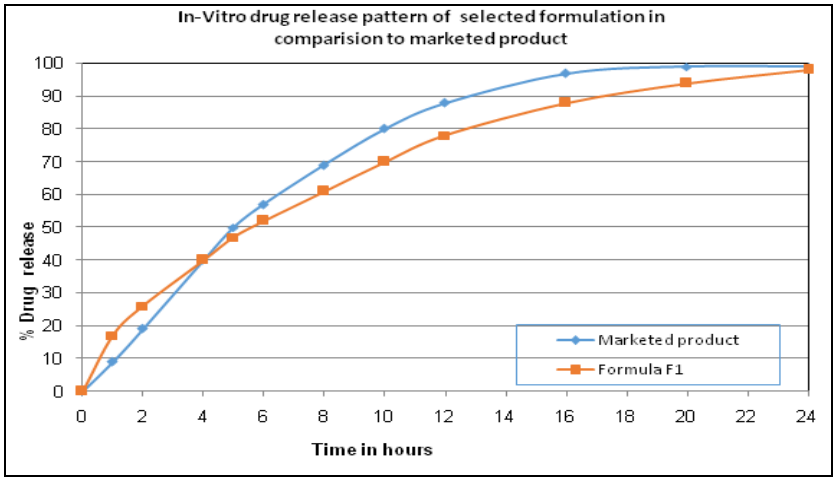

FIG.3: *IN-VITRO* DRUG RELEASE PATTERN OF SELECTED FORMULATIONS IN COMPARISON TO MARKETED PRODUCT

The selected Quetiapine ER Tablets formulation is compared with tablets manufactured by wet granulation method. So, to compare the release pattern from two different formulations of the same drug f2 factor can be used. Similarity factor analysis between the prepared tablets (Dry granulation method and wet granulation method) for the release of Quetiapine Fumarate showed an f2 factor (f2 = 72.3) greater than 50. As shown in **Fig. 4**, the f2 factor confirms that the release of QF from the prepared tablets was similar to that of the wet granulation method.

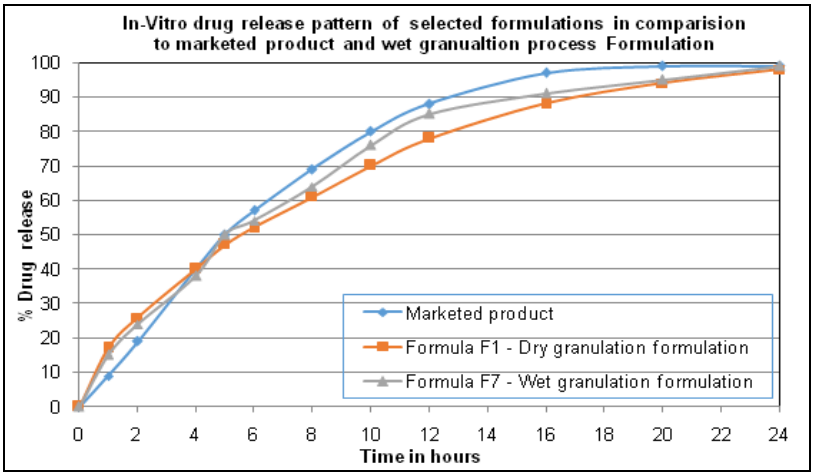

FIG. 4: *IN-VITRO* DRUG RELEASE PATTERN OF SELECTED FORMULATIONS IN COMPARISON TO MARKETED PRODUCT AND WET GRANULATION PROCESS FORMULATION

Drug release mechanism:

The obtained release data from the in-vitro dissolution study from various formulations was fitted to the mathematical models. The kinetic models included First order, Higuchi equation (matrix system) and Korsmeyer-Peppas model. **Table 5** shows the data obtained from the model fitting, for all the 6 formulations studied (F1-F6) along with their R2 values, K constant, and n exponential value. The overall curve fitting showed that the drug release from the sustained release matrix tablets followed either Higuchi equation or the Korsmeyer- Peppas model. The values of the exponential factor 'n' were found to be in between 0.2871- 0.3637 indicating the Fickian diffusion-controlled drug release. The correlation co-efficient R2 was same time best fitting to the Matrix system and some time to the Korsmeyer-Peppas equation which was adequate from the sustain release systems. However, looking at the negligible variation in the R2 values for the release of the drug Quetiapine Fumarate, the release data analysis applying these mathematical models can be purely empirical.

TABLE 5: RELEASE KINETICS OF THE PREPARED FORMULATIONS

	R^2				n	k
	Zero- order	1st order	Higuchi	Korsmeyer-Peppas		
F1	0.7880	0.9621	0.9821	0.9899	0.3637	25.64
F2	0.7470	0.9485	0.9841	0.9573	0.3007	15.93
F3	0.7456	0.9387	0.9478	0.9805	0.2984	29.22
F4	0.6634	0.9202	0.9564	0.9839	0.3152	32.16
F5	0.5166	0.8526	0.9293	0.9812	0.2871	39.65
F6	0.6498	0.9305	0.9529	0.9808	0.2903	30.88

CONCLUSION: All the prepared formulations with HPMC polymer grades had good flow properties before compression and the tablets showed weight uniformity and mechanical strength. All the formulations resulted in slow drug release depending upon the type and concentration of the polymer grade. Drug release was found to be affected by the concentration of the polymer; increasing concentration resulted in decreased drug release. The formulation containing 12% of K4M CR grade of HPMC showed satisfactory results sustaining the effect of the drug over 20 hrs. to give

once daily dose. The formulation irrespective of Co-povidone concentration at 0% OR 2.5% behaved identical with similar dissolution profile at 20% polymer concentration. The similarity factor (f2) value above 50 indicated the similarity between the marketed and prepared tablets. Further based on *in vitro* drug release profile it's of the opinion that the manufactured tablets behave analogous to tablets manufactured by wet granulation process. The dry granulation process comes with a series of advantages that includes but not limited to cost effective, robust and reproducible. The manufacturing process is independent of extensive Critical process parameters as seen in Wet granulation process.

With the development of dry granulation approach for Quetiapine Extended-Release Tablets using HPMC K4M as a rate controlling polymer, found to be innovative and much suitable than wet granulation. With further process optimisation and variation studies a bio-equivalent formulation to Marketed product can be achieved

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REFERENCES:

1. AM Raggi; R Mandrioli; A Ferranti; J. Pharm. Biomed. Analysis., 2003, 32, 1037-1044. P Colombo; Adv Drug Del Rev.1993:11; 37-57.
2. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of Quetiapine: an atypical antipsychotic. Clin Pharmacokinet. 2001; 40(7):509–522.
3. Volgyi G, Baka E, Box KJ, Comer JE, Takacs-Novak K. Study of pH-dependent solubility of organic bases. Revisit of Henderson–Hasselbalch relationship. Anal Chim Acta. 2010; 673(1):40–46.
4. J. Siepmann, H. Kranz, R. Bodmeier and N. A. Peppas, "HPMC-Matrices for Controlled Drug Delivery: A New Model Combining Diffusion, Swelling and Dissolution Mechanisms and Predicting the Release Kinetics," Pharmaceutical Research.1999; 16(11):1748-1756.
5. Colombo P, Bettini R, Santi P and Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance.Pharm. Sci.Technol.Today, 2000; 3:198-204.
6. Kiil S. and Dam-Johansen K. Controlled drug delivery from swellable hydroxy propyl methylcellulose matrices: model-based analysis of observed radial front movements. Journal of Controlled Release. 2003; 90(1): 1-21
7. Ford JL, Rubinstein MH and Hogan JE. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. Int. J.Pharm 1985; 24: 339-350.
8. B. Narasimhan and N. A. Peppas. Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *J. Pharm. Sci.1997;* 86:297–304.
9. USFDA Dissolution data base. Accessed on August 26, 2015.
10. KR Reddy; S Mutalik; S Reddy. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech., 2003;4(4):61,1-9.
11. HK Raslan; H Maswadeh, *In vitro* dissolution kinetic study of theophylline from mixed controlled release matrix tablets containing hydroxypropylmethyl cellulose and glycerylbehenate Ind. J. Pharm. Sci. 2006;44: 308-312.
12. Avachat, A.; Kotwal, V. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. AAPS PharmSciTech.2007; 8(4):88-96.

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