EFFECT OF HPMC ON DISSOLUTION QUETIAPINE FUMARATE EXTENDED RELEASE TABLETS

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ABSTRACT

The objective of this present investigation was to study the effect of different matrix based extended release tablets of Quetiapine fumarate (QF). Different batches of Quetiapine fumarate Extended release tablets were prepared by granulation and followed by coating technique using different polymers and to elucidate the dissolution release pattern of drug from ER matrix tablets, and compare with the theoretical extended release profile of Serquoel (Quetiapine Fumarate) tablets. And the different polymers used are Hydroxypropylmethylcellulose different grades (Methocel K4 CR, K15M, K100M, K100LV and HPMC E6 for polymer coating) were used as polymers and by comparing the combination of different polymers was found to provided better-controlled release characteristics with excellent drug release. The prepared tablets were evaluated for Physical parameters (weight variation, friability, hardness, thickness) and in vitro dissolution studies. From the In vitro dissolution studies it is clear that as the concentration of polymer increased, drug release was found to be retarded and which was compared with innovator (Serquoel XL Tablets 400mg). Formulation F1and F6 gave better-controlled drug release in comparison to the other formulations.

Keywords:

Hydroxypropylmethylcellulose (Different Grades), Extended tablets, Quetiapine fumarate, Kinetics.

INTRODUCTION

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT2) and dopamine D1- and D2- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic a1 receptors, with a lower affinity at adrenergic a2 and serotonin 5HT1A receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors. The indications for

Quetiapine Fumarate and its extended release form, have been extensively amended in recent years and with this formulation further extensions are proposed.

Quetiapine is currently indicated for:

•Treatment of schizophrenia

•Bipolar disorder including:

-Maintenance treatment of bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes.

-Treatment of depressive episodes associated with bipolar disorder; -Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate.

Quetiapine Fumarate XR is currently indicated for:

•Schizophrenia: Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy.

•Bipolar disorder including: -Maintenance treatment of Bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes.

-Treatment of depressive episodes associated with bipolar disorder.

-Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate. Efficacy of Quetiapine Fumarate XR in the treatment of bipolar disorder indications was established in part, on the basis of extrapolation from the established effectiveness of Quetiapine.

•Major Depressive Disorder: -Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies.

Hydroxypropyl methyl cellulose (HPMC) is the most commonly hydrophilic retarding agent for the preparation of oral Extended release drug delivery system [1,2]. The transport phenomena involved in the drug release from hydrophilic matrices are complex because themicrostructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels and finally dissolves slowly [3]. The gel becomes viscous acting as a protective barrier to both, the influx of water and the efflux of drug in solution [4, 5].

As reported by Ford et al, [6] 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. Dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of the drug release are found to increase with use of lower viscosity grades of polymers. 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.

MATERIALS AND METHODOLOGY

Materials used:

Materials Quetiapine fumarate was provided as a gift sample by Aurobindo Research Center (Hyderabad, India). HPMC 2208, HPMC 2910 with various viscosity grades (Methocel Methocel K4M CR, K15M, K100M and K100LV, HPMC E6) was received as a gift sample from Colorcon Asia, Pvt. Ltd. (Mumbai, India). Microcrystalline cellulose (Avicel pH 102) and Lactose Monohydrate (Pharmatose 200M), Titanium dioxide, Macrogal-400, Trisodium citrate dihydrate was received as a gift sample from Signet chemical Co-operation, Mumbai, Magnesium stearate were purchased from Nitika Pharmaceuticals Ltd.,. All other chemicals and reagents were of analytical grades.

Manufacturing process (Methodology):

The tablets are manufactured by wet granulation and followed by coating:

The process involves weighing of the starting materials, wet granulation and milling, drying and dry milling, mixing, compression, coating.

Preparation of tablets Matrix tablets were prepared by wet granulation method the composition of various formulations is given in Table 1. Quetiapine fumarate and the polymer grades used of HPMC 2208, HPMC 2910 with various viscosity grades (Methocel K4M CR, K15M, K100M and K100LV), Microcrystalline Cellulose and Lactose monohydrate were initially passed through ASTM #25 sieve. The drug and the polymer used were then proportionately mixed in Rapid Mixer Granulator 15 mins. Granulation was done using Purified water. The wet mass was dried in Rapid Dryer at 60^{o}C for 30-50 mins. The dried granules were again passed through ASTM # 20 sieve and blended with magnesium stearate (which is passed through ASTM # 60).

Tablets were compressed on 16.00 mm flat punch on a 5 station mini press tableting machine (Chanduma). And coating was done using the HPMC E6 polymer, Titanium Dioxide, Macrogol 400 and Trisodium Citrate dihydrate. These tablets were evaluated for drug release and to study the effect of polymer concentration on drug release.

Tablet 1: Different Tablet Compositions

Name of Ingredients	F1	F2	F3	F4	F5	F6
Intragranular	**Quantity (mg) per Tablets**					
Quetiapine Fumarate	400.00	400.00	400.00	400.00	400.00	400.00
HPMC K4M CR	25.00		25.00	-	20.00	45.00
HPMC K15LV	20.00	25.00	-	25.00	10.00	-
HPMC K100LV	-	20.00	20.00	20.00	15.00	-
Lactose Monohydrate	20.00	20.00	20.00	20.00	20.00	20.00

Microcrystalline Cellulose (Avicel 102)	26.50	26.50	26.50	26.50	26.50	26.50
Granulating Solvent						
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Extra granular						
HPMC K100M	40.00	40.00	40.00	40.00	40.00	40.00
Microcrystalline Cellulose (Avicel 112)	25.00	25.00	25.00	25.00	25.00	25.00
Magnesium Stearate	3.50	3.50	3.50	3.50	3.50	3.50
Core Tablet weight	560.00	560.00	560.00	560.00	560.00	560.00
`Film Coating						
HPMC E6	20.00	20.00	20.00	20.00	20.00	20.00
Titanium Dioxide	10.00	10	10	10	10	10
Macrogol 400	5.00	5	5	5	5	5
Trisodium Citrate dihydrate	5.00	5	5	5	5	5
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total	600.00	600.00	600.00	600.00	600.00	600.00

Physical parameters Evaluation:

Evaluation of tablets Weight variation:

Twenty tablets were selected randomly and the average weight was determined. Then the individual tablets were weighed and the individual weight was compared with the average weight which is shown in table 3.

Hardness: Hardness of the tablets (n=10) was determined using Monsanto hardness tester.

Friability of the tablets: (Roche friabilator)

Pre-weighed sample of tablets (n=10) was placed in the friabilator, it was operated for 100 revolutions. Tablets were then dusted and reweighed [8] which is shown in table 3. The experiment was repeated three times.

Estimation of drug content:

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 5 mg/10mg of drug was transferred into 100 ml volumetric flask and extracted with pH 6.8 buffer by keeping in a sonicator for 2 hours, then it was filtered , suitable dilutions were made and absorbance was recorded by using UV spectrophotometer (Elico) at 248 nm and the results were shown in table 3.

DRUG-EXCIPIENT COMPATABILITY STUDIES: [10]

Studies of drug-excipients compatibility represent an important phase in the Preformulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutically properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipients interaction like physical & chemical

By physical observation

It was determined as per procedure given in method section the following table illustrated the result.

Physical compatibility studies

Test	Observation	Inference
Physical compatibility	No change of color	These materials are compatible for formulation

Procedure by compatibility Studies [11]

The HPLC (By UV detector) of Quetiapine Fumarate with excipients were taken by preparing Solution with Dissolve 2.6 g/L of dibasic ammonium phosphate in water.and Mobile phase: Methanol, acetonitrile, and Buffer (54:7:39) Diluent: Acetonitrile and water (50:50)injected in HLPC. The transmission minima (absorption maxima) in the chromatogram obtained with the sample in corresponded in position and relative size to those in the chromatogram obtained with the standards.

Table 2: Chemical computability studies:

S.no	Composition	Ratio	Related Substances	Limits	Initial	40oC/75%RH 1 month stability
1	Quetiapine Fumarate	NA	Quetiapine related compound G	0.2%	ND	0.01
			Quetiapine related compound H	0.2%	0.01	0.03
			Any unspecified impurity	0.2%	ND	ND
			Total impurity	**NMT 0.4%**	**0.01**	**0.04**
	Quetiapine Fumarate +Hypromellose	1:1	Quetiapine related compound G	0.2%	ND	0.03
			Quetiapine related compound H	0.2%	ND	0.02
			Any unspecified impurity	0.2%	ND	ND
			Total impurity	**NMT 0.4%**	**0.00**	**0.05**
	Quetiapine Fumarate +Lactose Monohydrate	1:1	Quetiapine related compound G	0.2%	ND	0.03
			Quetiapine related compound H	0.2%	0.02	0.05
			Any unspecified impurity	0.2%	ND	0.04
			Total impurity	**NMT 0.4%**	**0.02**	**0.12**

	Quetiapine Fumarate +Microcrystalline Cellulose	1:1	Quetiapine related compound G	0.2%	ND	0.06
			Quetiapine related compound H	0.2%	ND	0.02
			Any unspecified impurity	0.2%	0.03	ND
			Total impurity	**NMT 0.4**	**0.03**	**0.8**
	Quetiapine Fumarate +Magnesium Stearate	1:1	Quetiapine related compound G	0.2%	ND	0.01
			Quetiapine related compound H	0.2%	ND	0.05
			Any unspecified impurity	0.2%	ND	ND
			Total impurity	**NMT 0.4**	**0.07**	**0.06**
	Quetiapine Fumarate +Titanium Dioxide	1:1	Quetiapine related compound G	0.2%	ND	0.03
			Quetiapine related compound H	0.2%	0.07	0.06
			Any unspecified impurity	0.2%	ND	ND
			Total impurity	**NMT 0.4**	**0.07**	**0.09**
	Quetiapine Fumarate +Macrogol 400	1:1	Quetiapine related compound G	0.2%	0.04	0.08
			Quetiapine related compound H	0.2%	ND	ND
			Any unspecified impurity	0.2%	0.03	0.06
			Total impurity	**NMT 0.4**	**0.07**	**0.14**
	Quetiapine Fumarate +Trisodium Citrate dihydrate	1:1	Quetiapine related compound G	0.2%	ND	ND
			Quetiapine related compound H	0.2%	0.02	0.04
			Any unspecified impurity	0.2%	0.03	0.02
			Total impurity	**NMT 0.4**	**0.05**	**0.6**
	Quetiapine Fumarate +Hypromellose+ Lactose Monohydrate + Microcrystalline Cellulose + Magnesium Stearate+ Titanium Dioxide+ Macrogol 400+ Trisodium Citrate dihydrate	1:1:1:1:1 :1:1:1	Quetiapine related compound G	0.2%	0.04	0.06
			Quetiapine related compound H	0.2%	0.05	0.08
			Any unspecified impurity	0.2%	0.05	0.07
			Total impurity	**NMT 0.4**	**0.14**	**0.21**

Note: ND: Not Detected , NMT: NOT MORE THAN

In vitro drug release studies:

Dissolution studies were performed using the USP II, paddle-rotating method (Electrolab dissolution tester,TDT-08, India) at 37 °C ± 0.5 °C and 50 rpm using 0.1 N HCl in the initial 2 hours and phosphate buffered solution, pH 6.8 (PBS) till the end of the study , as the dissolution media. Dissolution studies were carried out in triplicate. 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 spectrophotometrically at 246 nm.

Calculation of similarity factor (f2) :

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well as comparison of test formulations to the theoretical release profile. The data were analyzed by the following formula.

$f2 = 50 \log \{[1+ (1/N) \Sigma (Ri – Ti)2]-0.5 \times 100\}$

Where N = number of time points

Ri = % release from marketed product or Theoretical release profile Ti = % release from test formulation at time i

If f2 value is in between 50-100, it is to be considered that 2 products share similar drug release behaviors.

Table 3: Physical properties of Formulations Prepared

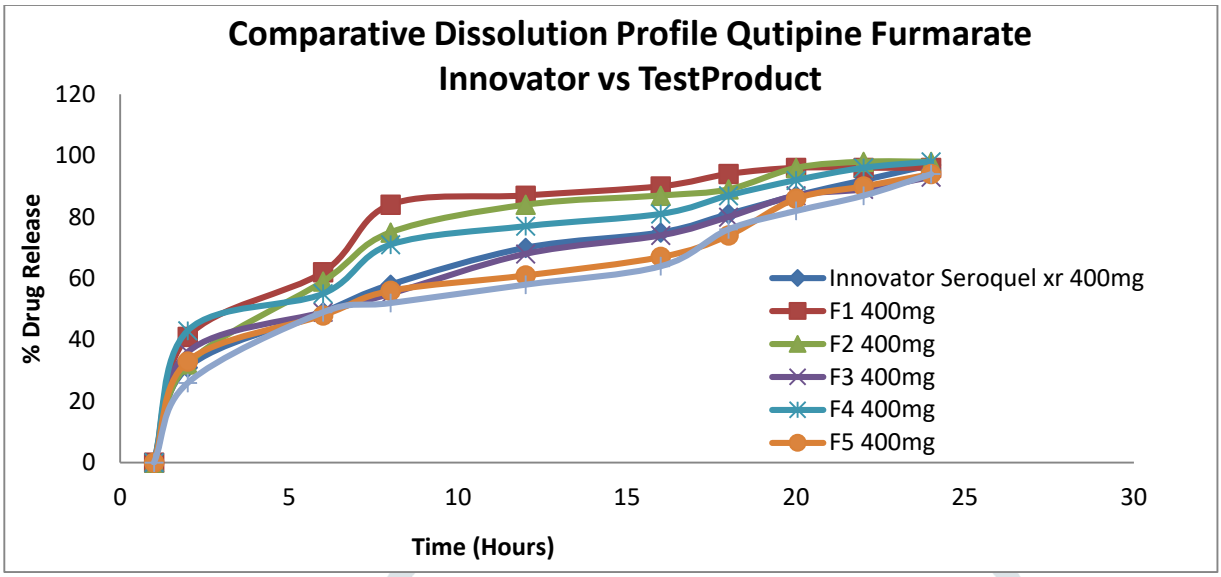
Test for core tablets	F1	F2	F3	F4	F5	F6
Weight variation (mg)± 5%	0.16	0.18	0.11	0.16	0.15	0.19
Hardness (kP)	5-7	4-8	5-8	5-7	5-9	5-9
Thickness (±0.30mm)	3.48±0.30	3.56±0.30	3.50±0.30	3.45±0.30	3.50±0.30	3.56±0.30
Friability (%)	0.23	0.24	0.22	0.27	0.30	0.22
Coated tablets						
Drug content (%)	98.7	99.7	99.0	98.6	98.0	99.7

Table 4: Dissolution profiles of marketed product (Seroquel XR 400mg) vs different formulation in 0.1N HCl and 6.8 Phosphate buffer

(The cumulative % drug release was calculated for the formulations and the drug release data were curve fitted)

Formulation type	Innovator Seroquel XR Tablets	F1	F2	F3	F4	F5	F6
Time (Hours)	400mg	400mg	400mg	400mg	400mg	400mg	400mg
1	0	0	0	0	0	0	0
2 NMT- 30%	24	41	32	36	43	33	19
6	38	62	59	49	55	48	49
8	48	84	75	55	71	56	52
12 NMT-60%	53	87	84	68	77	61	58
16	75	90	87	74	81	67	64
18	81	94	89	80	87	74	76
20 NLT- 80%	87	96	96	87	92	86	82
22	92	96	98	89	96	90	87
24	97	96	98	93	98	94	94
F2		34	39	55	42	57	58

Graph 1: Comparative dissolution profile between Innovator and Test formulation.



Mechanisms of drug release:
To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations [7, 8, 9]:

Zero- order equation: Q = k0t
Where, Q is the amount of drug released at time t, and k0 is the release rate

First- order equation: log (100-Q) = log100 – k1t
Where, Q is the percentage of drug release at time t, and k1 is the release rate constant

Higuchi's equation: Q = k2 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∞ = k tn
Where, Mt/ M∞ is the fractional solute release, t is the release time, k is the kinetic constant and n is an exponential value

Table 5: Release kinetics of the prepared formulations

	R^2			
	Zero- order	**First order**	**Higuchi**	**Korsmeyer-Peppas**
RLD	0.969	0.936	0.973	0.803
F1	0.759	0.965	0.936	0.693
F2	0.832	0.936	0.970	0.739
F3	0.892	0.970	0.989	0.716
F4	0.827	0.936	0.968	0.687
F5	0.893	0.906	0.976	0.723
F6	0.909	0.939	0.981	0.759

Influence of different filler Excipients on drug release

The fillers used were lactose monohydrate and microcrystalline cellulose K4Mwhich is very common filler in most of the formulations and using HPMC different grade for drug release.

Conclusion

The approach has been used in this study as a strategy for the design of a extended release tablet formulation, with a desired in vitro drug release behavior, was evaluation of hydrophilic matrix type extended release formulations, as well as the observation of formulation related variable effects on influences the kinetic release profiles.

Formulation with different HPMC polymer grade were manufactured by using wet granulation had good flow properties during compression and the tablets showed weight uniformity and mechanical strength and other physical parameters. All the formulations resulted with different dissolution profile with polymer of HPMC. 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 in vitro drug release. The formulation (F6) containing with HPMC K4M CR and HPMC K100M grade of HPMC showed satisfactory results sustaining the effect of the drug over 24 hrs to give once daily dose.

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