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Formulation and evaluation of quetiapine fumarate sustained release tablets

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ABSTRACT

Sustained release tablets of Quetiapine fumarate were prepared by wet granulation method using different polymers polymers HPMC K 4M , HPMC K 100M & EC in different ratios(F1 to F7)Dissolution was carried out in 0.1N Hcl & pH6.2 buffer. Dissolution tests are performed for successive batches and polymers were changed in each formulation. For seventh formulation maximum %Drug release was observed, in which ratio of two polymers HPMC K 4M & ETHYL CELLULOSE is 1:2. The % Drug release was very poor for polymers HPMC K 100M when compared to polymers HPMC K 4M & ETHYL CELLULOSE is 1:2.The dissolution profile of final batch(HPMC K 4M & ETHYL CELLULOSE 1:2.)compared with reference product which were found to be comparable with the reference product

Key words : Quetiapine fumarate, HPMC K 4M,ethyl cellulose, Sustained release tablets.

INTRODUCTION

The main objective of present study is to develop quetiapine sustained release tablets for the treatment of schizophrenia. Quetiapine acts by blocking D2 receptors in the dopamine pathways of the brain. Dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. By blocking the dopamine receptors in this pathway quetiapine fumarate controls psychotic experiences.For decreasing the dosage regimen of drug sustained release quetiapine fumarate tablets are necessary, for this purpose formulations containing drug in a sustained release tablet are prepared and evaluated using standard recommended tests.

MATERIAL AND METHODS

Quetiapine fumarate was prepared by wet granulation method using Lactose monohydrate ,Micro crystalline cellulose ,Sodium citrate anhydrous ,HPMC K 100M ,HPMC K 4M,EC, Magnesium stearate. Preformulation studies of pure drug and mixed blend were carried out using organoleptic character, angle of repose ,bulk density, tapped density,carr's index,and fourier transform spectroscopy. After compression the tablets were evaluated for thickness, hardness, friability, weight variation, drug content uniformity and *invitro* dissolution studies.

Characterization of tablets

The properties of enteric coated tablet, such as thickness, hardness, friability, weight variation and content uniformity were determined using IP procedure.

Preparation of sustained release tablets

Drug, lactose, MCC cyclocel (101) passed through sieve no. 40. Sodium citrate anhydrous was passed through sieve no. 30 along with polymers. Magnesium stearate was passed alone through sieve no. 40 and kept a side. All the ingredients along with drug and lactose, MCC (cyclocel), sodium citrate anhydrous, magnesium stearate mixed Except magnesium stearate all the ingredients are mixed in the 900 ml bowl with an impellor speed of 300 rpm and a chopper speed of 1000 rpm for 2 min. With the same mixing speed water was added with 7 ml/min until a granulate was formed. Drying was done overnight in an oven at 60º temperature. Granules of different sizes are passed through sieve no. 20 mesh. Lubricant magnesium stearate is added to improve the free flowing property of granules. Compression was done in the punch size of 19.45x9.25mm s/c.

RESULTS AND DISCUSSION

Preformulation studies are carried out and the results are tabulated

Table 1: Flow properties of Granules

Batch no	Angle of repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	% Compressibility
F1	39°.16''	0.542	0.680	20.29
F2	37°.25''	0.621	0.7623	18.53
F3	36°.18''	0.603	0.735	17.95
F4	35°.13''	0.6412	0.7320	12.40
F5	28°.11''	0.684	0.757	9.64

Table 2: Physical parameters of tablets of each batch

Formulation number	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
F1	1062	6.7	15.2	0.21
F2	1057	6.75	14.3	0.12
F3	1083	6.75	14.8	0.48
F4	1098	6.77	14.5	0.19
F5	1069	6.99	16.3	0.24
F6	1100	6.44	16.1	0.32
F7	1083	6.18	14.9	0.29

Table 2: Dissolution profile (F 1) of quetiapine fumarate using HPMC k100m as a polymer

Time in hrs	Cumulative % Drug release
2	39.2
6	62.3
8	84.5
12	92.8
14	99.2

Table 3: Dissolution profile (F2) of quetiapine fumarate using hpmc k 4m as polymer

Time in hrs	Cumulative % Drug release
2	32.9
6	59.1
8	75.8
12	89.6
14	99

Evaluation of quetiapine fumarate granules

Physical evaluation

The bulk density, tapped density, compressibility index were observed as It reveals that all formulations blend having better flow characteristic and flow rate than raw material. Compare to all these formulations, formulation 7 having a good flow properties. So this formulation is selected for further process.

Table 1: Dissolution profiles of marketed product (seroquel xr) in 0.1N HCl and 6.2 buffer

Time in hrs	Cumulative % Drug release
2	31
6	48.8
8	57.9
12	68.9
16	75.1
18	81.8
20	87.4
22	92.6
24	99.3

Table 4: Dissolution profile (F3) of quetiapine fumarate by using hpmc k100m & hpmc k 4m 1:1 ratio

Time in hrs	Cumulative % Drug release
2	33.4
6	55.5
8	71.4
12	87.1
16	99.1

Table 5: Dissolution profile (F4) of quetiapine fumarate by using hpmc k100m & ethyl cellulose in 1:1 ratio

Time in hrs	Cumulative % Drug release
2	31.4
6	49.1
8	65.9
12	77.6
16	83.4
18	92.3
20	99.3

Table 6: Dissolution profile (F5) of quetiapine fumarate by using Hpmc k100m & ethyl cellulose in 1:2 ratio

Time in hrs	Cumulative % Drug release
2	32.7
6	49.9
8	55.3
12	68.6
16	79.8
18	85.3
20	91.8
22	99

Table 7: Dissolution profile (F6) of quetiapine fumarate by using hpmc k 4m & ethyl cellulose in 1:1 ratio

Time in hrs	Cumulative % Drug release
2	33.1
6	53.8
8	67.1
12	79.3
16	86.5
18	94.1
20	99.6

Table 8: Dissolution profile (F7) of quetiapine fumarate using hpmc k4m & ethyl cellulose in 1:2 ratio

Time in hrs	Cumulative % Drug release
2	31
6	48.8
8	57.9
12	68.9
16	75.1
18	81.8
20	87.4
24	99.5

Evaluation of quetiapine fumarate tablets

Four formulations of uncoated tablets were evaluated for physical appearance, weight variation, thickness, hardness, and friability, disintegration time,drug content,and *in vitro* dissolution studies and the results are tabulated. Among the all seven formulations F7 was found to be correlated with the specified limits

Table 9: Comparisons of dissolution profile of f3, f4, f5, f6, and f7 prepared with the polymers hpmc k 100m, hpmc k 4m & ethyl cellulose in different ratios

Time (hrs)	HPMC 100M & 4M 1:1 ratio F3	HPMC 100M & EC 1:1 ratio F4	HPMC 100M & EC 1:2 ratio F5	HPMC 4M & EC 1:1 ratio F6	HPMC 4M & EC 1:2 ratio F7
2	33.4	31.4	32.7	33.1	31
6	55.5	49.1	52.9	53.8	48.8
8	71.4	65.9	55.3	61.1	57.9
12	87.1	77.6	68.6	75.3	68.9
16	99.1	83.4	79.8	82.5	75.1
18		92.3	85.3	88.4	81.8
20		99.3	91.8	93.6	87.4
22			99	99.6	92.6
24					99.5

Table 9: Comparison of dissolution profile of f7 with marketed product seroquel xr-400

Time in hrs	Cumulative %Drug release formulation F7	Cumulative % Drug released SEROQUEL XR-400
2	31	30.9
6	48.8	51.2
8	57.9	62.2
12	68.9	73.2
16	75.1	82.6
18	81.8	86.1
20	87.4	90.7
22	92.6	94.9
24	99.5	99.3

Table 10: Physical parameter evaluation (Stability study conducted at 40°c ±2°c/75% RH ±5%.)

Test	Before	After 90 days	Inference
Hardness	14.8KP	14.8KP	No significant change was observed
Avg Weight	1049gm	1049gm	
Thickness	6.26mm	6.26mm	
Friability	0.29%	0.28%	

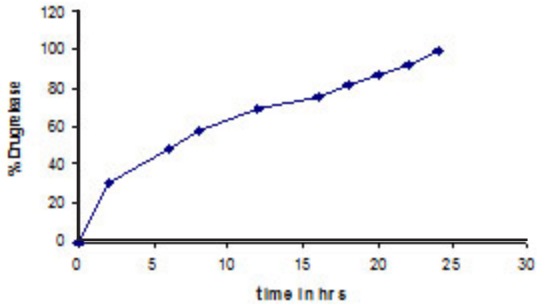

Fig. 1: Dissolution profileof quetiapine fumarate in 0.1N HCl and 6.2 buffer

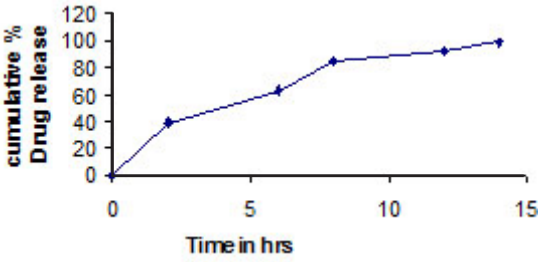

Fig. 2: Dissolution profileof quetiapine fumarate using HPMCK 100 M

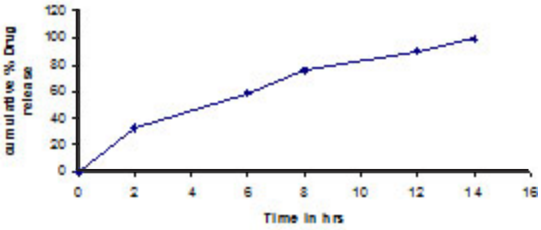

Fig. 3: Dissolution profileof quetiapine fumarate using HPMC K 4M

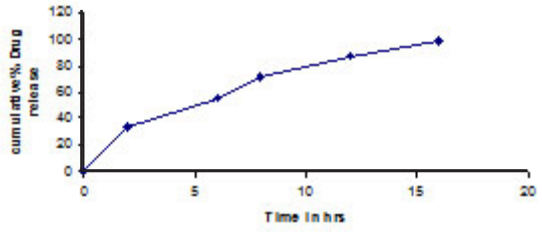

Fig. 4: Dissolution profileof quetiapine fumarate using HPMC K 100 M and 4M in 1:1 ratio

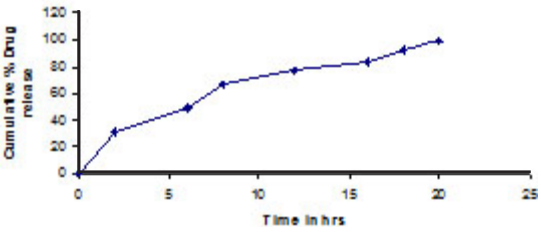

Fig. 5: Dissolution profile of quetiapine fumarate using HPMC K 100M & EC in 1:1 ratio

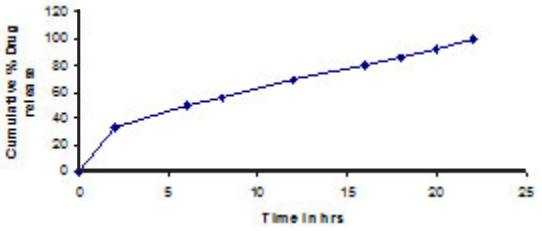

Fig. 6: Dissolution profile of quetiapine fumarate using HPMC K 4M EC in 1:2 ratio

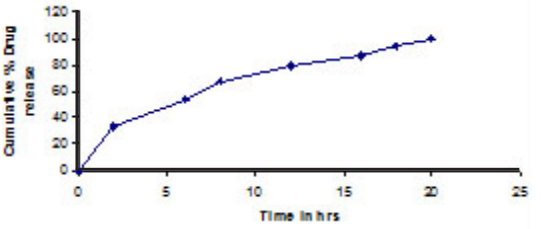

Fig. 7: Dissolution profile of quetiapine fumarate using HPMC K 4M EC in 1:1 ratio

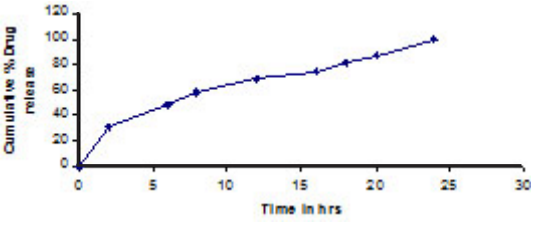

Fig. 8: Dissolution profile of quetiapine fumarate using HPMC K 4M EC in 1:2 ratio

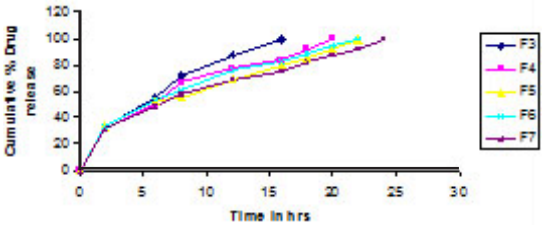

Fig. 9: Camparision of dissolution profile of quetiapine fumarate with three polymers in different ratios

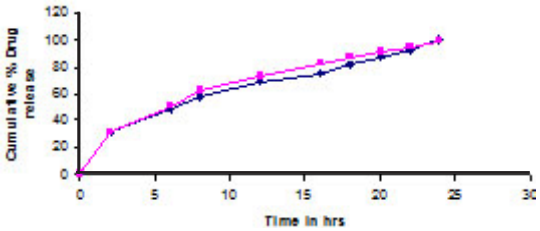

Fig. 10: Comparision of dissolution profile of quetiapine fumarate withmarketed product

CONCLUSION

Dissolution test for innovatory tablets are performed in 0.1N Hcl & 6.2 buffer. Dissolution tests are performed for successive batches and polymers were changed in each formulation. For seventh formulation maximum %Drug release was observed, in which ratio of two polymers HPMC K 4M & ETHYL CELLULOSE is 1:2. The % Drug release is very poor for polymers HPMC K 100M. The formulation with best % Drug release was compared with marketed product values.

The stability of product was determined by conducting accelerated stability testing in 40°c ± 2°c / 75% ± 5%RH conditions for 3 months as per ICH guidelines in PVC/PVDC blisters. Finally after the duration, the product was analyzed for physical appearance, dissolution, assay. By the stability studies the formulated quetiapine fumarate sustained release tablets were proved to be stable throughout the period of storage. Formulated quetiapine fumarate sustained release tablets by using polymers HPMC K 4M & EC in 1:2 ratio were found to be stable through out its shelf life and comparable with reference product.

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