ISSN: 0974-2115
Journal of Chemical and Pharmaceutical sciences

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF QUETIAPINE FUMARATE

*[1]HARINATHA REDDY P, [1]PRAGATI KUMAR B, [1]DURAIVEL S
[1]Department of Pharmaceutics, Nimra College of Pharmacy, Vijayawada, Andhra Pradesh, India
***Corresponding author Email:** harireddy87@yahoo.com

ABSTRACT

The present study was an attempt to formulate and evaluate controlled release matrix tablets of Quetiapine fumarate (QPF). Quetiapine fumarate is prescribed for the treatment of schizophrenia. It has a mean half life of 6 hours and it has to be administered atleast thrice a day. The main objective of the study is to design once a day dosage form which can release the drug for 24 hours. The tablets were prepared by direct compression method. In-vitro dissolution studies showed that F_7 has better release profiles compared to the other formulations. Though F_4 showed release of 22 hours, the drug release was not constant. The experiment clearly stated that the usage of Carbopol 934 has promoted the sustained release of QPF.

KEYWORDS: Quetiapine fumarate, controlled release matrix tablets, direct compression, Carbopol 934.

1. INTRODUCTION

Controlled and sustained release products provide an immediate release of drug that promptly reduces the desired therapeutic effect, followed by 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. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing (Leon lachman, 1990). Cellulose ethers, Eudragits and Carbopols 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 (Udaya S. Toti,2004). 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 H_1, and adrenergic alpha$_1$ and alpha$_2$ receptors. It is prescribed for the treatment of schizophrenia. It is a second generation antipsychotic (Hamner MB, 1996).

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 (Arvanitis LA, 1997), (Borison RL, 1996).

2. Materials and Methods

2.1. Materials: The active substance QPF was obtained from Shasun Chemicals, Pondy. Carbopol 934 from Lyka Labs, Mumbai, lactose monohydrate from Rolex Laboratories, microcrystalline cellulose from Himedia, Mumbai, and starch from S.D Fine Chemicals Ltd., talc was procured from Hetero drugs, Hyderabad, magnesium stearate from Himedia, Mumbai.

2.2. METHODS: Preparation of controlled release matrix tablets: QPF Controlled release matrix tablets were prepared by direct compression method. The drug and excipients except lubricants were sieved separately and mixed thoroughly. The dry blend was then lubricated and subjected to compression using a tablet punching machine (Yie W. Chien,1992), (Baldwin CM,2009), (Remingtons,1980).

Table no 1 Formulation table of Quetiapine fumarate tablets

S.No	Ingredients	Quantity in mg/tablet								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Quetiapine fumarate	200	200	200	200	200	200	200	200	200
2	Carbopol 934	20	20	20	40	40	40	60	60	60
3	Lactose monohydrate	74	-	-	54	-	-	34	-	-
4	Microcrystalline cellulose	-	74	-	-	54	-	-	34	-
5	Starch	-	-	74	-	-	54	-	-	34
6	Talc	3	3	3	3	3	3	3	3	3
7	Magnesium state	3	3	3	3	3	3	3	3	3

2.3. Bulk evaluation of the Drug and excipients used in the Formulation: Drug and excipients were subjected to the physical evaluation tests such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and the results have been tabulated in table 2. (Leon Lachman 2009), (Aulton M.E, 2001).

2.4. Evaluation of tablets: The post compression evaluation parameters such as weight variation, hardness, thickness, diameter, friability, and dissolution as per USP were evaluated and the results were tabulated in table 3. (Aulton M.E, 2001).

2.5. *In-vitro* dissolution studies: Drug release profile was evaluated *in vitro* using a dissolution test apparatus. One tablet containing 200 mg of QPF was placed in the 1000 ml dissolution medium and speed of paddle was set at 50 rpm. Samples (5 ml) withdrawn at a time interval of 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 &24 hours and same value of fresh medium was replaced. The samples were analyzed for drug content against 0.1 M HCl as blank at λmax 259.0 nm (UV Spectrophotometer Shimazdu-1700). The percentage drug release against time was determined. The values were tabulated in table 4.

2.6. Drug release kinetics: To analyze the mechanism of drug release from the prepared formulations, the data obtained from *In-vitro* release studies were subjected to Zero-Order, First-order, Higuchi's and Korsmeyer-Peppas models as shown in the tables 5 and 6.

3. RESULTS AND DISCUSSION

Drug was identified by Fourier Transform Infrared Spectroscopy (FTIR). FTIR spectra of pure drug QPF was recorded with FTIR spectrometer. The Compatibility studies were carried out by studying Differential Scanning Calorimetry analysis (DSC).The IR absorption spectra of the pure drug was taken in the range of 4600-400cm^{-1} using KBr disc method. From the FTIR peaks it was observed that no peak changes in drug and tablet.DSC thermographs of pure drug and formulations F1- F9 revealed that the melting point of pure drug is 234°Cand 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. The drug and excipients are having angle of repose values in the range of 24.54±0.41 to 29.44±0.43, which indicates that the powders are having an excellent flow property. The loose Bulk density is in the range of 0.682 ± 0.003 to 0.756 ± 0.002 and tapped density is in the range of 0.789 ± 0.004 to 0.871 ± 0.004. These values were used to calculate compressibility index and Hausner's ratio which were tabulated in table 2. All values are expressed as Mean ± S.D, number of samples is equal to 3. Weight variation was in range of 299.08±0.08 to 300.23± 0.30 and hardness was in range of 5.4± 0.0 to 5.83± 0.12 .Weight variations and hardness of QPF Tablets was within range. Thickness of the tablet was in the range of 3.45± 0.020 to 3.53± 0.016mm. Percentage friability of tablet was evaluated in 100 rotations and tablets passed the friability test and found to be in the range of 0.35±0.02to 0.58±0.02%. Each sample was analyzed in triplicate (n = 3). Capping of tablet was not observed.

The drug content in the tablets was ranged from 99.92 to100.38. The drug release rate was faster in F-3 and slower in F-7. The release of QPF was sustained as the proportion of Carbopol 934 was increased from 20 to 60 and the proportion of lactose was decreased from 74 to 34. The releasae of QPF optimised formula F-7 showed zero order release with regresson coefficient (r) value 0.996 as shown in table 5. The regression coefficient value of F-7 in Higuchi is 0.895 and it indicates the release is from a polymer matrix. From the Korsmayer-Peppas plots the value of slope (*n)* and the regression coefficient value in F-7 is 1 and 0.990 which are shown in the table 6. This indicates that F-7 does not follow First order and Higuchi's model. From this it can be understood that the drug release from formulation F-7 is non-linear and follows non-fickian diffusion.

Table no 2 Bulk evaluation of the Drug and excipients used in the Formulation

S. No	Ingredients	Angle of repose	Bulk density g/cc	Tapped density g/cc	Compressibility Index %	Hausner's Ratio
1	Quetiapine fumarate	26.80±1.07	0.685 ± 0.003	0.855 ± 0.004	19.85 ± 0.33	1.25 ± 0.005
2	Carbopol	27.70±0.79	0.695 ± 0.003	0.818 ± 0.007	15.02 ± 1.05	1.18 ± 0.015
3	Lactose monohydrate	24.54±0.41	0.706 ± 0.002	0.804 ± 0.002	12.19 ± 0.20	1.14 ± 0.003
4	Microcrystalline cellulose	27.27±1.22	0.682 ± 0.003	0.789 ± 0.004	13.64 ± 0.08	1.16 ± 0.001
5	Starch	29.05±0.76	0.714 ± 0.005	0.855 ± 0.006	16.41 ± 1.16	1.20 ± 0.017
6	Talc	29.44±0.43	0.732 ± 0.003	0.871 ± 0.004	15.96 ± 0.72	1.19 ± 0.010
7	Magnesium stearate	27.27±1.22	0.756 ± 0.002	0.860 ± 0.004	12.06 ± 0.36	1.14 ± 0.005

Table no 3 Evaluation of controlled release matrix tablets of Quetiapine fumarate

S. No	Weight uniformity (mg)*	Thickness (mm)*	Hardness (KP)*	% Friability*
F1	299.63±0.09	3.47±0.02	5.5±0.10	**0.41±0.02**
F-2	300.23±0.30	3.5±0.01	5.6±0.10	**0.51±0.02**
F-3	298.77±1.10	3.45±0.02	5.4±0.00	**0.37±0.03**
F-4	299.45±0.28	3.48±0.01	5.4±0.10	**0.53±0.03**
F-5	299.08±0.08	3.51±0.01	5.43±0.12	**0.41±0.02**
F-6	299.33±0.15	3.51±0.01	5.53±0.12	**0.58±0.02**
F-7	299.33±0.21	3.5±0.02	5.83±0.12	**0.36±0.02**
F-8	299.3±0.25	3.53±0.01	5.7±0.17	**0.43±0.03**
F-9	299.83±0.24	3.52±0.01	5.6±0.00	**0.35±0.02**

4. CONCLUSION

The drug excipient compatibility studies concluded that, the drug is in the same pure state even in the formulation without interacting with the polymer and excipients. Tablets were prepared by direct compression method. After compression the controlled release matrix tablets of Quetiapine Fumarate were of adequate strength. Studies on compression characteristics of Quetiapine Fumarate matrix tablets indicated that the weight variation, hardness, friability were uniform and reproducible. In-vitro dissolution studies concluded that formulation F7 showed desired drug release profiles compared to the other formulations. Among the different diluents used Lactose showed better drug release profile. The controlled release drug delivery system of Quetiapine Fumarate was able to show controlled release of drug for 24 hours.

Table no 4 Comparitive study of the drug release profile of all the Formulations

S.NO	Time(hrs)	%Drug release of formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	2.60	2.60	10.31	1.98	1.52	4.12	1.68	1.52	2.06
3	1	11.16	11.16	22.12	3.98	10.67	11.55	2.76	10.67	12.00
4	2	20.92	20.92	31.55	11.33	21.57	22.61	8.27	21.57	22.44
5	4	29.05	29.05	43.41	27.12	29.02	30.44	21.98	29.02	29.29
6	6	38.44	38.44	51.81	32.92	38.72	40.07	26.99	38.72	40.06
7	8	46.90	46.90	62.10	42.72	47.33	49.15	35.00	47.33	47.53
8	10	53.87	53.87	71.07	49.21	54.84	56.82	45.65	54.84	55.27
9	12	61.20	61.20	83.43	55.40	62.09	67.28	51.68	62.09	63.44
10	14	74.67	74.67	90.91	61.65	75.71	78.49	62.88	75.71	77.53
11	16	84.62	84.62	100.11	75.81	85.29	88.00	70.48	85.29	87.27
12	18	92.33	92.33		86.07	94.15	100.09	78.34	94.15	94.38
13	20	100.38	100.38		92.18	100.02		85.40	100.02	99.92
14	22				100.10			92.30		
15	24							99.95		

Table no 5 Kinetic values for Quetiapine Fumarate Tablets

Formulations	Zero-order values		First-order values	
	Slope(n)	Regression coefficient (r^2)	Slope(n)	Regression coefficient (r^2)
F1	5.267	0.977	-0.051	0.906
F2	5.519	0.976	-0.044	0.930
F3	6.923	0.897	-0.064	0.953
F4	4.692	0.989	-0.046	0.899
F5	5.317	0.976	-0.055	0.884
F6	5.694	0.976	-0.049	0.937
F7	4.298	0.996	-0.043	0.92
F8	5.317	0.976	-0.055	0.884
F9	5.377	0.972	-0.057	0.89

Table no 6 Kinetic values for Quetiapine Fumarate Tablets

Formulations	Higuchi's values		Korsmayer-Peppas values	
	Slope(n)	Regression coefficient (r^2)	Slope(n)	Regression coefficient (r^2)
F1	19.44	0.934	0.860	0.954
F2	19.32	0.925	0.753	0.987
F3	23.37	0.984	0.599	0.982
F4	18.01	0.908	1.015	0.986
F5	19.63	0.934	0.95	0.920
F6	19.97	0.935	0.800	0.976
F7	17.15	0.895	1.075	0.990
F8	19.63	0.934	0.95	0.920
F9	19.88	0.938	0.891	0.930

5. REFERENCES

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), 1997 Aug 15, 233-46.

Aulton M.E, Pharmaceutics- The Sciences of Dosages form design, international student Edition, Churchill Livingston: 2001, 129-191.

Baldwin CM, Scott LJ. Quetiapine extended release in schizophrenia, ncbi, 23(3); 2009; 261-9.

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); 1996; pp. 158-69.

Hamner MB, Arvanitis LA, Miller BG, Link CGG, Hong WW, Plasma prolactin in schizophrenia subjects treated with SeroquelTM (ICI 204,636), Psychopharmacology Bull, 32(1) 1996, 107-110.

Leon lachman, Herbert A.Liberman, The Theory and Practice of Industrial Pharmacy, special Indian edition 2009; 317

Leon lachman, Joseph L. Kanig: The theory and practice of industrial pharmacy, 3rd edition: 1990, 71, 88, 183, 299, 316, 430-456,386-392.

Remingtons, Pharmaceutical Sciences, 6th Edition, Mack Publishing Company: 1980, 1677-1683

Udaya S. Toti, Tejraj M. Aminabhavi, Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride, Journal of Controlled Release, 24 March *2004,95(*3), *567-577*.

Yie W. Chien, Novel drug delivery Systems, 2nd Edition, Marcel Dekker, Inc. New York, 1992, pages:2, 36, 53, 139-196, 484.