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FORMULATION AND EVALUATION OF EXTENDED RELEASE MATIX TABLETS OF QUETIAPINE FUMARATE TABLETS

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ABSTRACT

Quetiapine is among the most widely used atypical antipsychotics, and has the least propensity to induce extrapyramidal motor symptoms. The main objectives of this work is to develop extended release matrix tablets of Quetiapine fumarate using different polymers viz. Carbopol, glyceryl behenate and vegetable oil. 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. The coating was done by Ethylcellulose as a film former and opadry yellow as coloring agent. 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 6.2 up to remaining hours. The effect of polymer concentration and polymer blend concentration were studied. Among all the formulations, Quetiapine Fumarate Extended matrix tablets F006 which contains carbopol release the drug which follows Zero order kinetics, and the release profile of formulation of Quetiapine Fumarate Extended release matrix tablets of F006 was comparable with marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that Quetiapine fumarate was stable in the matrix tablets.

KEYWORDS: *Absorption, Bioavailability, concentration time, Extended release, Gastrointestinal.*

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 extrapyramidal side effects. It is readily absorbed from the gastrointestinal track with oral bioavailability of about 83% and a plasma elimination half life ranging from 6-7hours. 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 schizophrenic 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. 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 preexisting dopaminergic pathologies, such as Alzheimer's disease and Parkinson's disease.

MATERIALS AND METHODS

Quetiapine fumarate (Hetero drugs limited), Lactose mono hydrate (DMV International), Microcrystalline cellulose (avicel ph 101) (FMC biopolymer), Dicalcium phosphate dehydrate (Signet), Magnesium stearate (Ferro), Carboxymethyl cellulose sodium (Lubrizole), Lubritab (Signet), carbopol (Pioa chemicals)were used for this study.

1. Preparation of Extended Release Tablets of Quetiapine Fumarate

The method of development of quetiapine fumerate extended release tablets is wet granulation method.[2]

Steps involved in the formulation:

Step 1: Sifting: Quetiapine fumarate, carbopol, dicalcium phosphate dihydrate are passed through #30. Microcrystlline cellulose, lactose monohydrate are passed through #40.

Step 2: Dry mixing: The mixture in step 1.1 and step 1.2 are taken into an RMG and were mixed for 15minutes with impeller at slow speed and chopper off.

Step 3: Preparation of binder solution.

Step 4: Wet granulation: The above mixture is granulated in RMG by adding binder solution with impeller at slow speed and Chopper off. The wet mass is kneaded for 1 minute with impeller and chopper at slow speed. The wet mass is unloaded from the granulator.

Step 5: Drying: The wet mass is loaded into an FBD and is dried.

Step 6: Sizing of dried granules: The granules are sifted by passing through sieve number 25. Oversized granules were milled in a multimill with 1 mm screen, medium speed and knives in forward direction, the milled granules are passed through #25.

Step 7: Sifting of extragranular material Magnesium stearate is sifted through #30.

Step 8: Pre lubrication: The mixture is pre-lubricated for 10 mins.

Step 9: Lubrication: The mixture is lubricated by adding magnesium stearate for 5 minutes.

Step 10: Film coating: Opadry yellow (03b22239) or ethyl cellulose was dispersed slowly to purified water under continuous stirring for 30 minutes. Core tablets were transferred into coating pan, warm the tablets while running the pan, until the tablet bed temperature reaches approximately 45±5ºc and continued the coating till the average tablet weight gain is 3.0±0.5% w/w of tablets. Weight with the following coating parameters.[3,4]

2. Evaluation of Extended release tablets

Tablets were evaluated for hardness, weight variation, friability, thickness, and percentage drug release as per the pharmacopoeia.

2.1 Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness14 of the tablets was determined using Dr. Schleuniger hardness tester. It was expressed in Newton (N). Ten tablets were randomly selected from each formulation and hardness of the same was determined. The average value was also calculated.

2.2 Friability: The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). About 6.5 g tablets (W-initial) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or 100 revolutions. The tablets were dedusted and weighed again (Wfinal). The percentage friability was calculated by,

F= Winitial- Wfinal/ Winitial× 100

% Friability of tablets less than 1 % was considered acceptable

2.3 Thickness: Twenty tablets were randomly selected from formulations and thickness was measured individually by using vernier calipers. It was expressed in millimeters and average was calculated.

3. Weight variation test: Twenty tablets were selected at random and their average weight was determined using an electronic balance (Shimadzu Aux200, Japan). The tablets were weighed individually and compared with average weight.

4. In- vitro dissolution study: According to the specifications the dissolution should be carried out in 2 stages, first in acid stage and the next is in buffer stage and was determined using USP dissolution testing apparatus I. Medium is 0.1 N HCL followed by pH 6.2 phosphate buffer. The dissolution testing was performed using 750ml of 0.1N HCl at 37±0.5°C temperature and speed 100 rpm. Sample of 10ml was withdrawn at prescribed time intervals i.e., 1,2hours in acid stage and 4,6,8,10,12,14,16,18,20,22,24hrs in buffer stage and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using UV.[5]

EQUATIONS

(1) Carr's index

Carr's index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's index:

$$\% \text{ Compressibility} = (Pt - PO / Pt) \times 100$$

Where, **Pt** = Tapped density

PO = Bulk density

(2) Haussner's Ratio

Haussner's ratio was determined as the ratio between the tapped density to that of the bulk density.

$$\text{Haussner's ratio} = \rho t / \rho o$$

Where, ρt= Tapped Density

ρ0= Bulk Density

(3) Higuchi Model

A form of the Higuchi Square Root law is given by equation

$$Q=Ks\sqrt{t}$$

Where, Q= Amount of drug dissolved at time t

Ks= Higichi rate constant

The Higuchi square root equationdescribes the release from systems where the solid is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

RESULTS

Extended release matrix tablets of Quetiapine Fumarate were successfully prepared by wet granulation using excipients like Lactose mono hydrate, Microcrystalline cellulose, Di calcium phosphate dihydrate, Magnesium stearate, Carboxymethyl cellulose sodium, Lubritab, Carbopol. Formulations were evaluated for pre and post compression parameters and also compared with marketed product for in-vitro dissolution. The FT-IR spectral analysis showed that there was no change of any characteristic peaks of pure drugs and excipients, which confirmed that the absence of chemical interaction between drug and excipients. The granules of the tablet were prepared by wet granulation method and evaluated for various physicochemical characteristics. The granules of different formulations were evaluated for angle of repose, Bulk and Tapped density, Compressibility index, Hausner's ratio. It showed that the results of all formulations of the granules were within limits and thus it confirmed that the granules have good flow property.

Table 1: Preformulation study results.

S. No	Characteristics	Results
1	Organoleptic character	White, odorless fine powder
2	Bulk density	0.27
3	Tapped density	0.47
4	Compressibility index	57.4
5	Hausner’s ratio	1.72
6	Particle size	24 microns

Table 2: Compression parameters.

S. No	Parameter	F001	F002	F003
1	Description	Quetiapine tablets	Quetiapine tablets	Quetiapine tablets

		are yellow capsule shaped tablets	are yellow capsule shaped tablets	are yellow capsule shaped tablets
2	Weight of 10 tablets(gm)	4.93	4.94	4.94
3	Weight of individual tablets(mg)	493 - 495	493- 496	
4	Hardness(kp)	22-24	23-25	22-24
6	Thickness(mm)	5.50-5.80	5.60-5.75	5.60-5.75
7	Friability(%w/w)	0.15%	0.14%	0.13%

Table 3: Dissolution profile comparison of various formulations.

Time(hrs)	Innovator % amount of drug release	F001	F002	F003	F004	F005	F006
0	0	0	0	0	0	0	0
1	22	41	30	36	30	23	22
2	39	64	46	52	42	42	41
4	44	71	50	58	50	48	47
6	55	79	65	62	58	56	54
8	66	86	79	69	66	60	63
10	74	90	84	76	75	64	75
12	84	91	88	80	83	71	82
14	86	93	91	87	87	75	86
16	88	96	92	89	90	79	88
18	90	97	94	94	93	82	89
20	91	99	96	97	95	86	90
22	93	100	98	99	98	88	92
24	94	101	99	100	99	89	94

Table 4: Comparison of F006 with innovator.

Time	% cdr of innovator	% cdr of F006
0	0	0
1	22	22
2	39	41
4	44	47
6	55	54
8	66	63
10	74	75
12	84	82
14	86	86
16	88	88
18	90	89
20	91	90
22	93	92
24	94	94

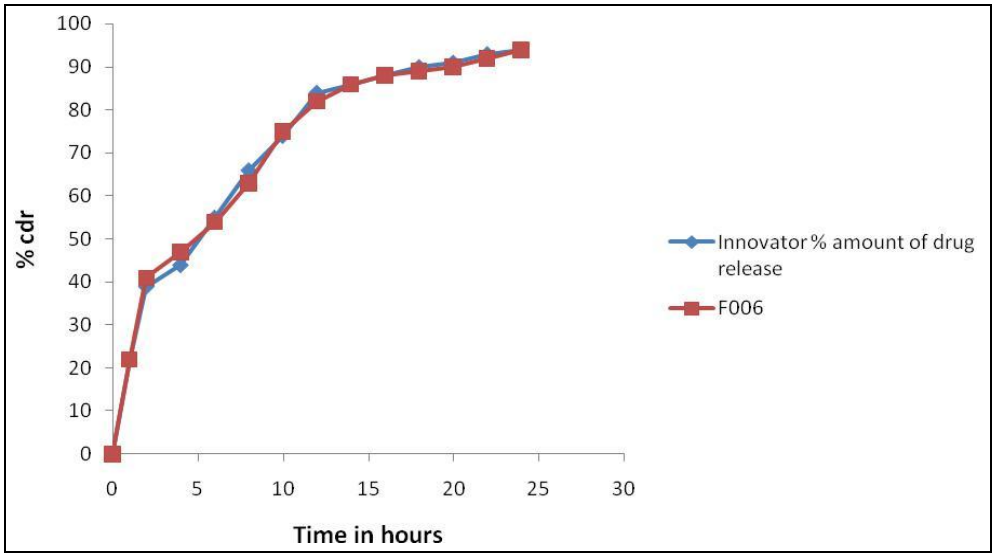

Fig. 1: Comparison of F006 with innovator.

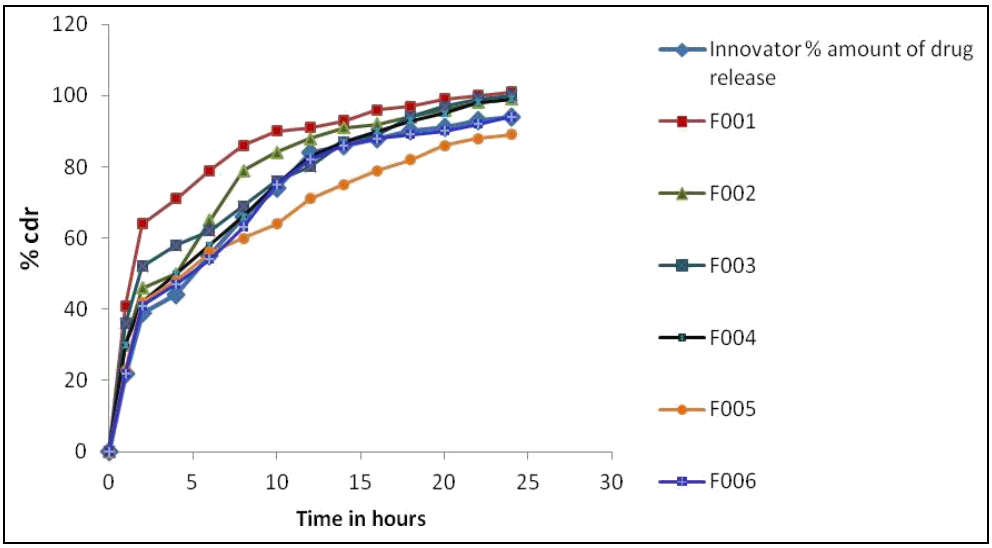

Fig. 2: Comparison of various formulations with innovator.

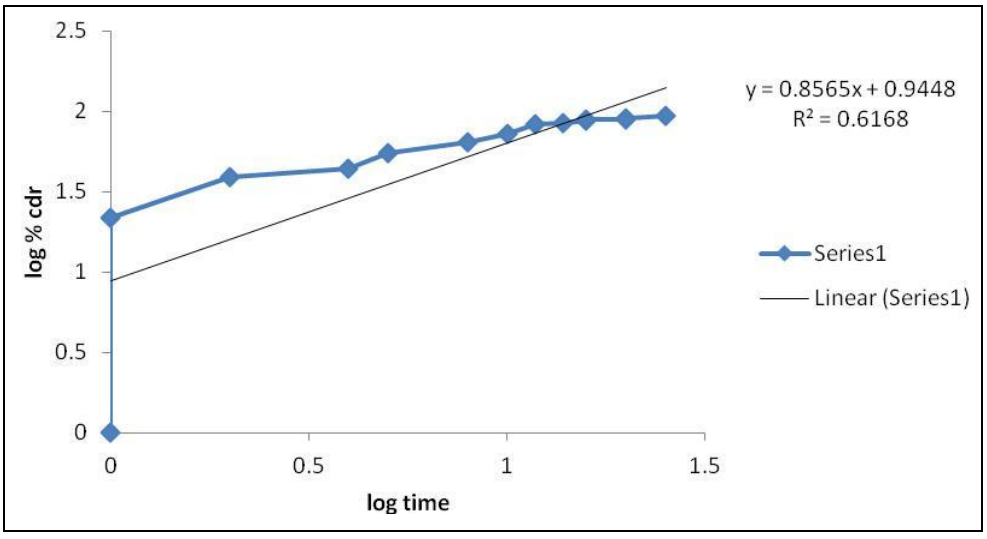

Fig. 3: Koser meyer peppas plot of innovator.

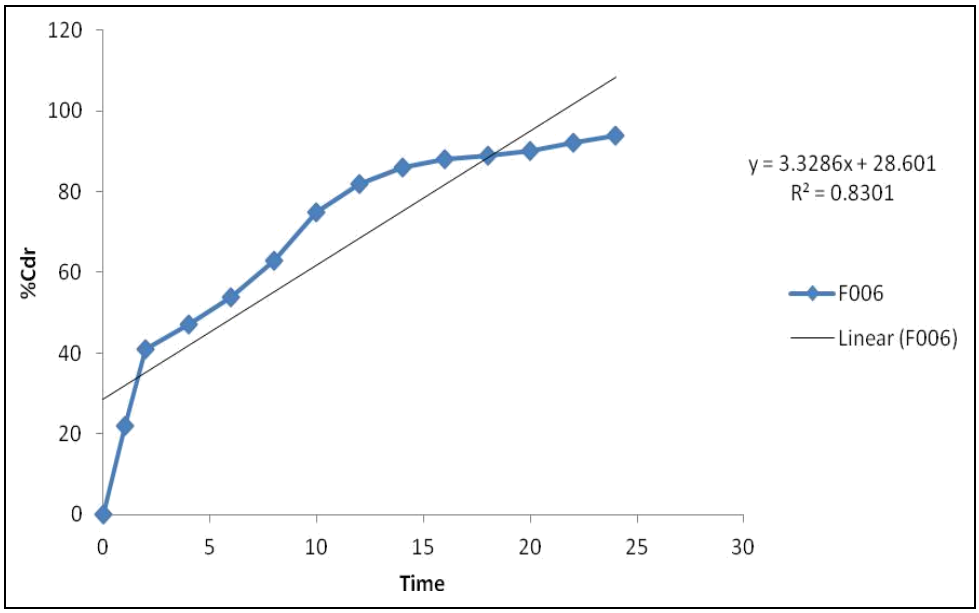

Fig. 4: Higuchi plot of optimized formulation.

DISCUSSION AND CONCLUSION

The present investigation concluded that Preformulation studies for drug-polymer compatibility by FT-IR spectroscopy gave confirmation about their purity and showed no interaction between the drug and selected polymers. Drug excipient compatibility study was conducted and the results obtained with different polymers and excipients showed good compatibility with quetiapine. Tablets were evaluated for micromeritic properties like bulk density, tapped density, car's index, hausner's ratio and angle of repose. The granules showed good flow properties.

In Vitro drug release behaviour is also dependent on the polymer concentration. From among all the developed formations, since F006 has a required drug release upto 94% at 24 hour was selected as the best formulation. The drug release mechanism of the optimized formulations followed zero order release mechanism. The present investigation concluded that most satisfactory formulation had showed no significant change In Vitro dissolution pattern after storage at 40 C/ 75%RH during stability studies for 3 months as per ICH guidelines. The selected formulation was compared with the marketed formulation (I). The comparison of final optimized with innovator was done by using similarity factor (F2) and dissimilarity factor (F1). Release kinetics was studied for all formulations and drug release followed zero order in all cases.

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REFERENCES

1. AM Raggi; R Mandrioli; A Ferranti; J. Pharm. Biomed. Analysis, 2003; 32: 1037-1044.
2. Phaechamud T, Mueannoom W, Tuntarawongsa S, Chitrattha S. Preparation of coated valproic acid and sodium valproate sustained-release matrix tablets. Int.J.Pharma, 2010; 2: 173-183.
3. The United States Pharmacopoeia, XXIV-NFXIX: Asian Edition, USP Convention Inc., 2000; 1739-1742.
4. Indian Pharmacopoeia Ministry of Health and Family Welfare, Government of India, New Delhi, 1996; 1: 328.
5. Gul Majid Khan, Zhu Jiabi. Formulation and invitro evaluation of ibuprofen-carbopol 974p-nf controlled release matrix tablets iii: influence of co-excipients on release rate of the drug. Journal of Controlled Release, 1998; 54(2): 185-190.
6. Aulton M.E., 'Granulation, Pharmaceutics, 'The science of dosage form design, Churchill Livingstone, Edin burgh, 187,188.
7. Dilip M.Parikh., High shear Mixer Granulators, Hand book of Pharmaceutical Granulation Technology, Marcel Dekker. ING, New York, 165-181.
8. Girish Kumar Jain, Orn Anand, Ashok Rampal, 'Extended release matrix tablets' in united states patent application publication(US2006/0159752A1), 2006.

9. Phaechamud.T., Mueannoom.W, Tuntarawongsa.S., Chitrattha.S., 'Preparation of coated valproic acid and sodium valproate sustained-release matrix tablets.' *Int.j.pharma*, 2010; 2(72): 173-183.
10. Robinson and Lee, 'Controlled drug delivery; fundamentals and applications, Marcel dekkar, 1978; 2: 24-26.