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Research Article

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Formulation development and evaluation of sustained release matrix tablets of quetiapine fumarate

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ABSTRACT

The objective of the present research was to study the effect of two different polymers such as Guar gum and Tara gum and two different fillers such as Microcrystalline cellulose (Avicel PH 101), Dicalcium phosphate in formulation of a sustained release (SR) matrix tablet of Quetiapine fumarate. Quetiapine fumarate and polymer compatibility studies were performed using Fourier transform infrared spectroscopy (FT-IR) and Differential scanning calorimetry (DSC). The pre-compression mixture formulation was evaluated for flow ability and compressibility. The tablets were prepared by direct compression method. The effect of concentration and type of polymers, type of diluent on in-vitro drug release and release kinetics was studied extensively. FT-IR and DSC studies revealed no interaction between Quetiapine fumarate and polymers. Flow ability and compressibility study of pre-compression powder formulation showed that these formulations were within the theoretical range for processing into tablet dosage form. In-vitro drug release studies exhibited that the drug release was sustained up to 12 h for SR matrix tablets prepared with both Guar gum and Tara gum but Guar gum showed better sustained action with good percent drug release when compared with Tara gum. Hence both type of polymers mentioned above can be used for the preparation of SR tablets of Quetiapine fumarate.

Key words: Guar gum, Tara gum, Microcrystalline cellulose, Dicalcium phosphate, in-vitro drug release

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INTRODUCTION

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] QF is readily absorbed from the gastrointestinal track with oral bioavailability of about 83% [2]. 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. 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

The chief objective of extended release systems [3] is to reduce the dosing frequency to an extent that a once daily dosage is sufficient for therapeutic management with a uniform plasma concentration at a steady state [4].

Matrix systems offer several advantages relative to other extended release dosage form like easy to manufacture, versatile, effective, low cost and can be made to release high molecular weight compounds [5]. Since the drug is dispersed in the matrix system, accidental leakage of the total drug components is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

The oral route is a route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, and show better patient compliance, and increase safety margin for high potency drugs. Polymers [6] which are used as release retarding materials in the design of extended- release dosage forms play a vital role in controlling the delivery of drug from these dosage forms [7].

Quetiapine Fumarate is the most recently introduced atypical antipsychotic and is indicated for the management of the manifestations of psychotic disorders and schizophrenia. Quetiapine fumarate has a mean half life of 6hrs and it has to be administered at least thrice a day. Hence the objective of the study was to develop and evaluate twice daily sustained matrix tablets of Quetiapine fumarate.

EXPERIMENTAL SECTION

Materials

Quetiapine Fumarate was obtained as gift sample from Honest Formulations Pvt Ltd, India. Guar Gum was a gift sample from Merck Specialities Pvt.Ltd. Mumbai. Tara Gum was a gift sample from Merck Specialities Pvt.Ltd. Mumbai. Microcrystalline Cellulose Avicel PH 101 was a gift sample from Indian Reasearch products, Madras. Dicalcium phosphate dehydrate was a gift sample from Finar chemicals. Magnesium stearate was a gift sample from SD-fine chemicals. Talc was a gift sample from SD-fine chemicals**.** All other reagents of analytical grade were used.

Preparation of matrix tablets

Compressed tablets of QF using different polymers were prepared by direct compression method, as per formulae given in Table 1.1. Accurately weighed quantities of drug, polymer was passed through sieve no #40 and remaining ingredients were added to the blend in a polybag and mixed well for 10 minutes. Sufficient quantities of Micro crystalline cellulose/Dicalcium phosphate were used to raise the total bulk of the tablets to a weight of 200mg each. The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 8 mm round punches to the hardness of 6-8 kg/cm^2.The formulations are shown in Table 1.1.

Table 1.1. Composition of matrix tablets of Quetiapine Fumarate Ingredients (mg/tablet)

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
QF	50	50	50	50	50	50	50	50	50	50	50	50
Guar Gum	100	50	25	-	-	-	100	50	25	-	-	-
Tara Gum	-	-	-	100	50	25	-	-	-	100	50	25
MCC (Avicel PH 101)	46	96	121	46	96	121	-	-	-	-	-	-
DCP	-	-	-	-	-	-	46	96	121	46	96	121
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

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 1.2.

Hardness and Friability

Hardness of the tablets (n=3) was determined using Monsanto hardness tester. Friability of the tablets were checked using Roche friabilator. Preweighed 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 1.2. The experiment was repeated three times.

Estimation of drug content

Twenty 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 1.2.

Table 1.2 post compression properties of all formulations

Parameters / Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
F1	6.37 ± 0.05	0.7	200 ± 0.14	50 ± 1.25
F2	6.70 ± 0.10	0.8	200 ± 0.12	48 ± 1.98
F3	6.57 ± 0.15	0.6	200 ± 0.15	49 ± 1.67
F4	6.81 ± 0.10	0.6	200 ± 0.10	50 ± 1.25
F5	6.20 ± 0.10	1.2	200 ± 0.04	50 ± 0.98
F6	6.37 ± 0.12	0.7	200 ± 0.06	50 ± 0.65
F7	6.81 ± 0.08	0.9	2000 ± 0.08	49 ± 0.54
F8	6.53 ± 0.06	1.1	200 ± 0.04	48 ± 0.78
F9	6.66 ± 0.15	0.8	2000 ± 0.01	50 ± 0.85
F10	6.71 ± 0.12	0.8	2000 ± 0.02	49 ± 0.97
F11	6.72 ± 0.11	0.6	2000 ± 0.03	48 ± 0.36
F12	6.50 ± 0.10	0.9	2000 ± 0.05	50 ± 0.84

In vitro drug release study

In vitro release studies were conducted by using USP eight station dissolution test apparatus (Electrolab).The dissolution medium consisted of 0.1N HCl (pH 1.2) for the first 2 hours and phosphate buffer (pH 6.8) for the subsequent 10 hours.900 ml of dissolution medium was maintained at 37±0.5 C ,at 50 rpm (paddle method).Aliquots of 5 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh buffer maintained at the same temperature was replaced. The samples were suitably diluted and analysed by measuring the absorbance at 248 nm.

Data Analysis

Release data were analysed as per zero order, first order, Higuchi equation [9] and Peppas equation [10] models to assess the drug release kinetics and mechanism of release from the tablets.

RESULTS AND DISCUSSION

The fabricated formulation were subjected to weight variation, hardness, friability and estimation of drug content. All the formulated tablets complied with the weight variation test requirement. Hardness of the tablets was in the range of 5-6 Kg/cm^2.Weight loss in the friability test was less than 0.84% in all the cases. All the matrix tablets prepared contained the drug with in 100±2% of the labelled claim. Thus, all the physical parameters of the prepared tablets were practically within control. Two different polymers (Guar gum, Tara gum) were studied at different concentrations as drug release retardants. As the concentration of polymer is decreased the release rate of the drug was increased. Initially when the concentration of polymer is high in the formulation the release rate of drug was decreased; it may be due to formation of more viscous gel layer around the tablet at high concentration of gum. Sustained release of drug from the Tara gum matrix system (F4 to F6) with better percent of drug release at the end of 12 hrs is due to rapid swelling and gelling capacity of the polymer. In the present study, Guar gum, Tara gum was used as the hydrophilic matrixing agent because it forms a strong viscous gel on contact with the aqueous media, which may be useful in the controlled delivery of water- soluble drugs. As the concentration of gum in the formulations (F1 to F12) was decreased, the drug release was significantly prolonged (Table4). The formulations F1, F2, F3 were formulated by direct compression method using Guar Gum at a concentration of 50, 25 and 12.5% (W/W) respectively with MCC (Avicel Ph 101) as diluent. In FI the Guar Gum prolonged the drug release until 12hr, but with less percent of drug release, with about 62.38%, it may be due to formation of more viscous gel layer around the tablet at high concentration of gum. So, F2 was formulated by decreasing the conc. of guar gum and the release was high when compared to F1 i.e. 80.59%. In order to show better sustained action along with high percent drug release F3 was formulated with 12.5 %(W/W) concentration of Guar gum. The formulation F3 not only showed sustained action but also gave high percent drug release at the end of 12hr with about 90.33%. F4, F5, F6 are the formulations with Tara gum as the release retardant at the conc. of 50, 25, 12.5 % (W/W) respectively with MCC (Avicel pH 101) as the diluents. Formulation F4 showed 84.96% at the end of 12 hr. Formulation F5 showed 96.61% at the end of 12hr . In order to observe further decrease of polymer on the effect of drug release F6 was formulated, in F6, Tara gum could not prolong the drug release until 12hr ,instead the tablet dispersed completely at the end of 10hr with about 98.64% . Among the F4, F5, F6 formulations F5 showed better sustained action with high percent drug release with about 96.61% at the end of 12 hr which is shown in table 1.3. Formulations F7, F8, F9 were prepared with Guar gum at a concentration of 50, 25

and 12.5% (W/W) respectively with DCP (Dicalcium phosphate) as diluent. The percent drug release at the end of 12hr for the formulations F7, F8, F9 was 65.59, 70.48, and 87.32 % respectively. Among the F7, F8, F9 formulations, F9 formulation showed sustained release with high percent drug release of with about 87.32 %. Formulations F10, F11, F12 were prepared with Tara gum at a concentration of 50, 25, and 12.5% (W/W) respectively with DCP (Dicalcium phosphate) as diluents. The percent drug release at the end of 12hr for the formulations F10, F11, F12 was 65.78, 71.96 and 85.50 % respectively which is shown in table 1.4. The results were analyzed with the help of release kinetics. Dissolution profiles of the formulations were fitted to various mathematical models for describing the release mechanism like Zero-order, first order, Higuchi, Koresmeyer-Peppas release models shown in table 1.5.

Table: 1.3 Cumulative Percent drug releases with standard deviation for formulations F1, F2, F3 (Guar gum, Microcrystalline cellulose) F4, F5, F6 (Tara gum, Microcrystalline cellulose)

Time(Hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
`0.5	23.08 ± 1.34	29.82 ± 0.68	35.74 ± 0.71	18.38 ± 0.23	26.24 ± 0.063	30.64 ± 0.24
1	29.90 ± 0.27	37.63 ± 0.39	48.03 ± 0.45	26.17 ± 0.08	41.50 ± 0.78	43.25 ± 0.73
2	37.32 ± 0.06	51.49 ± 1.25	65.36 ± 0.15	44.09 ± 0.75	55.83 ± 0.47	63.17 ± 0.57
4	51.28 ± 1.13	68.89 ± 1.38	79.48 ± 0.27	61.79 ± 0.17	71.67 ± 1.38	79.35 ± 0.18
6	54.66 ± 1.56	73.64 ± 0.83	81.96 ± 1.12	67.66 ± 0.15	78.03 ± 1.25	84.18 ± 0.08
8	55.96 ± 0.25	75.18 ± 0.32	84.05 ± 1.18	74.10 ± 0.63	82.24 ± 0.63	89.09 ± 1.27
10	58.16 ± 0.69	76.91 ± 0.76	86.99 ± 0.58	77.78 ± 1.12	88.67 ± 0.28	98.64 ± 0.68
12	62.38 ± 0.82	80.59 ± 0.17	90.33 ± 0.24	84.96 ± 0.83	96.61 ± 0.33	-

Table: 1.4 Cumulative Percent drug releases with standard deviation for formulations F7, F8, F9 (Guar gum, Dicalcium phosphate) F10, F11, F12 (Tara gum, Dicalcium phosphate)

TIME(Hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
`0.5	24.09 ± 0.46	26.68 ± 0.38	36.17 ± 0.25	16.18 ± 0.27	21.70 ± 0.26	28.83 ± 0.27
1	29.83 ± 0.94	35.03 ± 1.05	51.48 ± 0.36	23.87 ± 0.46	32.14 ± 0.22	45.83 ± 0.41
2	42.81 ± 1.04	49.32 ± 1.46	61.93 ± 0.83	35.61 ± 0.08	41.53 ± 0.82	58.44 ± 0.18
4	53.82 ± 0.18	60.99 ± 1.73	70.72 ± 0.87	47.70 ± 0.28	54.36 ± 0.53	78.22 ± 0.12
6	56.77 ± 0.93	65.43 ± 1.16	73.59 ± 0.04	52.31 ± 0.21	59.34 ± 0.45	80.20 ± 0.06
8	58.22 ± 0.64	67.43 ± 0.47	78.65 ± 0.38	56.07 ± 1.26	64.59 ± 0.47	82.54 ± 0.27
10	62.20 ± 0.65	69.51 ± 0.27	85.09 ± 0.24	62.28 ± 0.48	67.34 ± 0.28	83.87 ± 1.61
12	65.59 ± 0.27	70.48 ± 0.58	87.32 ± 0.63	65.78 ± 1.43	71.96 ± 1.43	85.50 ± 0.52

Table: 1.5 The Rate Constant and Regression values for all the formulations

Formulations	Zero order		First order		Higuchi	Peppas	
	K	R^2	K	R^2	R^2	n	R^2
F1	4.03	0.741	0.068	0.977	0.925	0.483	0.958
F2	5.30	0.720	0.122	0.965	0.913	0.452	1
F3	5.60	0.662	0.169	0.985	0.875	-	-
F4	6.24	0.848	0.144	0.966	0.975	0.448	1
F5	6.52	0.802	0.232	0.945	0.957	0.432	1
F6	6.32	0.785	0.350	0.911	0.952	-	-
F7	4.23	0.734	0.075	0.944	0.920	0.446	0.936
F8	4.60	0.695	0.090	0.915	0.898	0.493	1
F9	4.23	0.675	0.145	0.908	0.879	-	-
F10	4.70	0.840	0.081	0.930	0.974	0.409	0.950
F11	4.88	0.797	0.093	0.993	0.957	0.457	0.993
F12	5.61	0.678	0.149	0.931	0.882	0.473	0.971

TABLE: 1.6 PERCENT DRUG RELEASE AT THE END OF 12 HR

TYPE OF POLYMER USED (AT 25 % CONC.)	TYPE OF DILUENT USED	
	MCC (AVICEL PH 101)	DCP
GUAR GUM	80.59	70.48
TARA GUM	96.61	71.96

From the above data it was clear that the release retardant effect among the natural polymers used was as follows:

Guar gum >Tara gum

Among the two polymers used Guar gum showed maximum retardation effect than Tara gum because of its more swelling and gelling tendency which is shown in table 1.6. The release retarding capacity among the diluents used was as given below

DCP >MCC (Avicel PH 101)

This was because DCP is insoluble diluent so it releases the drug slowly when compared to the MCC (Avicel PH 101) which is partially soluble diluent in water.

- At the end of 2 hr the drug release was in the order

F10 < F1 < F11 < F7 < F4 < F8 < F2 < F5 < F12 < F9 < F6 < F3

- At the end of 12 hr the drug release was in the order

F1 < F7 < F10 < F8 < F11 < F2 < F4 < F12 < F9 < F3 <F5

CONCLUSION

Hence, the release rate of drug from the matrix tablets can be governed by the type of the polymer and the concentration of the polymer employed in the preparation of the tablets. The matrix tablets prepared with Guar gum and diluent could extend the drug release up to 10-12 hours. The hydrophilic matrix of Guar gum could control the drug release up to 12 hours but with less percent of drug release. The hydrophilic matrix Tara gum could extend the drug release effectively for 12 hours with better percent of drug release. The order of increasing release rate controlling efficiency observed with polymers was Guar gum > Tara gum. It is evident from the results that among both the hydrophilic matrices, Tara gum, is a better system for controlled delivery of partially water- soluble drugs like Quetiapine fumarate

• The best combination selected was Tara gum (at 25% conc.) with MCC (Avicel pH 101) as the diluents i.e. formulation FV, Formulation FV was selected to be the best formulation with about 55.83% drug release at the end of 2hr and 96.61% drug release within 12hr.
• The natural polymers have many advantages than the synthetic polymers since they are inert, non-toxic, less expensive, biodegradable and widely available. Hence in the present investigation natural polymers like guar Gum, Tara gums have been used as drug release retarding polymers.
• The sustained release matrix tablets of Quetiapine fumarate were successfully prepared using natural polymers in an economical way and are much preferable when compared to immediate release tablets for to immediate release tablets for better therapy and patient compliance.

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