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Research Article

AN INVESTIGATION OF HYDROPHILIC NATURAL GUMS IN THE FORMULATION OF QUETIAPINE FUMARATE MATRIX TABLETS

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ABSTRACT

The aim of the study was to formulate and evaluate matrix tablets of quetiapine fumarate using natural polymers (AVG, GK, GX) alone and in combination. FTIR revealed the absence of drug polymer interactions. Matrix tablets of quetiapine fumarate (50 mg) were produced by wet granulation method. Various combinations of polymers viz.,100:0, 80:20, 20:80,40.:60,60:40,0:100 of aloe vera gel powder: gum karaya(or xanthan gum) were formulated. The formulated tablets were characterized for their pre compression and post compression parameters. The *in vitro* drug release studies were carried out in p^H 1.2 buffer for 2 hours and then in p^H 6.8 phosphate buffer. Drug release was extended for more than 10 hours in most of the formulations. The best fit release kinetics was achieved with first order followed by higuchi and fickian diffusion. According to the similarity factor (f_2) ,QAK2 and QAX2 were found to be the most similar formulations to Quetipine SR, taken as reference product.

Keywords: Oral controlled drug delivery system, Natural gums, Quetiapine fumarate, Fickian diffusion.

INTRODUCTION

In the present scenario with the changing life style and busy daily tasks people of all age groups are suffering from different types of psychological disorders and hence there is an increase in demand for the psychotropic drugs. In this context many novel drugs always try to capture existing markets which offer some additional benefits in terms of safety, reducing the side effects etc. Quetiapine fumarate is one such novel second generation, atypical anti psychotic drug often clinically recommended in conditions of schizophrenia, depression, mania. It interacts with a broad range of receptors and antagonizes both dopamine and serotonin receptors to alleviate its antipsychotic activity. It has mean elimination half life of 6 hours and hence there is a need for twice or thrice daily administration. Hence formulating it into sustained release dosage form can increase patient compliance and offer clinical safety.

Literature survey has revealed the formulation of quetiapine fumarate sustained release matrix tablets using hpmc K 15 M and pvp K 30 alone and in combination,[1] Gastroretentive system of quetiapine fumarate was formulated using sodium alginate, sodium corboxy methyl cellulose as hydrophilic natural polymers.[2] QF has also been developed in to P^H independent matrix and coated release systems using succinic acid as the p^H adjuster, and Eudragit-RSPO was used as matrix former.[3,4]

Developing an oral controlled –release tablets for highly acidic soluble drugs have been always a problem, if these systems have not been formulated properly they may release drug at faster rate and cause un desirable effects. Hence selections of polymers play an important role in designing such a drug delivery systems. Hydrophilic natural polymers are one such widely employed polymers for controlling the drug release. The continual quest and maneuvering in exploring novel excipients, natural polymers came into light with a broad range of advantages. The fact for increase in importance of plant based natural material is that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw materials. Aloe vera gel powder is obtained from the leaves of aloe vera (family: liliaceace).Avg powder is being employed in various pharmaceutical formulations.[5-8] Gum karaya is a dried exudate from trees of Sterculia urens, Sterculia villosa belonging to the family Sterculiaceae. Xanthan gum is another such exocellular polysaccharide obtained from *Xanthomonas campestris* and is used in oral, topical pharmaceutical formulations, cosmetics and food products.[9-14]

MATERIALS

Quetiapine fumarate was obtained as a gift sample from Hetero Drugs, Baddi. Aloe vera gel powder was obtained from Madvik research pvt.ltd. Gum karaya and xanthan gum was obtained from Girijan co-operative corporation Ltd, Visakhapatnam. All other ingredients are of analytical grade.

METHODS

Preparation of granules

The granules were prepared by wet granulation method using PVP K-30 as the binding agent, iso propyl alcohol as the wetting agent with appropriate quantities of aloe vera gel powder, gum karaya and xanthan gum. After enough cohesiveness was obtained, the mass was passed through sieve no 10 # and were dried at 50°C in hot air oven till constant weight was reached. The dried granules were then passed through sieve no16#. The granules obtained were evaluated for various micromeritic properties.

Table 1: Composition of matrix tablet formulations containing gums alone.

Ingredients	QA_1	QA_2	QA_3	QK_1	QK_2	QK_3	QX_1	QX_2	QX_3
QF (mg)	58	58	58	58	58	58	58	58	58
AVG(mg)	50	100	150	-	-	-	-	-	-
SG(mg)	-	-	-	50	100	150		-	-
XG(mg)	-	-	-	-	-	-	50	100	150
Lactose (mg)	82	32	29.5	82	32	29.5	82	32	29.5
PVP (%)	3	3	3	3	3	3	3	3	3
IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs
MS (%)	1	1	1	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1	1	1	1
Total weight (mg)	200	200	250	200	200	250	200	200	250

Table 2: Composition of matrix tablet formulations using combination of polymers

Ingredients	QAK_1	QAK_2	QAK_3	QAK_4	QAX_1	QAX_2	QAX_3	QAX_4
QF (mg)	58	58	58	58	58	58	58	58
AVG (mg)	120	30	60	60	120	30	60	60
SG(mg)	30	120	90	90	-	-	-	-
XG	-	-	-	-	30	120	90	90
Lactose (mg)	29.5	29.5	29.5	29.5	29.5	29.5	29.5	29.5
PVP (%)	3	3	3	3	3	3	3	3
IPA	qs	qs	qs	qs	qs	qs	qs	qs
MS (%)	1	1	1	1	1	1	1	1
Talc (%)	1	1	1	1	1	1	1	1
Total weight(mg)	250	250	250	250	250	250	250	250

Characterization of Granules

Granules were evaluated for their characteristic parameters. Angle of repose was determined by funnel method, bulk density (BD) and tapped density (TD) were determined by cylinder method. Carr's index (CI) and Hausner ratio were calculated using following equations.[15]

$$Hausner\ ratio = TD/BD$$

$$\%CI = \ (TD - BD)/TD\ X\ 100$$

Characterization of Matrix Tablets

After evaluation of granules, the blend was compressed using Cadmac tablet compression machine, equipped with beveled 8 mm flat-faced punches. The prepared matrix tablets were evaluated for hardness, friability, thickness, and content uniformity. Hardness was determined by using Pfizer hardness tester. Friability was determined using Roche friability testing apparatus. Thickness was measured using Vernier calipers. Content uniformity was performed according to the I.P method.[16] The tensile strength can be applied once load required to fracture the tablet has been determined and can be calculated from the following formula.

$$T = \frac{2C_S}{\pi Dt}$$

Where, C_S = Crushing strength, D = diameter, t = thickness, T = tensile strength

Determination of swelling index

The swelling properties of the matrix tablets were determined by weight basis method. The swelling behavior was studied in buffer solutions, p^H 1.2, 6.8 phosphate buffers. Tablets of known weight were placed in Petri dish containing 25ml of swelling medium and allowed to swell at room temp. The swollen tablets were removed and weighed periodically. The wet weight of swollen tablets was determined by blotting them with filter paper to remove moisture adhering on the surface immediately followed by weighing on an electronic balance. The percent swelling of tablets was calculated from the following formula.

$$\text{Swelling index} = \frac{W_t - W_i}{W_i}$$

Table 3: Pre compressional characteristics of granules

Formulation code	Angle of repose(°)	Bulk density(g/cc)	Tapped density(g/cc)	Carr's index(%)	Hausner ratio
QA_3	29.59±1.973	0.570±0.004	0.605±0.004	5.83±1.215	1.05±0.015
QK_3	27.7±1.125	0.585±0.008	0.619±0.001	6.01±1.17	1.06±0.01
QX_3	28.76±0.647	0.581±0.007	0.619±0.008	6.04±0.141	1.06±0.001
QAK_1	29.59±1.97	0.595±0.004	0.627±0.004	5.07±0.08	1.05±0.01
QAK_2	28.95±1.41	0.599±0.004	0.634±0.011	5.45±0.791	1.05±0.001
QAK_3	27.63±1.34	0.603±0.004	0.638±0.008	5.52±0.702	1.058±0.007
QAK_4	28.77±0.47	0.603±0.004	0.633±0.004	4.76±0.745	1.048±0.007
QAX_1	28.5±0.583	0.611±0.004	0.646±0.005	5.30±0.046	1.05±0.01
QAX_2	28.68±0.656	0.615±0.004	0.654±0.009	5.9±0.763	1.06±0.007
QAX_3	27.98±0.121	0.625±0.021	0.681±0.024	8.16±0.132	1.08±0.005
QAX_4	28.2±0.54	0.654±0.009	0.688±0.005	5.02±1.52	1.05±0.017

Table 4: Characterisation of matrix tablets

Formulation code	Hardness (Kg/cm^2)	Friability (%)	%Drug content	Tensile strength(Kg/cm^4)
QA3	5.93±0.23	0.82	100.8±1.322	13.46±0.525
QK3	6.4±0.2	0.36	97.8±1.014	14.52±0.455
QX3	5.86±0.11	0.39	100.7±1.442	13.31±0.265
QAK_1	5.73 ±0.115	0.67	97.23±1.001	13.01±0.259
QAK_2	5.86 ±0.305	0.4	96.48±1.001	13.31±0.692
QAK_3	5.66 ±0.115	0.54	102.76±1.650	12.86±0.259
QAK_4	5.53±0.115	0.68	101.93±1.285	12.55±0.265
QAX_1	6.06±0.23	0.42	100.5±0.818	13.76±0.525
QAX_2	5.53±0.305	0.58	97.8±1.014	12.55±0.692
QAX_3	6.13±0.115	0.68	100.5±1.814	13.92±0.259
QAX_4	5.53±0.115	0.6	102.46±1.006	12.55±0.265

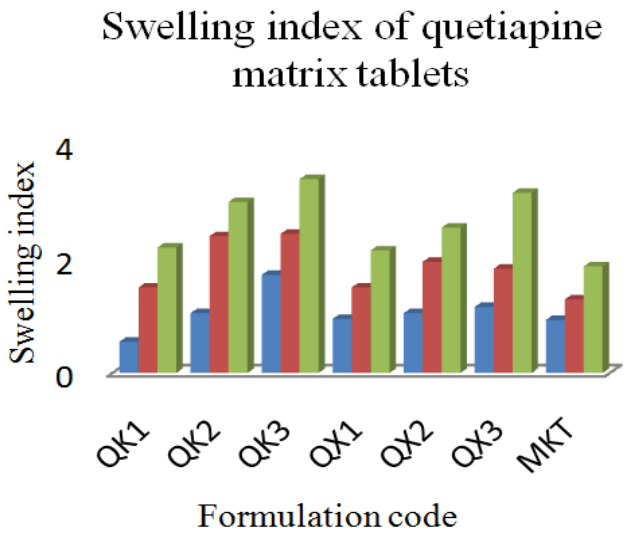

Fig. 1a: swelling studies for matrix tablets formulated using gums alone

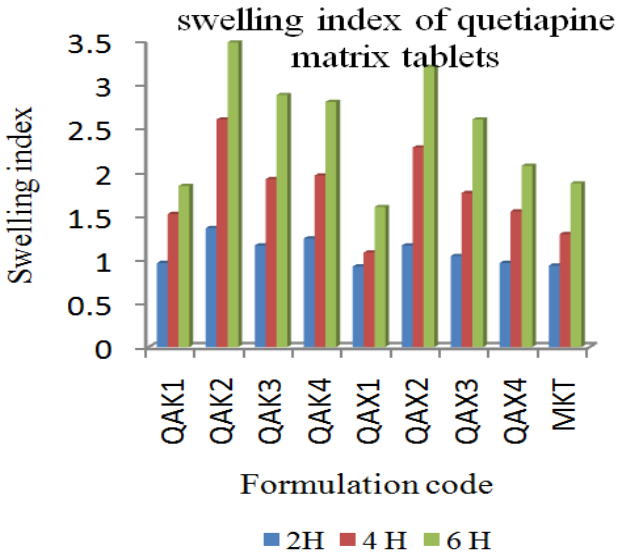

Fig. 1b: swelling studies for matrix tablets formulated using gums in combination

Fig. 1c: photographs showing the swelling of optimised matrix tablets and marketed formulation

Drug Release Study

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 10h using a six station USPXXII type II apparatus at 50 rpm. The dissolution studies were carried out at 37±0.5ºc in triplicate using 900 ml 0.1N HCl for 2 hr followed by phosphate buffer (pH 6.8) for subsequent 6 hours. 5 ml of sample was withdrawn from the dissolution medium at predetermined intervals and then replaced with the fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed at 246nm by a UV-spectrophotometer. The dissolution experiments were conducted in triplicate and average values were taken.

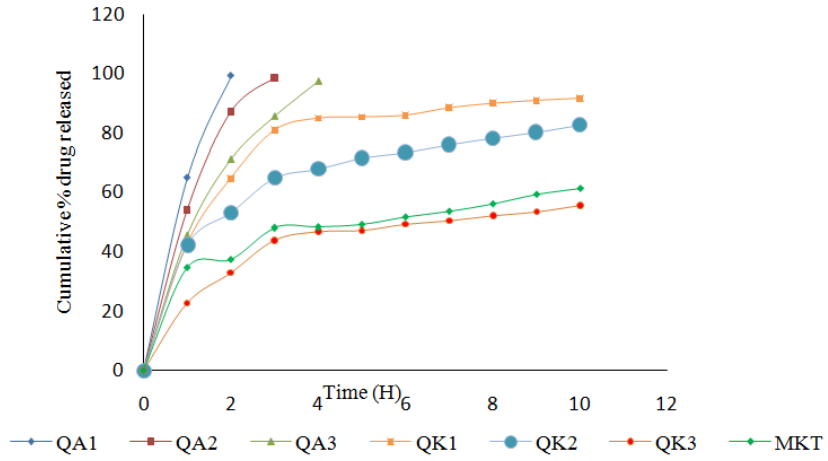

Fig. 2a: Drug release profiles of matrices containing the gum alone

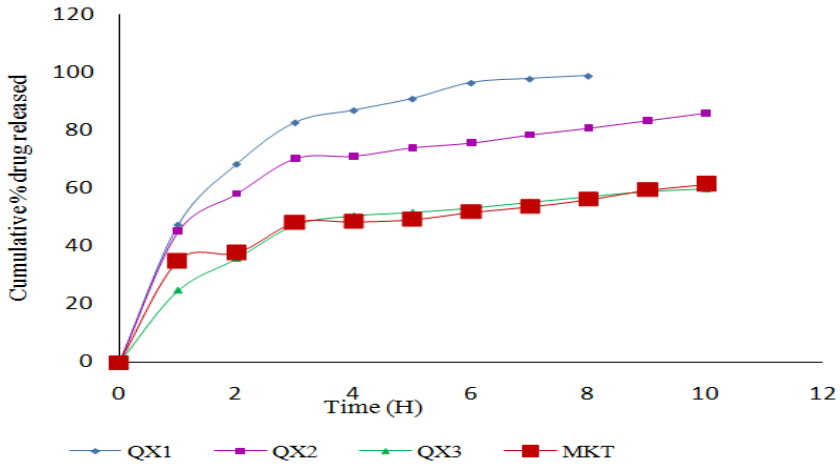

Fig. 2b: Drug release profiles of matrices containing xanthan gum alone

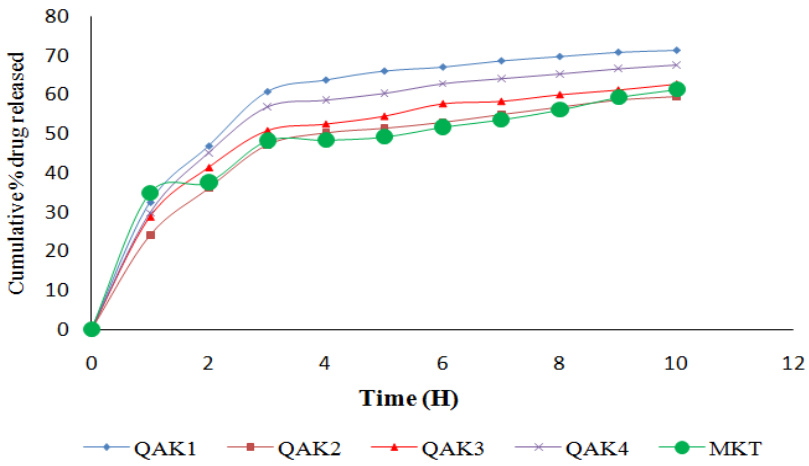

Fig. 2c: Drug release profiles of matrices containing Avg and GK in combination

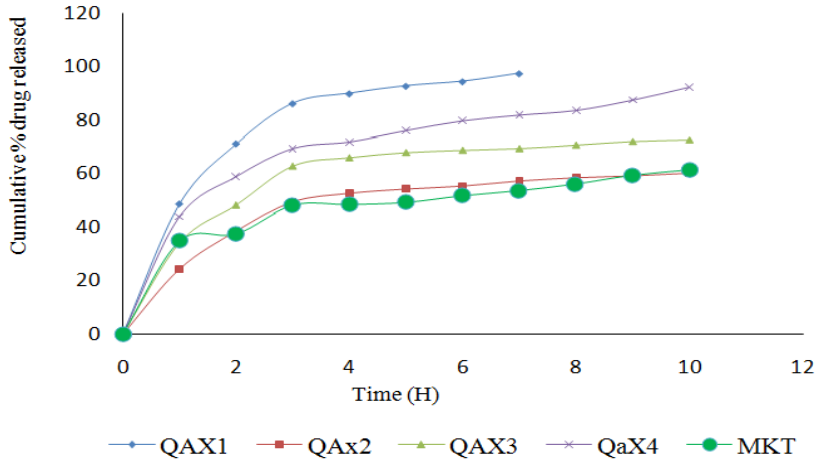

Fig. 2d: Drug release profiles of matrices containing Avg and XG in combination

Release Kinetics

To analyze the mechanism of drug release from the matrix tablets, the release data was fitted into various mathematical models viz., Zero order, first order and Higuchi equation.[12] These models fail to explain drug release mechanism due to swelling (upon hydration) of the matrix. Therefore, the dissolution data was also fitted to the well known experimental equation (Koresmeyer- Peppas equation), which is often used to describe the drug release behavior from polymer systems.[17]

$$\log (Mt/Mf) = logK + nlogt$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time; K is a release rate constant incorporating structural and geometrical characteristics of the tablet and n is the differential exponent indicative of the mechanism of drug release.

To clarify the release exponent for the different batches of matrix tablets, the log value of %drug was plotted against log time for each batch according to the equation 4. A value of n=0.45 indicates Fickian (case I) release; >0.45 but <0.85 for non Fickian (anomalous) release; > 0.89 indicates super case II type of release. Case II gradually refers to the erosion of the polymeric chain and anomalous transport (non- Fickian) refers to a combination of both diffusion and erosion controlled drug release.[18]

Similarity factor analysis (f_2)

Similarity factor f_2 is the measurement of similarity of 2 different dissolution curves (predicted and experimentally observed). Generally f_2 values greater than 50 ensure sameness of the 2 curves. The value is determined by the following equation.[19]

$$f_2 \approx 50 \log\left\{\left[1+\frac{1}{n}\sum\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\}$$

Where, n= number of dissolution sample times and R_t and T_t are the individual percentages dissolved at each time point t for the reference and test dissolution profiles respectively.

Table 5: Mathematical modelling of matrix tablets

Code	Zero order		First order		Higuchi		Peppas			f_2	$T_{50\%}$
	K_0 (mg/h)	r	K_1 (h^{-1})	r	k_H ($\%h^{-0.5}$)	r	k_p (h^{-n})	r	n		
QK_3	7.154	0.853	0.069	0.904	9.892	0.947	25.4	0.915	0.36	70.08	3.49
QX_3	7.574	0.803	0.108	0.876	13.60	0.906	38.99	0.933	0.305	47.11	3.3
QAK_1	9.594	0.815	0.108	0.885	17.3	0.892	36.98	0.941	0.321	47.51	2.6
QAK_2	7.737	0.854	0.075	0.904	10.69	0.949	27.28	0.956	0.364	84.54	3.23
QAK_3	8.204	0.833	0.082	0.899	11.38	0.929	31.4	0.966	0.325	70.87	3.04
QAK_4	8.988	0.822	0.096	0.886	12.53	0.925	34.11	0.944	0.325	53.11	2.78
QAX_1	18.04	0.853	0.499	0.989	21	0.961	52.6	0.95	0.343	16.03	1.38
QAX_2	7.984	0.833	0.078	0.888	11.04	0.934	28.31	0.924	0.362	77.21	3.13
QAX_3	9.774	0.803	0.11	0.876	13.59	0.906	38.37	0.942	0.31	47.13	2.55
QAX_4	11.61	0.849	0.209	0.97	16.08	0.937	46.55	0.984	0.293	31.38	2.15
MKT	7.724	0.834	0.069	0.891	10.72	0.913	33.96	0.971	0.239	-	3.23

RESULTS AND DISCUSSION

The granules of quetiapine fumarate matrix tablets were prepared by wet granulation method according to the formula given in table 1and table 2. The granules were characterized with respect to angle of repose, bulk density and tapped density. The angle of repose was less than 30º indicates satisfactory flow behavior. Physical characteristics of the prepared granules were given in table 3.

The matrix tablets were evaluated for hardness, friability, content uniformity, uniformity of weight and *in vitro* drug release studies. The hardness of the tablets in all the batches was found to be in the range of from5.53 to 6.46 kg/cm^2. The friability of the tablets was in the range of 1.0%. The drug content was found to be uniform for all the batches of tablets prepared and was found to be within 90-110% of labeled claim. Evaluation data of the matrix tablets were given in table 4. The hardness and friability values indicated good handling properties of the prepared matrix tablets. The prepared matrix tablets were also studied for swelling and *in vitro* drug release studies.

***In-vitro* drug release studies**

From figure 2a and 2b it can be concluded that faster drug release was observed in case of matrices having aloe vera gel powder when compared to gum karaya and xanthan gum. When aloe vera is the only retarding material it was unable to sustain the drug release and hence the study was focused on the combination of aloe vera gel

powder with GX and GK.The mean amounts of quetiapine fumarate released at different time intervals from the matrix tablets QAK_1 – QAK_4, QAX_1- QAX_4 and Quetiapine SR (Sun pharma) formulation are shown in figure 2c and 2d indicating that the combination have significant sustaining ability than gums alone. All the 8 combinations appear to control the release of quetiapine fumarate, but with a varying degree. When the quetiapine fumarate matrix tablets of come into contact with the dissolution medium, they take up dissolution medium or biological fluid and swell, forming a gel layer around the matrix. Then the dissolved drug diffuses out of the swollen matrix at a rate determined by the amount and viscosity of polymers in the tablet formulation. The degree of swelling of polymer blends can be visualised from the figures 1a, 1b and 1c. All the formulations showed a biphasic release profile. There was a faster drug release from 0 to 3 hours, followed by a slower release from 3 to 10 hours. Such a biphasic release pattern may be beneficial in providing the initial therapeutically effective plasma concentration followed by an extended plasma concentration. The drug present on the surface of the matrix tablet might have resulted in the initial fast release of the drug from the formulation. All the formulations were fitted best with fickian diffusion with a first order release and QAK2 was selected as the best formulation as it has highest similarity factor of 84.54. the results were given in table 5.

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ABBREVIATIONS

QF = Quetiapine fumarate. GX = Xanthan gum. GK =Gum karaya. AVG= Aloe vera gel powder. BD = Bulk density. TD = Tapped density. CI = Carr's index. MkT = marketed quetiapine SR tablet.

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