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Formulation and Evaluation of Gastroretentive Floating Tablets of an Antipsychotic Drug

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ABSTRACT

The present study was carried out in fabricating gastro retentive formulation of an antipsychotic drug using semi synthetic and natural polymers. Floating tablets were prepared by direct compression method using directly compressible microcrystalline cellulose as vehicle. Gum Xanthan and hydroxypropyl methylcellulose (HPMC E4M) were used as polymers for sustaining the drug release and sodium bicarbonate was used as an effervescent agent. Tablets were characterized for their pre compression and post compression parameters. Floating characteristics like floating lag time, floating time were evaluated and were considered as one of the factor for selecting the best formulation. The *in vitro* release studies were carried out in pH 1.2 buffer for 8hrs. The content uniformity was found to be within the compendial requirements and the release was extended for more than 8hrs. The best fit release kinetics was achieved with zero order followed by higuchi and non-fickian diffusion. The release of Quetiapine fumarate was significantly influenced by the concentration of polymer.

Keywords: Gastro retentive floating tablet, HPMC, Quetiapine fumarate, Xanthan gum

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INTRODUCTION

In 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 market which offers some additional benefits in terms of safety, reducing the side effects. Quetiapine fumarate is one such novel II generation drug often clinically recommended in condition of schizophrenia, depression and mania[1]. Fabrication of prolonged drug delivery systems is a need to treat various psychological disorders which require chronic therapy. Rate controlled release or target specificity cannot be achieved with conventional oral administration. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the gastrointestinal tract (GIT). Gastro retentive drug delivery systems (GRDDS) are designed to prolong the gastric residence time, Increase the drug bioavailability and diminish the side effects of irritating drugs[2]. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Quetiapine Fumarate (QF) is an atypical psychotropic agent of dibenzothiazepine class. QF shows pH dependent solubility. QF is highly soluble in acidic pH and slightly soluble in basic pH. Gastroretentive floating tablet would be more beneficial to retain the drug in stomach for prolonged duration so as to achieve maximum absorption and bioavailability[3].

MATERIALS AND METHOD

Quetiapine fumarate was obtained as a gift sample from Hetero drugs, Baddi. Gum Xanthan and HPMC were procured form drugs India, Hyderabad. All other ingredients are of analytical grade.

Methods

All the floating tablets, each containing Quetiapine fumarate equivalent to 50 mg, were prepared by direct compression method. Drug is mixed with appropriate quantities of GX, HPMC (0.5%, 1.0%, 1.5%, 2.0% and 2.5%), microcrystalline cellulose and sodium bicarbonate for 10min to ensure uniform mixing in geometrical ratio. Powder mixture was evaluated for angle of repose bulk density (BD) and tapped density (TD). Carr's index (CI) and Hausner ratio were calculated using following equations[4]. After evaluation this powder mixture was blended with lubricating agents (1% w/w magnesium stearate and 1% w/w talc) and compressed using 16 station rotary punching machine, equipped with flat-faced, round punches of 8-mm diameter. Composition of the floating tablets and precompression data of the powder mixture were given in the Table 1 and

2 respectively

Table 1: Composition of Quetiapine Fumarate floating tablets

Ingredients	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**
Quitiapine fumarate	58	58	58	58	58	58	58	58	58	58
Micro Crystalline Cellulose	124.5	99.5	74.5	49.5	24.5	124.5	99.5	74.5	49.5	24.5
GX	25	50	75	100	125	-	-	-	-	-
HPMC	-	-	-	-	-	25	50	75	100	125
$NAHCO_3$	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
MS	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250	250	250	250	250

All the ingredients in the formulations are mentioned in mg/tablet.

Determination of Hardness, Friability and Drug Content

The prepared floating tablets were evaluated for hardness, friability, thickness, uniformity of the weight 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. Uniformity of the weight and content uniformity were performed according to the I.P method[5,6]. The tensile strength of the tablets was measured by using the following formula and the values were given in the Table 3.

$$T = \frac{2 C_S}{\pi D t}$$

Where, C_S = crushing strength, D= diameter, t = thickness, T = tensile strength.

***In Vitro* Buoyancy Study[7]**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a 100-ml beaker containing 0.1N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time. The floating lag time values of the formulated tablets were mentioned in Table 4**.**

Drug Release Studies

The *in vitro* drug release studies were assessed by USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml of 0.1N HCl for 8 hours, maintained at 37°C ± 0.5°C. An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 246 nm. The dissolution studies were carried out in triplicate. The amount of drug present in the sample was calculated with the help of appropriate calibration curve

constructed from reference standards.

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 Highuchi equation[8]. the dissolution data was also fitted to the well known experimental equation (Koresmeyer's Peppas equation), which is often used to describe the drug release behavior from polymer systems[9].

$$\log\left(\frac{Mt}{Mf}\right) = logK + nlogt$$

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[10]. Mean dissolution time (MDI) was calculated for dissolution data using the following equation[11].

$$\mathrm{MDI} = \left(\frac{\mathrm{n}}{\mathrm{n}+1}\right) \times \mathrm{K}^{-1/\mathrm{n}}$$

Where n= release exponent and K= release rate constant.

RESULTS AND DISCUSSIONS

Quetiapine fumarate floating tablets were prepared by using Xanthan gum and HPMC as release retardants and sodium bicarbonate as gas generating agent. Sodium bicarbonate induces CO_2 generation upon contact with acidic dissolution medium. The gas generated was trapped and protected within the gel formed by hydration of polymers thus decreasing the density of tablets to less than 1g/cc and then tablet becomes buoyant.

The micromeritics parameters of the powder blend of different formulation batches are shown in Table 2. The angle of repose was less than 29° indicates satisfactory flow behavior. The tablets of all formulations were found to be white, smooth, flat faced circular with no visible cracks. The floating tablets were evaluated for hardness, friability, content uniformity, uniformity of weight, tensile strength and *in vitro* drug release studies. The hardness of the tablets in all the batches was found to be in the range of 5.23 – 7.93 Kg/cm^2. The friability of all the formulations

was less than 1%. The drug content was found to be uniform for all the batches of tablets prepared and was found to be within range of labeled claim. The tensile strength of the tablet ranges from 11.89 – 16.94. Evaluation data of the floating tablets were given in Table 3.

Table 2: Pre compression parameters of formulation blends (mean ± S.D; n=3)

Formulation code	Angle of repose (°)	Bulk density (g/cc)	Tapped density(g/cc)	Carr's index (%)	Hausner's ratio
F_1	25.59±1.97	0.536±0.004	0.552±0.005	7.830±0.11	1.08±0.001
F_2	26.30±1.37	0.499±0.007	0.531±0.008	5.890±0.005	1.06±0.000
F_3	28.20±0.56	0.502±0.003	0.558±0.009	9.520±1.47	1.10±0.010
F_4	27.56±0.92	0.433±0.006	0.472±0.007	8.32±0.192	1.14±0.096
F_5	24.30±1.37	0.606±0.004	0.682±0.014	11.07±1.306	1.12±0.020
F_6	28.1±0.486	0.507±0.007	0.53±0.008	4.390±0.215	1.04±0.002
F_7	27.63±1.34	0.402±0.045	0.442±0.005	8.960±0.169	1.09±0.002
F_8	25.3±0.571	0.635±0.005	0.734±0.008	13.47±0.878	1.15±0.010
F_9	28.5±0.583	0.611±0.004	0.646±0.005	5.300±0.046	1.05±0.010
F_{10}	27.98±0.12	0.625±0.021	0.681±0.024	8.16±0.132	1.08±0.005

Table 3: Physical characteristics and drug content of the floating tablets (mean ± S.D; n=3)

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Tensile strength	Weight variation
F_1	6.76±0.23	0.42	100.5±0.824	15.37±0.525	249±0.001
F_2	5.86 ±0.30	0.4	96.48±1.005	13.33±0.692	250±0.001
F_3	7.45±0.20	0.35	99.11±1.045	16.94±0.53	248±0.001
F_4	6.93±0.11	0.64	98.23±0.763	15.76±0.53	251±0.001
F_5	5.56±0.346	0.45	97.70±1.031	12.64±0.866	200±0.001
F_6	6.13±0.11	0.48	101.86±1.61	13.94±0.305	249±0.001
F_7	7.93±0.23	0.43	101.8±1.497	18.03±0.611	248±0.001
F_8	5.23±0.152	0.35	99.91±0.57	11.89±0.351	249±0.001
F_9	6.42±0.13	0.41	98.64±0.34	14.60±0.305	250±0.001
F_{10}	6.46±0.15	0.51	97.52±0.765	14.69±0.305	251±0.001

Table 4: *In vitro* buoyancy of floating tablets

Formulation code	Floating lag time(Sec±SD)	Total floating time
F_1	23±1.52	>8H
F_2	36±2.51	>8H
F_3	44±2.64	>8H
F_4	54±3.05	>8H
F_5	77±6.24	>8H
F_6	24±3.00	>8H
F_7	39±5.13	>8H
F_8	47±4.5	>8H
F_9	57±2.08	>8H
F_{10}	83±9.53	>8H

The hardness and friability values indicated good handling properties of the prepared floating tablets. All the tablets were prepared by effervescent approach. Sodium bicarbonate was added

as a gas-generating agent. Floating lag time and total floating time of the prepared tablets were reported in Table 4. It was found that as the concentration of polymer increases, it will take more time for getting hydrated hence floating lag time increases and all the formulations shows appreciable floating lag time less than 2 min and able to float above the dissolution medium for more than 8h.

In vitro dissolution studies of all formulations were carried out in 0.1N HCl solution (pH 1.2 buffer). From the release profile of different formulations it was observed that the formulations F_1 and F_6 with the polymer concentration of 0.5% gum Xanthan and HPMC respectively released the whole drug within 3h. Figure 1 and 2 depicts the release profile of Quitiapine fumarate from the floating tablets of different concentrations of gum Xanthan and HPMC respectively. Results indicated that release rate of quitiapine decreased with increase in the concnetration of both the polymers. The order of release was $F_1>F_2>F_3>F_4>F_5$ in case of GX and $F_6>F_7>F_8>F_9>F_{10}$ incase of HPMC. An increase in the polymer concentration causes increase in the viscosity of the gel as well as the formation of the gel layer with longer diffusion path. This could cause a decrease in effective diffusion coefficient of drug and therefore a reduction in drug release rate. The *in vitro* release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi and Korsemeyer's models in order to determine the mechanism of drug reelase. Table 5 indicates the data analysis of release profiles according to different kinetic models. The drug release fitted zero order kinetics and mechanism of release is by non fickian release which refers to a combination of both diffusion and erosion controlled drug release.

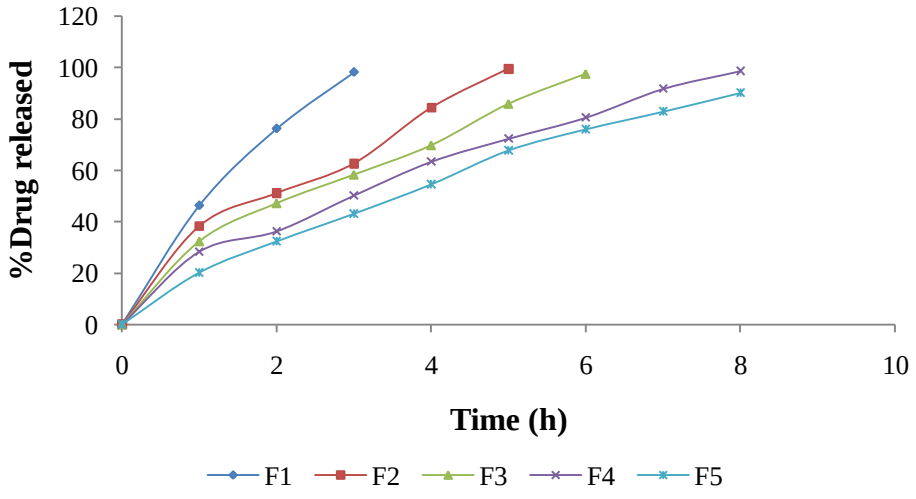

Figure 1: *In vitro* dissolution profile of floating tablets containing gum Xanthan as release retardant

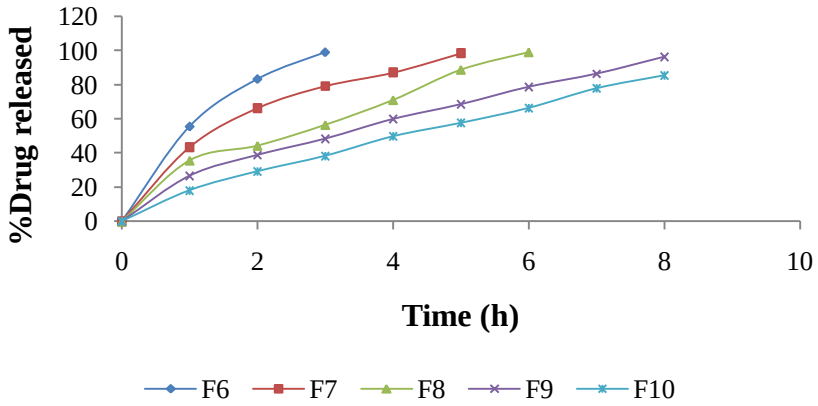

Figure 2: *In vitro* dissolution profile of floating tablets containing HPMC as release retardant

Table 5: Mathematical modelling of floating tablets

Code	Zero order		First order		Higuchi		Korse-meyer Peppas			$T_{50\%}$ (h)
	K_0(mg/h)	r	$K_1(h^{-1})$	r	K_0(mg/h)	r	$K_1(h^{-1})$	r	n	
F_1	32.43	0.985	1.266	0.941	27.00	0.992	45.921	0.998	0.696	0.77
F_2	18.49	0.981	0.884	0.853	20.34	0.984	36.645	0.979	0.586	1.352
F_3	15.07	0.982	0.527	0.914	18.33	0.987	30.69	0.995	0.613	0.658
F_4	11.58	0.984	0.444	0.909	16.30	0.985	25.822	0.99	0.63	2.158
F_5	11.00	0.989	0.276	0.983	14.74	0.976	19.453	0.997	0.74	2.272
F_6	32.51	0.962	1.522	0.949	28.77	0.998	55.59	0.994	0.532	0.768
F_7	18.19	0.946	0.743	0.942	22.30	0.997	44.055	0.993	0.505	1.374
F_8	15.37	0.982	0.656	0.878	18.57	0.981	32.21	0.977	0.584	1.626
F_9	11.09	0.984	0.32	0.941	15.74	0.988	25.234	0.997	0.621	2.254
F_{10}	10.24	0.994	0.225	0.977	13.40	0.969	17.218	0.998	0.757	2.441

CONCLUSION

In the present investigation gastro retentive floating tablets of Quitiapine fumarate with satisfactory release charateristic were successfully prepared by direct compression method using the selected polymers. Fabricated tablets showed acceptable weight variation, hardness and unoformity of drug content. Study indicated that increase in amount of the polymers in the tablets resulted in a reduction in the release rate. Overall results revealed that the retarding effect of gum xanthan was on par with the HPMC E4M for sustaining release of Quetiapine fumarate from developed formulations.

ABBREVIATIONS

HPMC – Hydroxy propyl methyl cellulose, GX- Gum Xanthan, MS – Magnesium stearate $NaHCO_3$ – Sodium bicarbonate, QF – Quetiapine fumarate.

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REFERENCES

1. Sweetman C. in: Martindale, the complete drug reference. London: The pharmaceutical press; 2002: 1023.
2. Baumgartner S, Kristl J, Vrecer F, Vodopivec P. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm 2000; 195:125-135.
3. Ravikumar U, Gautham S, Suresh J, Vipin S, Nilesh and Sohiny S. Design and characterization of controlled release gastro retentive floating tablets of an atypical psychotropic agent. J Pharma BioalliedSci. 2012 March; 4 (1): S88-S89.
4. Aulton ME, Wells TI. Pharmaceutics: The science of Dosage Form Design. London, UK: Churchill Livingstone; 1998: 207.
5. Government of India Ministry of Health and Family Welfare. The Pharmacopoeia of India. Delhi, India: Controller of publication; 1997: 1020-1022.
6. Leon Lachmann, Lieberman HA and Kanig JL. The Theory and practice of Industrial Pharmacy. Special Indian edition; New Delhi, India: CBS publishers and distributors; 2009: 297-301.
7. Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm 1994; 105:65-70.
8. Highuchi T. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52: 1145-1149.
9. Korsmeyer RW, Gurny R, Docler E, Buri P Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25-35.
10. Peppas NA. Analysis of Fickian and Non-Fickian drug release from polymers. Pharma Acta Helv 1985; 60: 110-111.
11. Mockel JE, Lippold BC. Zero order release from hydro-colloid matrices. Pharm Res 1993; 10: 1066-1070.