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Development of Gastroretentive Floating Tablets Quetiapine Fumarate

Priyanka Lekhwar[1], Dr. P. K. Sahoo[2], Ravindra Agarwal[3], Amit Sharma[4]

[1]Department of Pharmaceutics, Master in Pharmaceutics, Delhi, India
[2]Department of Pharmaceutics, Delhi Institute of Pharmaceutical Sciences & Research, Delhi, India
[3]Senior Manager, Production Department Sun Pharma, Scientist, Delhi, India
[4]Scientist, Production Department Sun Pharma, Scientist, Delhi, India

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ABSTRACT

The idea of the study is to prepare and characterize a sustain release floating tablets of Quetiapine Fumarate for Schizophrenia. Materials which are used in making of effervescent Tablets are hydroxy-methylcellulose HPMC. For the buoyancy sodium bicarbonate is used. Initially for the selection of formulation Definitive screening design is used which allows to study the effect of large number of factors in relatively small experiment. The optimized formulation is tested for release rate, buoyancy, hardness, thickness, floating time, swelling study and release rate. These studies shows that optimized tablet remains in stomach for 24h and shows release rate of 91% which is very desirable.

Keywords: *Quetiapine Fumarate, Effervescent Tablet, HPMC, Definitive Study Design*

INTRODUCTION

An approach for prolonging gastric residence time, with targeting the upper part of Gastrointestinal is known as the gastro-retentive drug delivery. They are needed for sustained drug delivery systems. Since they release drug in very optimal way by release it before the absorption window. The increased gastric retention time further increases bioavailability, decreases drug wastage, and enhances solubility property of drug which are minimal soluble in increased pH environment. Quetiapine Fumarate is widely antipsychotic used for schizophrenia disorder. It is used in the initial stages of the disease. Its sustained release tablet dose regimen is 300mg once daily. Solubility of quetiapine fumarate is pH dependent it is highly soluble in the acidic environment while less in basic.

When the formulation goes into the solution the layer of gel is retained with the alongside hydrocolloid layer turns hydrated. The trapped air in the bloated polymer keeps density below unity and provides buoyancy to the formulation.[1]

The floating formulation has many merits since they are less susceptible to gastric emptying Which minimises the divergence in plasma drug levels, very proficient for narrow absorption windows drugs, minimise dosing and elevate patient compliance, slashes the C max and extend level of drug above minimum effective concentration. Quetiapine Fumarate has site specific absorption which gives good rationale for its use as a gastroretentive dosage form.[2]

Characteristics of Gastro-Retentive Tablets

1. Acts in stomach e.g antacids[3]
2. Absorb in stomach e.g amoxicillin[4]
3. Interrupt colonic microbes e.g antibiotics for H.pylori[5]
4. Degraded in colon e.g metformin[6]
5. Absorbed instantly from GIT e.g Metronidazole[7]

Experimental Materials

S. N	Experimental Materials	Details
1.	Quetiapine Fumarate	Sunpharma Laboratories
2.	HPMC K100M	Sunpharma Laboratories
3.	HPMC K100LVCR	Sunpharma Laboratories
4.	Sodium Bicarbonate	Sunpharma Laboratories
5.	Sodium Alginate	Sunpharma Laboratories
6.	Talc	Sunpharma Laboratories
7.	Colloidal Silica	Sunpharma Laboratories
8.	Magnesium Stearate	Sunpharma Laboratories
9.	MCC 101 Grade	Sunpharma Laboratories
10.	Lactose	Sunpharma Laboratories

Formulation Preparation

Direct compression method was used for the preparation of Quetiapine Fumarate. All the excipients are passed through ASTM50. Then all excipients are weighed individually and mixed to get consistent polymer mixture.[8] Then API was mixed with the polymer mixture for getting an uniform blend of the drug.[9] Then powder mixtures with the help of magnesium sterate gets lubricated and compressed for obtaining tablets.[10] Formulation and Composition of Quetiapine fumarate effervescent tablet shown in **Fig. 1**

Composition of Floating Tablets (MG) Fig. 1

Sr. No.	Qutiapine Fumarate	Sodium Bicarbonate	Sodium Alginate	HPMC K100M	Talc	Silica	LVCR	Lactose	Mg Stearate	MCC
F1	230.27	40	30	166	4.5	4.5	0	20.23	4.5	50
F2	230.27	20	0	90	4.5	4.5	0	146.23	4.5	50
F3	230.27	10	0	90	4.5	4.5	30	136.23	4.5	50
F4	230.27	10	30	128	4.5	4.5	30	68.23	4.5	50
F5	230.27	20	30	166	4.5	4.5	30	10.23	4.5	50
F6	230.27	40	0	128	4.5	4.5	0	88.23	4.5	50
F7	230.27	20	15	128	4.5	4.5	15	78.23	4.5	50
F8	230.27	20	15	128	4.5	4.5	15	78.23	4.5	50
F9	230.27	40	15	166	4.5	4.5	0	75.23	4.5	50
F10	230.27	40	30	90	4.5	4.5	15	81.23	4.5	50
F11	230.27	10	0	166	4.5	4.5	15	75.23	4.5	50
F12	230.27	40	15	90	4.5	4.5	30	81.23	4.5	50
F13	230.27	10	30	90	4.5	4.5	0	136.23	4.5	50
F14	230.27	40	0	166	4.5	4.5	30	20.23	4.5	50

In Vitro Studies-

1. Total Floating Time

The in vitro buoyancy was determined by the floating lag time. The time taken by the tablet to rise to the floating surface was determined by the buoyancy lag time and the timings of all the formulated tablets are determined by placing them in 100 ml beaker contains 0.1 N HCl **(Fig. 2)**

TIME	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14		T14
1	37	53	14	12	17	31	15	17	14	50	18	36	16	12		12
2	44	60	22	20	25	37	25	28	26	60	26	54	25	20		20
6	56	67	48	42	48	56	49	55	41	74	48	70	45	39		39
8	69	70	58	53	55	63	58	64	50	77	55	74	53	47		47
10	71	69	65	59	66	68	65	71	54	80	62	79	59	52		52
12	73	69	69	63	68	64	68	75	59	83	67	82	63	58		58
16	75	76	74	67	78	78	77	82	84	84	73	85	69	67		67
20	77	77	74	68	79	77	78	82	86	90	83	86	70	71		69
24	78	78	77	68	79	77	79	83	88	92	85	84	77	72		71

Fig. 2

IN VITRO DISSOLUTION STUDIES

Quetiapine Fumarate effervescent tablet release rate was determined by using USP II apparatus (Paddle type). This test ia performed by using 900ml 0.1N HCl at 37 ± 0.5°c a sample was taken 7 ml from the dissolution apparatus at systematic time intervals upto 24 hours (1, 2, 4, 6, 8, 10, 12, 16, 20, 24)hrs. and the sample is continuously changed with the same volume the fresh dissolution medium. Using membrane filter of 0.45µ samples are filtered out and they were analysed by UV/Visible spectrophotometer Shimadzu 1800 at 290 nm.

SWELLING AND EROSION STUDY

After immersing in the medium the medium uptake and erosion was calculated. Sample are weighed and placed in dissolution baskets containing 0.1 N HCl at 37±2°C. After regular time interval the tablet from dissolution basket taken out, soaked up to eliminate excess water and reweighed on the analytical balance. The dampen samples are then dried for 24 hours at 70°C in oven then allowed to cool in the dessicators and weighed until the final constant dry weighed obtained. The medium uptake is the increase in the weight of wet mass it is calculated

according to the equation :

$Q = 100(W_w - W_f) / W_f$

Absorbed liquid = Q

W_w = hydrated sample before drying

W_f = hydrated sample final mass

The percentage erosion (E) estimated using equation 2

$E = 100 (W_I - W_f - W_t)/W_I$

Where, W_I = initial dry weight

W_f = final mass and partially eroded sample

W_t = theoretical weight of soluble component

Three different samples measured at varied time point. All experiments done in triplicate

DEFINITIVE SCREENING DESIGN

A definitve screening design (DSD) allows to study the effects of large number of factors in a relatively small experiment. DSD are an improvement on standard screening

design (like plackett burman) that prevents confounding of factors and can also detect non-linear responses. DSDs can estimate quadratic (curvy linear) effects when the model contains only main effects and quadratic effects.

Trials were performed at 14 possible factors the amount of sodium alginate (X1), the amount of sodium bicarbonate, HPMC K100M, and Lactose they were selected as independent variables, the time required to 50% and 90% drug dissolution and in vitro floating lag time they were selected as dependent variables.

RESULTS

DRUGS SOLUBILITY

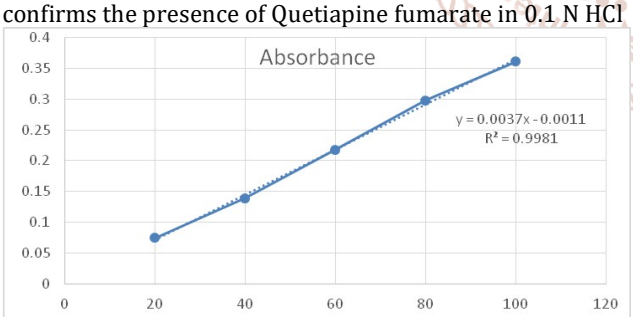
Quetiapine fumarate has pH dependent solubility highly soluble in acidic pH while very poor solubility in alkaline pH. It has quantitative solubility of 33.2 mg/ml in 0.1 N HCl as the pH rises solubility tremendously decreases i.e. 4.2 mg/ml in pH 4.5 acetate buffer, 1.8 mg/ml in pH 6.8 phosphate buffer.

CHARACTERIZATION OF QUETIAPINE FUMARATE TABLET

Variety of combinations are used of sodium alginate, sodium bicarbonate, HPMC K100M, HPMC K100 LVCR. They were used to make the matrix tabelts for sustained release of Quetiapine fumarate with effervescent property. There are all acceptable physical parametrs in all formulation due to their good flow and compressible property. Weight of all the tablets were in the range of 650±5mg. Thickness of all the formulation is between 5.17 to 5.61. Tablet hardness 12.8 to 15.5 kps. Weight loss in the friability test was 0.2-0.5% in all formulations. All the tablets are not disintegrating in the water.

RATE KINETIC ANALYSIS

Quetiapine Fumarate was analysed over the range 200-300nm for λmax determination. The observed peak was at 290nm in UV spectrophotometer (Fig). Standard curve confirms the presence of Quetiapine fumarate in 0.1 N HCl



S. No.	Conc.	Aborbance
1	20	0.075
2	40	0.139
3	60	0.218
4	80	0.298
5	100	0.361

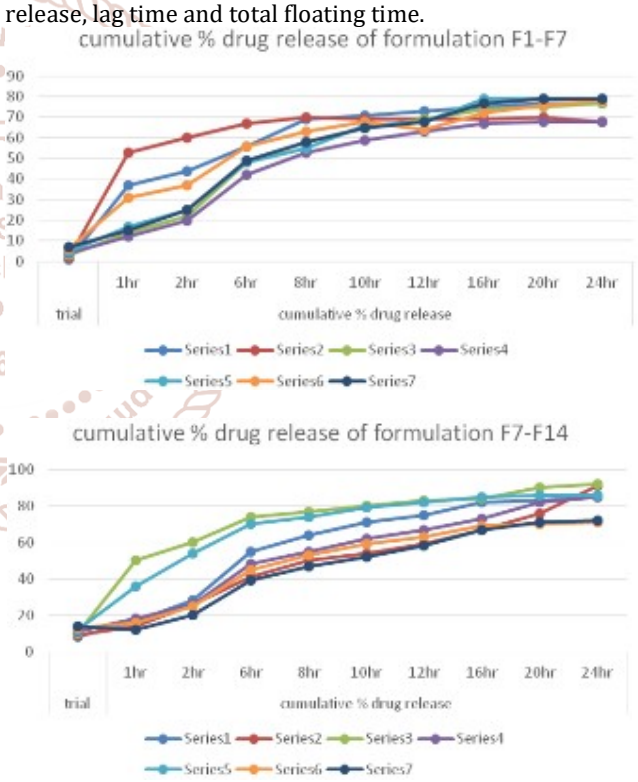
IN VITRO BUOYANCY STUDY

There were 14 formulations made and then characterized for their buoyancy lag time and total floating time. Sodium bicarbonate with HCl mainly responsible for the buoyancy in formulation. Buoyancy lag time range of all formulation found to be 20 seconds to 2 minutes. As the total floating time more than 12 hours for all formulation it shows stable gel formation by all polymers

FORMULA CODE	BUOYANCY LAG TIME(sec)	TOTAL FLOATING TIME (hours)
F1	93	>12
F2	45	>12
F3	No floating	-
F4	No floating	-
F5	40	>12
F6	20	>12
F7	112	>12
F8	No floating	-
F9	43	>12
F10	28	>12
F11	No floating	-
F12	35	>12
F13	No floating	-
F14	No floating	-

IN VITRO DISSOLUTION STUDIES

The formulations T10 and T11 they were using HPMC K100 M, HPMC LVCR, Sodium Carbonate, and the % drug release was found to be 89 and 85 % in 24 hours. Formulations T9 they were developed by using sodium bicarbonate, sodium alginate, lactose was found to be 91%. Formulation T9 selected as optimised formulation based on the better drug release, lag time and total floating time.



OPTIMIZATION OF FORMULATION

Trial 9 exhibit extended drug release profile with desirable floating lag time, consequently this trial was selected for definitive screening design studies to optimize the formulation and effects of variables on formulation. Effects of main variables are estimated in two stages and their combined effects.

The two stages are :
Stages 1 – Main effects estimates
Stages 2 – Even order effects estimates

Combined model parameters estimates (HPMC K100 M, Sodium bicarbonate)

Definitive screening of design for Dissolution

Conclusion of stages parameter: As the concentration of sodium bicarbonate increases, dissolution time also increases. However, no effect of sodium alginate in dissolution time. Further, as the concentration of HPMC K100 M increases dissolution time also decreases. Consequently, the gastric residence time increases.

FLOATING TIME

Floating time increases with increases in concentration of sodium bicarbonate. Sodium alginate ,HPMC K100 M and HPMC K100 LVCR has no effects in floating time.

Summary and Conclusions:

Present study illustrates the formulations of extended release effervescent based floating drug delivery system. Different polymers in different concentrations like sodium bicarbonate, sodium alginate, HPMC K100 M and HPMC K 100 LVCR were used to achieve the desired formulation of gastroretentive floating tablet. Definitive screening design unveil that the amount of sodium bicarbonate, HPMC K 100 M , sodium alginate and HPMC k 100 LVCR had a remarkable effect on release rate of drug so therefore a suitable combination of polymer in appropriate concentrations were used to achieve desired dissolution profile. Based on Evaluations, Trail 9 was selected for optimization. Evaluation parameters like floating lag time, Buoyancy period and in vitro drug release were used and found better than other formulations. optimized formulation was compared with the marketed sustained Seroquel tablet. It was found that the release rate of gastro retentive Quetaipine fumarate has comparable release rate as marketed sustained Seroquel. Short floating time. Extended release of drug indicates higher residence time in the stomach and finally improves the Bioavailbility is the major issue in conventional quetiapine fumarate tablets.

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