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Original Research Paper

Pharmaceutical

DEVELOPMENT AND CHARACTERIZATION OF FLOATING MUCOADHESIVE TABLETS CONTAINING QUETIAPINE FUMARATE

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ABSTRACT Quetiapine Fumarate is a recently introduced atypical antipsychotic and is indicated as the first line option for treatment of psychotic disorder manifestations & was developed utilizing both concepts of adhesiveness and floatation, in order to obtain unique drug delivery system which could remain in stomach for much longer period of time. Floating Mucoadhesive tablets were developed to prolong its release and improve bioavaibility. Tablets were prepared by direct compression using HPMC, Xanthan gum, Avicel Ph, MCC, Magnesium stearate & Talc. Tablets were evaluated for friability, weight variation, content uniformity, floating lag time and mucoadhesive strength. Sodium bicarbonate is used as effervescent base for buoyancy of tablets. By increasing concentration of polymer the drug release rate decreases.

KEYWORDS : Floating-Mucoadhesive tablet, Quetiapine Fumarate, Xanthan Gum, Sodium bicarbonate, Direct Compression

INTRODUCTION:

Oral route is the most preferred means of any drug delivery. Oral delivery of the drug is the most preferred and convenient option as the oral route provides maximum active surface among all drug delivery system. It is due to convenience, ease of administration, greater flexibility and low cost of such a system.

More than 50% of the drug delivery systems available in the market are oral drug delivery systems. About 90% of all drugs used to produce systemic effects are administered by oral route. Fast gastric emptying associated with conventional oral formulations leads to bioavailability issues for many drugs. Drugs that are absorbed from GIT and have short half lives are eliminated quickly and thus frequent dosing is needed to achieve therapeutic activity. Gastro-retentive is an approach to prolong gastric residence.

Floating drug delivery system promises to be a potential approach for gastric retention.The bioavailability and sustain release properties can be improved by floating drug delivery system. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GIT is to control the Gastric Residence Time (GRT), i.e. Gastro Retentive Dosage Form (GRDF).

Gastro retentive delivery is one of site specific delivery of drugs at stomach. It is obtained by retaining dosage form into stomach and drug is released at sustained manner to specific site either in stomach or intestine. Rapid GI transit can prevents complete drug release in absorption zone and reduced the efficacy of administered dose since majority of drugs absorbed in stomach or the upper part of small intestine.

Muco-adhesive drug delivery system is the system in which drug is delivered to mucosa that prolongs the residence time of the dosage form at the site of application or absorption. It can be achieved by mucoadhesive polymer. This polymer can intimate contact with the absorption membrane (mucosa) and dosage form (drug) to improve and enhance bioavailability of drug.

MATERIALS & METHOD

Quetiapine Fumarate (Intas pharma), HPMC K4M (Colorcon Asia Pvt Ltd), Xanthan Gum (Lesar Chemicals Ltd), Avicel Ph (Chemodyes Corporation), Guar Gum (Lesar Chemicals Ltd), Carbopol (SDFCL), Magnesium stearate (Acme Chemicals Ltd) and Talc (Acme Chemicals Ltd)

METHOD:

Preparation of floating mucoadhesive tablets:-

Direct compression method was used for manufacture of floating-mucoadhesive tablets of Quetiapine Fumarate. All the selected polymers (Xanthan gum, Guar Gum), drug (Quetiapine Fumarate) and excipients were passed through sieve no.40 # before using into formulation.

Excipients like MCC, Sodium bicarbonate, Talc, Magnesium stearate were selected for the study. Sodium bicarbonate is used for the gas generating agent.

Steps involved in the manufacturing of the Tablets:

Accurately weighed all the polymers, drug, excipient and pass through sieve no. 40 # and geometrically mixed in mini mixer at 15 minutes. Then, the mixture was lubricated by adding the Magnesium stearate & Talc. Then again mixed in mini mixer for at least 5 minutes. The floating-mucoadhesive tablets were compressed in 12 mm diameter punch, die using 10 station rotary tabled punching machine. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm^2.

EVALUATION OF POWDER:

- **Bulk density:**

Weigh accurately 5 gm of powder blend and transferred in100 ml graduated cylinder. Carefully level the powder blend without compacting and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula:
Bulk Density = Mass/Apparent volume

- **Tapped Density**

It was determined by placing a graduated cylinder, containing a known mass of drug excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by:
Tapped Density = Mass/Tapped volume

- **Carr's Index** :

Carr's Index: It is expressed in percentage and is expressed by:
d tap - d bulk d tap

Where, d tap = Tapped density or True density, d bulk = Bulk density.

- **Hausner's Ratio:**

The Hausner's ratio is a number that is correlated to the flow ability of a powder blend material.
Hausner's Ratio = Tapped Density/Bulk Density

- **Angle of repose :**

The angle of repose of powder blend was determined by the funnel

method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation,

Angle of Repose ( ) = tan-1 (h/r)
Where, h = Height of the powder blend cone
r = Radius of the powder blend cone

Evaluation of Tablets:

- **Diameter:** It was measured by Vernier Callipers. It is expressed in mm. An average value is calculated by using tablets in triplicate and then the mean ± standard deviation values of thickness are notified.
- **Thickness:** It was measured by Vernier Callipers. It is expressed in mm. An average value is calculated by using tablets in triplicate and then the mean ± standard deviation values of thickness are notified.
- **Hardness:** Hardness of tablet was determined using Monsanto hardness tester. It is expressed in kg/cm^3.
- **Friability:** Friability of each batch was determined using Roche friabilator. Ten pre-weighed tablets were rotated at 25 rpm for 4 min or total 100 times dropping a tablet at height of 6 inches in each revolutions, the tablets were then reweighed and the percentage of weight loss was calculated by the following equation. Limit of friability is less than 1%.
- **Weight variation test:** Twenty tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 7.5%. It's specification as per I.P. is shown in below table.
- **Content uniformity:** Ten tablets were weighed and powdered in a glass mortar. Quantity of powder equivalent to 40mg was accurately weighed and transferred in a 100ml volumetric flask. Make final volume in volumetric flask up to 100ml using 0.1N HCl and filter through whatman filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 233nm against blank using UV visible spectrophotometer.
- **In vitro Dissolution study:** The in vitro dissolution study of fast dissolving tablet was performed as described in Indian Pharmacopoeia 2010 using USP apparatus II at 50 rpm, using 900ml of 0.1N HCl as a dissolution media maintaining the temperature at 37±0.50C. Aliquot of 10ml dissolution medium was withdrawn at a specific time intervals and filter through a whatman filter paper, diluted and assayed at 254nm against 0.1N HCl as a blank using UV visible double beam spectrophotometer. The volume of dissolution fluid was adjusted to 900ml by replacing each 10ml aliquot withdrawn with 10ml of fresh 0.1N Hcl.
- **In-vitro Mucoadhesive Strength:** The apparatus consists of modified physical balance**.** It consists of balance with two arms on which weights are suspended, the weight corresponding to the detachment force being determined. In this method the formulation is located between two tissue layers in glass beaker containing a defined amount of fluid. Weights are gradually added to one arm of balance. Mucoadhesive strength is measured in gram.

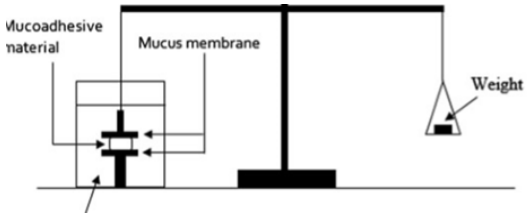

Figure 1: Measurement of Mucoadhesive strength

FORMULATION:-

Table 1: Formulation of preliminary batches F1-F5

Ingredients	F1	F2	F3	F4	F5
Quetiapine Fumarate	173	173	173	173	173
HPMC K4M	100	150	200	100	150
Carbopol	50	75	100	-	-
Xanthan gum	-	-	-	50	75
Guar gum	-	-	-	-	-
Sodium bicarbonate	50	50	50	50	50
Avicel Ph101	165	90	15	165	90
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6

Table 2: Formulation of preliminary batches F6-F10

Ingredients	F6	F7	F8	F9	F10
Quetiapine Fumarate	173	173	173	173	173
HPMC K4M	200	100	150	200	
Carbopol	-	-	-	-	100
Xanthan gum	100	-	-	-	50
Guar gum	-	50	75	100	-
Sodium bicarbonate	50	50	50	50	50
Avicel Ph101	15	165	90	15	215
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6

150 mg Quetiapine=173 mg Quetiapine fumarate

DRUG EXCIEPIENT COMPABILITY STUDY

Drug- excipients interactions play a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. FTIR studies revealed that Quetiapine Fumarate showed two typical bands at 1600 and 1412 cm-1 due to N-H stretching vibration and a stretching of Sulfonyl Group, band at 3317 cm-1 due to C-H stretching, and characteristics bands at 765 and 989 cm-1 assigned to =C-H stretching.

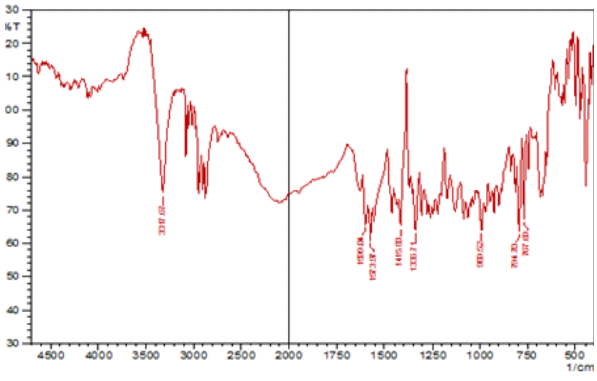

Figure 2: FTIR Spectra of Quetiapine

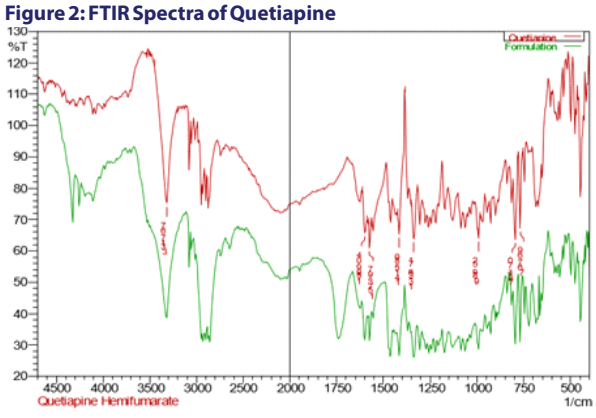

Figure 3: Overlay of Quetiapine Fumarate and Quetiapine Fumarate formulations

IN-VITRO DRUG RELEASE STUDIES:

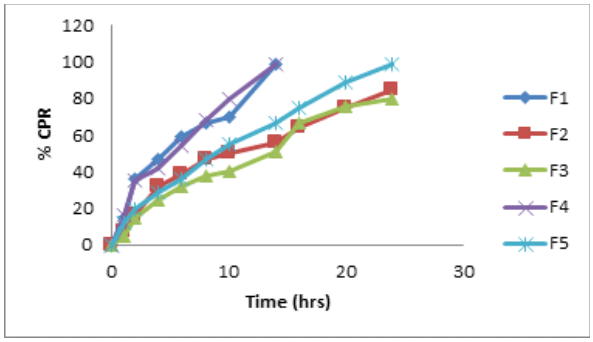

Figure 4: In vitro drug release studies of preliminary batches of F1 to F5

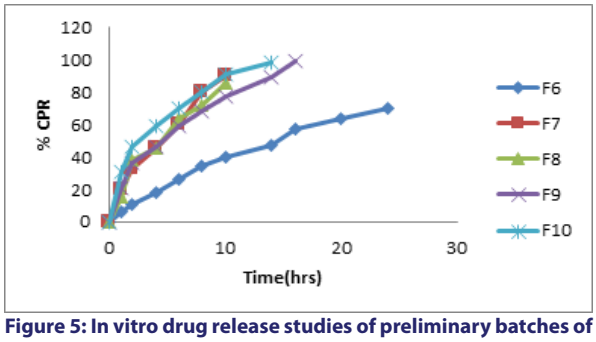

Figure 5: In vitro drug release studies of preliminary batches of F6 to F10

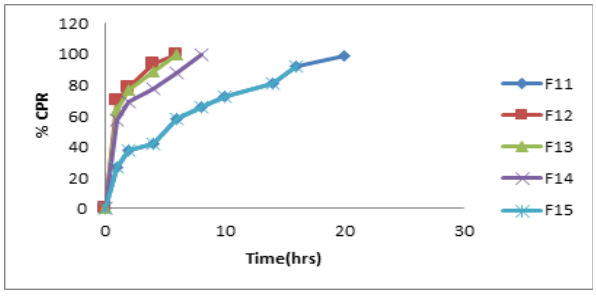

Figure 6: In vitro drug release studies of preliminary batches of F11 to F15

In-vitro drug release studies:

The pharmacokinetic parameters of Quetiapine fumarate were used to calculate a theoretical drug release profile for 24 hrs dosage form. It was carried out by using 0.1 N HCl using USP dissolution apparatus type II. From the dissolution profile of all batches it was found that there was fast drug release at initial state of dissolution of F1 to F4, where as F6 to F10 showed drug release within 15 mins. The batch containing 75 mg Xanthan Gum showed optimized drug release as it has least dissolution time.

4.9 OPTIMIZATION OF VARIABLES USING CENTRAL COMPOSITE DESIGN.

Central composite design (CCD) is one of the most commonly used optimization technique in Response Surface Designs. As CCD was first developed by Box & Wilson it is also called Box-Wilson Central Composite Design. For estimation of curvature, CCD contains an imbedded factorial or fractional factorial design i.e with center points. It is having `star points' which are in group.

The design consists of three distinct sets of experimental runs:
1. A factorial (or fractional) design, each having two levels.

2. A set of centre points, whose values of each factor are the medians of the values used in the factorial portion.

3.A set of axial points (star points),whose values of each factor are below and above the values of the two factorial levels.

Table 4: Formulation of Quetiapine Fumarate CCD Batches

Formulation Ingredient (mg)	FORMULATION BATCH CODE (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
QF	173	173	173	173	173	173	173	173	173
HPMC K4M	125	125	175	175	150	114.65	150	185. 35	150
Xanthan gum	60	80	60	80	70	70	55.85	70	84.15
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Avicel PH 101	96	86	71	61	78.5	96.17	85.57	60.82	47.62
Mag. St	12	12	12	12	12	12	12	12	12
Talc	12	12	12	12	12	12	12	12	12

FULL & REDUCED MODELS:

1) Full model for FLT (sec)

$Y1=84.998 -10.441(X_1) -11.972 (X_2) +1.3761(X_1X_2) -0.3743(X_2X_2) -4.75(X_1X_2)$

2) Full model for Mucoadhesive strength (Y2)

$Y1=15.79927 +1.279168 (X_1) + 1.518854 (X_2) -0.07456 (X_1X_2) -0.67474 (X_1X_2) -0.2 (X_1X_2)$

3) Full model for Q_{12}(%)

$Y1=70.4294– 8.26611(X_1) – 5.74451 (X_2) – 1.94262 (X_1X_2) + 0.208034(X_1X_2) -0.968826 (X_1X_2)$

4) Full model for t_{90}(hr)

$Y1=17.70987 + 1.654662 (X_1) + 1.345286 (X_2) -0.08054 (X_1X_2) - 0.45565 (X_1X_2) + 0.8375 (X_1X_2)$

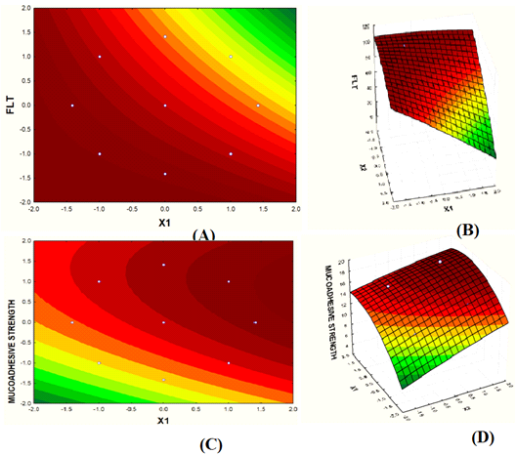

Figure 7:
(A) Response contour plot for FLT (sec)
(B) Response surface plot for FLT (sec)
(C)Response contours plot for Mucoadhesive strength
(D) Response surface plot for Mucoadhesive strength

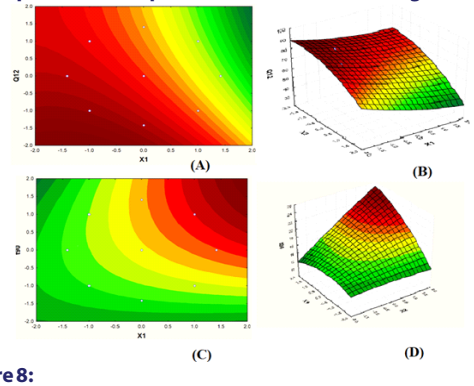

Figure 8:
(A) Response contours plot for Q12 (%)
(B) Response surface plot for Q12 (%)
(C) Response contours plot for t90 (hr)
(D) Response surface plot for t90 (hr)

CONCLUSION:

The present investigation was aimed to developed and characterize floating mucoadhesive tablets of Quetiapine Fumarate were prepared by direct compression method based on natural as well as synthetic polymers and sodium bicarbonate as gas generating agents.

FTIR spectroscopy indicates that the drug is compatible with all the excipients. The drug content was uniform in all the formulation of the tablets prepared.

In preliminary batch study, mucoadhesive polymers like HPMC K_4M, Carbopol, Xanthan Gum and Guar Gum were used. It was observed that HPMC K_4M has good retard release rate and Xanthan Gum has good mucoadhesive property. Therefore HPMC K_4M and Xanthan Gum were further used for preparation of CCD batches. From the CCD it was concluded that different polymer concentration of HPMC K_4M and Xanthan Gum has effect on floating lag time, mucoadhesive strength, Q_{12} and t_{90}.

So increase in polymer concentration shows increase in mucoadhesive property and decrease in drug release rate.

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