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RESEARCH ARTICLE

# PREPARATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS: OF QUETIAPINE FUMARATE

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**ABSTRACT**

The present study is performed by preparation and evaluation of floating tablets of quetiapine fumigate as model drug for prolongation of gastric residence time. Floating effervescent tablets were formulated by various materials like hydroxypropyl methylcellulose HPMC ( K4M , K100M, KE15, PLAIN ) , Sodium CMC, PVPK 30, crospovidone, Ethylcellulose, MCC, PGMS, polymers with excipients sodium bicarbonate ,citric acid, lactose, magnesium stearate and talc and evaluated for floating properties, hardness, friability, dissolution, tap density and in vitro drug release studies. The gastro-retentive delivery systems of Quetiapine fumarate were successfully developed in the form of hydrodynamically balanced tablets to improve the local action and its bioavailability, which reduces the wastage of drug and ultimately improves the solubility for drugs that are less soluble in high pH environment thereby improving h, the patient compliance.

Key words: Quetiapine fumarate; floating; gastroretentive; crospovidone; microcrystalline cellulose; Ethylcellulose.

## INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence time The CRDDS possessing ability of being retained in the stomach are called gastro retentive drug delivery system (GRDDS) and they can help in optimizing oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window, for prolonged period of time.[1-3] Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patient [4]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying. [5]

Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and intersubject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and increased patient compliance, reduced C max and prolonged drug levels above the minimum effective concentration, and improved safety profile for drugs with side-effects associated with high Cmax.[6] As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated.[7] The air trapped in by swollen polymer maintains density less than unity and confers buoyancy to these dosage forms The hydro dynamically balanced system must comply with three major criteria-

- It must have sufficient structure to form cohesive gel barrier
- It must maintain an overall specific density lower than that of gastric content
- It should dissolve slowly enough to serve as reservoir for the delivery system.8-10

The aim of present study is to prepare and evaluate floating tablet of Quetiapine fumarate based on low density polymer that retains the dosage form in the stomach which provide an increased gastric residence time resulting in prolonged drug delivery in gastrointestinal tract using HPMC K4M, HPMC K100M, HPMC KE15 and Ethyl cellulose as sustain release polymers and to study the various formulation and process variables that ultimately affects the drug release. The selection and optimization of polymer concentration, type of filler and amount of low density polymer that has pronounced effect on tablet properties and drug release profile as well as buoyant properties of the formulations.[11]

The low bioavailability is owing to the rapid biotransformation in the liver with less biological half life of 6 h [12]. The short half life, poor bioavailability and faster solubility in acidic medium[5] make it a suitable for gastroretentive drug delivery system.

## EXPERIMENTAL

### Materials

Quetiapine fumarate antipsychotic drug was received as a gift sample from Micro Lab. Ltd., India. The other ingredients used in the preparation like Ethyl cellulose (Coating agent, viscosity enhancer), Hydroxypropylmethylcellulose (Tablet binder, tablet filler, film former), Microcrystalline cellulose (Diluent, disintegrate, lubricant), Polyvinyl pyrrolidone (Pharmaceutical aid), Lactose (Organic diluents), Sodium bicarbonate (Alkalizing agent, therapeutic agent), Pregelatinized maize starch (Tablet disintegrator. Diluents), Cross Povidone (Dissolution aid, disintegrating agent), Citric acid (Acidifying agent, Antioxident, Buffering agent), Sodium carboxy methyl cellulose (Extended release matrix, drug encapsulator), Magnesium stearate (Lubricant), Talc (Glidant, anti-cackling agent), were of analytical grade.

## METHODS

Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies. The standard calibration curve for Quetiapine fumarate is prepared by using UV spectrophotometer.

## PREPARATION OF GASTRO RETENTIVE FLOATING TABLETS

Floating tablets containing Quetiapine fumarate were prepared by direct compression technique using variable concentrations of HPMC K4M, HPMC K100M, KE15 and Ethyl cellulose with sodium bicarbonate. Different tablet formulation were prepared by direct compression method [13].All the powders were passed through 60 mesh sieve the required qty. of drug and lower density polymer were mixed geometrically and then tablets are compressed in compression machine at specified pressure with 10 mm round punch. (Table no: 1)

**Table 1: Ingredients.**

| INGREDIENTS | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Drug(Quetiapine fumarate) | 25 | 25 | 25 | 25 | 25 |
| ethyl cellulose | 20 | - | 20 | 20 | 20 |
| Hydroxypropylmethylcellulose(ke15) | 60 | 0 | 0 | 0 | 0 |
| Hydroxypropylmethylcellulose(k100m) | 0 | 60 | 0 | 60 | 0 |
| Hydroxypropylmethylcellulose(k4m) | 0 | 0 | 60 | 0 | 0 |
| Hydroxypropylmethylcellulose(plain) | 0 | 0 | 0 | 0 | 60 |
| Microcrystalline cellulose | 20 | 20 | 20 | 20 | 20 |
| Polyvinyl pyrrolidone(k30) | 25 | 25 | 25 | 25 | 25 |
| Lactose | 20 | 20 | 35 | 35 | 35 |
| Sodium bicarbonate | 100 | 100 | 100 | 100 | 100 |
| Pregelatinized maize starch | 20 | 20 | - | - | - |
| Cross Povidone | - | - | 20 | 20 | 20 |
| Citric acid | 15 | 15 | - | - | - |
| Sodium carboxy methylcellulose | - | 20 | - | - | - |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 |
| Talc | 10 | 10 | 10 | 10 | 10 |

**Swelling index (water uptake) study**

Polymer matrices representing swellable matrix drug delivery systems are porous in nature. When these matrices come in contact with water or aqueous gastrointestinal fluid, the polymer absorbs the water and undergoes swelling or hydration. The rapid formation of a viscous gel layer upon hydration suggests that swelling is associated with polymer chain relaxation with volume expansion. The liquid diffuses through the polymer matrix at a constant velocity, and the rate of diffusion of the liquid and that of macromolecular relaxation of the polymer are almost of the same magnitude or, possibly, the rate of diffusion of the liquid is relatively higher than that of relaxation of the polymer segment. [14-16]

This mechanism gives the idea regarding the water uptake study of various grades of polymer. This phenomenon is attributes to that the swelling is maximum due to water uptake and then gradually decreased due to erosion. Swelling measurement was performed separately in order to collect on the basis of weight increase over time. The swelling is due to presence of hydrophilic polymer, which gets wetted and allows water uptake leads to increase in its weight.

**In Vitro dissolution studies**

The release rate of Quetiapine fumarate from floating tablets was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 254 nm using a Simbazu UV-Vis double beam spectrophotometer 1700. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.[17]

**RESULTS AND DISCUSSION**

To identify the presence of pure drug IR spectra for Quetiapine fumarate and formulated tablets were recorded in a Fourier transform infrared spectrophotometer in which the IR spectrum of pure drug (Figure 1) was found to be similar to the standard spectrum of Quetiapine fumarate (Figure 2). The pure drug Quetiapine fumarate was scanned over a range 200-300 nm to determine its λmax.[18-20] The peak was observed at 254 nm in UV spectrophotometer (Table 2) (Figure 3) and the standard calibration curve obtained conforms the identification of Quetiapine fumarate in 0.1N HCL.

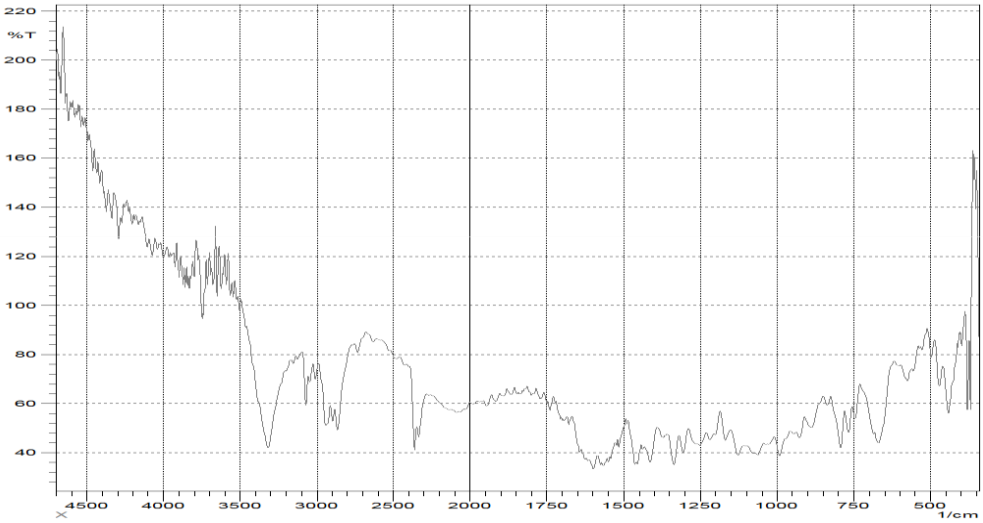



**Fig. 1: IR spectrum of pure Quetiapine fumarate.**

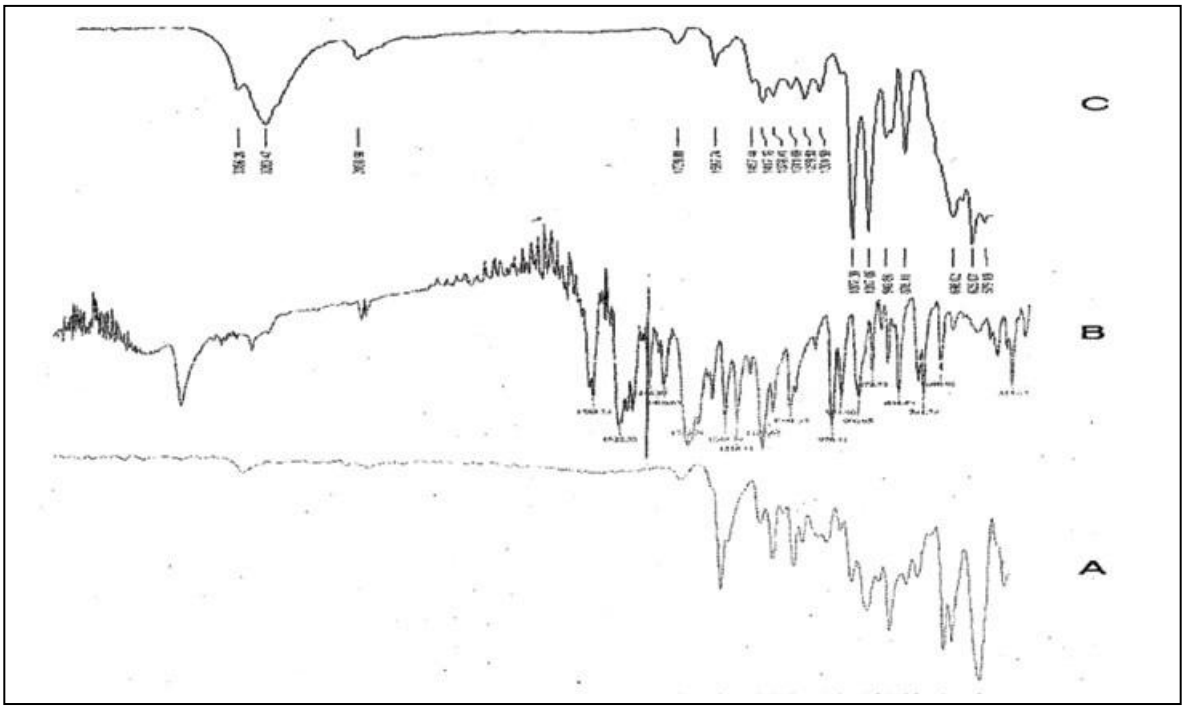



**Fig 2: IR spectrum of Quetiapine fumarate Formulation**

**Table 2: Calibration Curve**

| SNO | CONCENTRATION(UG) | ABSORBANCE |
|---|---|---|
| 1. | 10 | 0.314 |
| 2. | 20 | 0.572 |
| 3. | 30 | 0.905 |
| 4. | 40 | 1.266 |
| 5. | 50 | 1.6 |
| 6. | 60 | 1.926 |

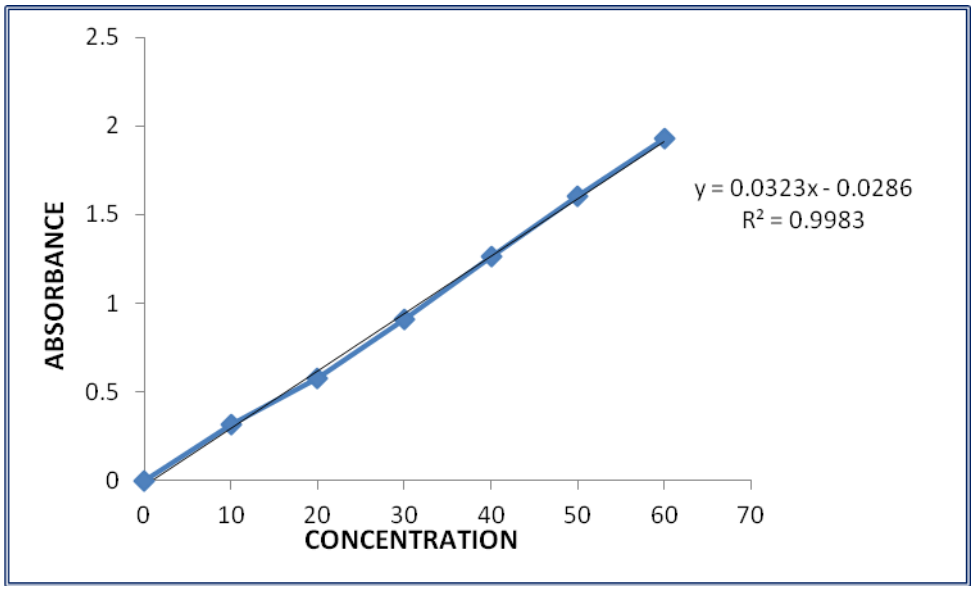



**Figure No: 3 Calibration Curve.**

The preformulation studies like melting point determination of Quetiapine fumarate was found to be in the range of 160-170$^0$C to value as reported in literature,[21] thus indicating purity of the drug sample and the drug has also been proved to have good solubility properties. The prepared tablets were evaluated for pre-compression parameters like bulk density, tapped densisity, angle of repose and post-compression parameters like hardness, friability, thickness, weight variation [22] which proved that the tablets are with sufficient hardness and good mechanical strength. The formulated tablets were also evaluated for floating lag time and total floating time.

Table 3 shows the results obtained for angle of repose, bulk density and tapped density of all the formulations. The values were found to be in the range of 23$^0$ 76' to 28$^0$.22'. All formulations showing angle of repose within 30$^0$, indicates a good flow property

of the granules. [23] The loose bulk density and tapped bulk density for all the formulations varied from0.5840 gm/cm$^3$ to 0.7632gm/cm$^3$ and 0.7069gm/cm$^3$ to 0.8904gm/cm$^3$ respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder. The thickness of the tablets was measured by using vernier callipers [24] by picking the tablets randomly. The mean values are shown in Table 4. The values are almost uniform in all formulations. Thickness was found in the range of 4.5 mm to 5.0 mm. Hardness test was performed by Monsanto hardness tester.[25] Hardness was found to be within 4.5 kg/cm to 5.1 kg/cm. The hardness of all the formulations was almost uniform in specific method and possesses good mechanical strength with sufficient hardness. Friability tests approve that all Formulations possess good mechanical strength. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±10 %. The weight of all the tablets was found to be uniform.

The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT). The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time [26]. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. Floating lag time of F1 –F5 was in the range of 1min 2sec -1min 8sec, F2 Shows good floating lag time of 1min 2 sec. (Table 5) Total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).All formulations a show TFT more than 10 hrs and F2 shows good total floating time that is more than 12 hrs.

In-vitro water uptake studies are of great significance as variation in water content causes a significant variation in mechanical properties of formulations [27] (Table 6). The capacity of the formulation to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of the drug. Invitro drug release study was performed using USP II (paddle) dissolution test apparatus at 50 rpm using 900 ml of 0.1N HCL maintained at 37$^0$ ± 0.5$^0$C as dissolution medium. The results were shown in table 7. Among the five formulations F1 to F3 have released 85 to 97% drug in 8 hours, whereas F4 to F6 formulations have released 94 to 99% drug in 8 hours.F2 Shows comparatively similar drug release rate with marketed drug. (Figure 5)

**Table 3: Precompression Parameters.**

| parameters | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| Bulk Density (g/cc) | 0.7632 | 0.7241 | 0.5840 | 0.6066 | 0.6241 |
| Tapped Density (g /cc) | 0.8904 | 0.8119 | 0.7069 | 0.7800 | 0.7645 |
| Angle of Repose (θ) | 25.35 | 24.33 | 27.70 | 28.22 | 23.76 |

**Table 5: Floating lag Time and Total floating time of designed formulations**

| S.NO | FORMULATION | FLOATINGLAG TIME(MIN) | TOTAL FLOATING TIME(TFT) |
|---|---|---|---|
| 1 | F1 | 1.3 | >11 hrs. |
| 2 | F2 | 1.2 | >12 hrs. |
| 3 | F3 | 1.5 | >10 hrs. |
| 4 | F4 | 1.7 | >11 hrs. |
| 5 | F5 | 1.8 | >10 hrs. |

**Table 6: Percent (%) of swelling index.**

| Time (min) | % Swelling index | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 38 | 38 | 39.6 | 32.14 | 40.38 |
| 30 | 53.38 | 51.9 | 49 | 35.71 | 51.92 |
| 60 | 67.73 | 71.15 | 64.15 | 55.35 | 69.23 |
| 120 | 84.61 | 84.6 | 84.9 | 76.8 | 88.46 |
| 180 | 103 | 101.9 | 105.66 | 91.07 | 119.2 |
| 240 | 115.38 | 119.23 | 128.3 | 101.78 | 123.07 |
| 300 | 121.15 | 126.9 | 132 | 108.92 | 134.61 |
| 360 | 134.61 | 136.53 | 137.7 | 116 | 150 |
| 420 | 138.46 | 142.3 | 143.39 | 123.21 | 153.84 |
| 480 | 145.84 | 146.84 | 150.05 | 121.65 | 160.35 |

**Fig. 4: Percent (%) of Swelling Index.**

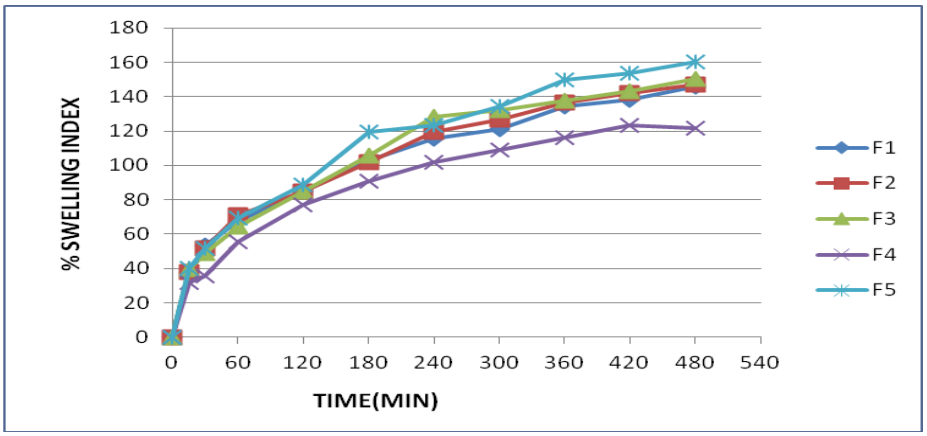
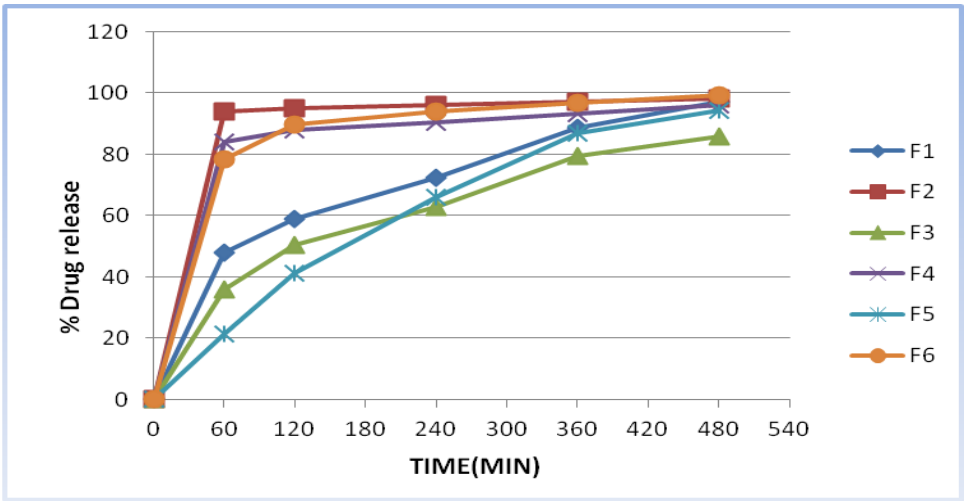



**Table 7: % DRUG RELEASE**

| S.NO | TIME | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1hr | 48.0 | 93.95 | 35.76 | 84 | 21.48 | 78.4 |
| 3 | 2hr | 58.92 | 95.15 | 50.48 | 87.92 | 41.32 | 89.6 |
| 4 | 4hr | 72.2 | 95.96 | 62.84 | 90.36 | 66.08 | 93.8 |
| 5 | 6hr | 88.68 | 97.07 | 79.56 | 93.16 | 87.04 | 96.8 |
| 6 | 8hr | 97.16 | 98.18 | 85.68 | 96 | 94.28 | 99.2 |

**Fig 5: Comparative Drug Release Of F1 – F6.**




## CONCLUSION

*In vitro* buoyancy studies were performed for all the formulations, F1 to F5 by using 0.1 N HCl solutions at 37oC. All the formulations were floated but F2 shows good floating property that is floating lag time of 1min 2sec, which containing 60 mg of HPMC K100M, 20 mg of NACMC, and 100 mg of sodium bicarbonate and 15mg of citric acid showed total floating time more than (12 hours) than other formulations. *In vitro* dissolution studies were also performed, percentage drug release was found to be 98.18. Thus F2 was identified as ideal batch based on its results. Finally, it was concluded that HPMC K100M, SCMC, sodium bicarbonate and citric acid can be successfully used in the formulation of Quetiapine fumarate sustained release gastro retentive floating drug delivery system. Gastric retention time can be increased for a drug like Quetiapine fumarate, by formulating it in a floating dosage form, which enhances the absorption of Quetiapine fumarate in the initial part of small intestine and hence giving the desired pharmacological effect. And the so developed formulation holds promising for other drugs, which has an absorption window in stomach and upper part of the small intestine.

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