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Development and *In-vitro* characterization of floating drug delivery system of ketoconazole

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ABSTRACT

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high level of patient compliances. Floating drug delivery system (FDDS) float in the gastric fluid and prolong GRT to obtain sufficient drug bioavailability, because of their lower bulk density compared to that of the aqueous medium. The aim of the present study is to prepare floating tablets as a delivery system for controlled release of Ketoconazole. Ketoconazole is a drug of choice in antifungal category and gives significant result. Floating tablets containing Ketoconazole were prepared by direct compression technique using varying concentrations of different grades of polymers of Hydrxy Propyl Cellulose & Xanthan gum. To evaluate the prepared floating tablets for various parameters like hardness, friability, uniformity of drug content, in-vitro floating studies, in-vitro dissolution studies.

Keywords: Ketoconazole, Floating drug delivery system, Hydrxy Propyl Cellulose, Xanthan gum

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INTRODUCTION

Oral route was one of the most convenient and preferable ways for drug administration. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled-Release drug delivery system (CRDDS) provides drug release at a predetermined, predictable and controlled rate. Controlled-Release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period: enhancement of activity of duration for short half-life drugs elimination of side effect*s: reducing frequency of dosing and wastage of drugs: optimized therapy and better patient compliances. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolong gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. Floating systems or hydro dynamically balanced systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and a better control of the fluctuations in plasma drug concentrations.[1-7]

METHODS

Preformulation [8-10]

Characterization of Drug:

Physiochemical Properties of Ketoconazole

Organoleptic evaluation

It was done by evaluation of sensory characters like taste, appearance, odor etc.

Solubility (at room temperature):

Solubility can be defined as the property of a solute (solid, liquid, or gaseous chemical substance) to dissolve in a solid, liquid, or gaseous solvent to form a identical solution of the solute in the solvent. The solubility of a substance is the quantity of that solute that will dissolve in a given quantity of solvent. It is a important parameter for dosage form designing.

Procedure:

Approximately 1 gram of drug was weighed accurately and transferred to 5 different 10 ml. volumetric flasks. Different solvents (DCM, ether, water, Ethanol, Methanol, Chloroform) were added to the flask respectively and the solubility was observed.

Melting point:

It is one of the parameters for the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure for determine melting point:
A small quantity of drug was placed into a capillary tube, and then it was placed in the melting point determining apparatus containing liquid paraffin. The temperature of the liquid paraffin was gradual increased automatically and reading was taken at which sample started to melt till all sample gets melted.

Bulk Properties:

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all Preformulation lots is necessary to avoid misleading predictions.

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:

Approximately 4 gram of powdered drug was accurately weighed and poured into the measuring cylinder carefully and level of the powdered drug without compacting was recorded. After that powdered drug was compressed by tapping the measuring cylinder for around 50 times on the palm and the compressed level was recorded. Finally the Bulk density was calculated in gm per ml gm/cc, by the formula:

Bulk density = Bulk Mass/ Bulk Volume

Table 1: Bulk Density of Ketoconazole

S. No.	Density	Ketoconazole
1	Untapped Density	0.714g/cc
2	Tapped Density (after 50 tapping)	0.769g/cc

(H) Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{100\,(V0-Vf)}{V0} \quad OR \quad C.I. = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Table 2: Carr's index range

S. No.	% Comp. Index	Properties
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair – passable
4	23-25	Poor
5	33-38	Very Poor
6	>40	Extremely poor

Determination of λ max of Ketoconazole

The absorption maxima of ketoconazole was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Calibration curve of Ketoconazole

Preparation of Standard Stock Solution:

10mg of ketoconazole was weighed accurately and transferred to 10 ml volumetric flask, and the volume was adjusted to the mark with the 0.1 N Hcl to give a stock solution of 1000 ppm or µg/ml.

Preparation of Working Standard Solution:-

From stock solutions of Ketoconazole 1 ml was taken and diluted up to 10 ml separate volumetric flask. From this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with mobile phase, gives standard drug solution of 5, 10, 15, 20, 25µg/ml concentrations of Ketoconazole.

Formulation Development [12-14]

Preparation of Floating tablets[10-11]

Floating tablets containing Ketoconazole were prepared by direct compression technique using varying concentrations of different grades of polymers of HPC & Xanthan gum with sodium bicarbonate, citric acid, Lactose are geometrically mixed all the powders were passed through sieve. No #80. Magnesium stearate and talc were finally added as glidant and lubricant respectively. The blend was directly compressed using tablet compression machine. The tablets were off white, round and flat. The hardness of the tablets was kept constant. Ten formulations were prepared and coded them from F1 to F10.

Evaluation of Pre-compression Parameter

1. **Angle of repose (θ)**: The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$
$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definit height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed

Table 3: Relationship between Angle of Repose (θ) and flow properties

S. No.	Angle of Repose (θ) (degrees)	Flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable*
4.	>40	Very poor

*Adding glidant E.g. Talc may improve flow properties

2. **Bulk density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

3. **Carr's Compressibility index**: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Table 4: Grading of the powders for their flow properties according to Carr's Index

S. No.	Carr's Compressibility index	Flow
1.	5 – 15	Excellent
2.	12 – 16	Good
3.	*18 – 21	Fair to passable
4.	*23 – 35	Poor
5.	33 – 38	Very poor
6.	>40	Very very poor

***Adding glidant E.g. Talc should improve the flow properties**

4. **Hausners ratio:** It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter[15-16]

1. Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

2. Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

3. Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with the average. The U.S. Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed

Table 5: Percentage deviation in weight variation

S. no.	Average weight of a tablet	Percentage deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5
3.	324 mg or more	5

In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

4. Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

5. Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight/Initial weight}) \times 100$$

The test complies if tablets not loose more than 1% of their weight

6. Uniformity of drug content:

The test is mandatory for tablets. Ten randomly selected tablets from each formulation (F1 to F10) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 222.00 nm for Ketoconazole.

Method for Preparation of Ketoconazole Floating tablet:

Direct compression was followed to manufacture the gas generating floating tablets of Ondansetron Hydrochloride. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9 & F10) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed and all the formulations were used for further evaluations parameters. Excipients like Sodium bicarbonate, citric acid anhydrous, Magnesium Stearate were selected for the study. Sodium bicarbonate and citric acid were used as gas generating agent. Citric acid was also used as an antioxidant. Steps involved in the manufacture of tablets, first the drug, polymer and other excipients selected were passed through 40- mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into

polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min.

Evaluation of tablets:

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N Hcl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λ max of 414.0 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed separately in a 100 ml glass beaker containing 2simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Ketoconazole tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^{0}C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCL and take the absorbance at 222.0 nm using spectroscopy.

Figure 1: Photographs taken during *in-vitro* Dissolution study of floating Tablets in 0.1 N HCL.

RESULTS

Preformulation

Characterization of Drug:

Physiochemical Properties of Ketoconazole

It was found white crystalline powder, Odorless & tasteless.

Solubility (at room temperature):

Table 6: Solubility studies of Ketoconazole

S.No.	Solvent	Solubility
1	Dichloromethane	Freely Soluble
2	Chloroform	Soluble
3	Methanol	Soluble
4	Ethanol (95%)	sparingly soluble
5	Water	Practically insoluble
6	Ether	Slightly soluble

It was found that ketoconazole was practically insoluble in water; freely soluble in DCM, soluble in chloroform & methanol, slightly soluble in ether**.**

Melting point:

Melting point was determined by Melting point apparatus and found to be 148-152^0**C**.

Bulk Properties:

Bulk density of powder was found to be **0.833g/cc** and **0.714g/cc** for ketoconazole.

Table 7: Bulk Density of Ketoconazole

S. No.	Density	Ketoconazole
1	Untapped Density	0.714g/cc
2	Tapped Density (after 50 tapping)	0.769g/cc

The compressibility index of Ketoconazole was found to be 8.360% and 7.152%.

M) Determination of λ max of Ketoconazole

The absorption maxima of ketoconazole was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

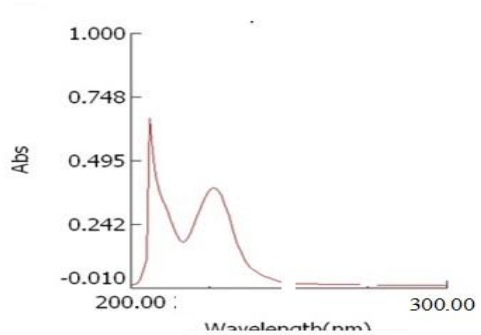

Figure 2: Determination of λ max of Ketoconazole

Calibration curve of Ketoconazole

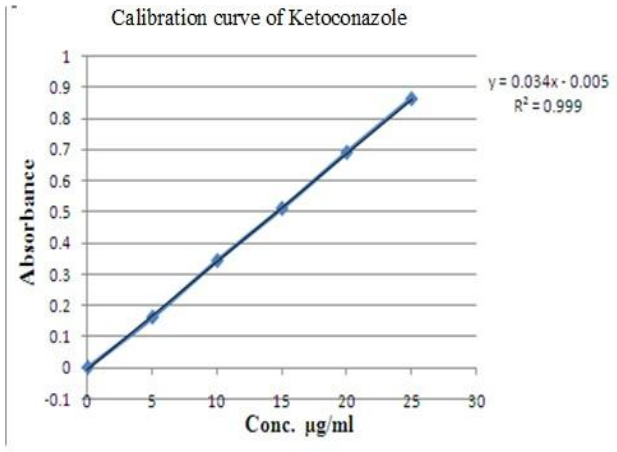

Figure 3: Calibration Curve of Ketoconazole

Method for Preparation of Ketoconazole Floating tablet:

Table 8: Composition of Ketoconazole Tablets

Ingredients (mg)	Formulation code									
	F1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Ketoconazole	200	200	200	200	200	200	200	200	200	200
HPC	100	200	300	_	_	_	50	100	50	100
Xanthan gum	_	_	_	100	200	300	50	100	50	100
Sodium bicarbonate	50	50	50	50	50	50	50	50	100	100
Citric acid	25	25	25	25	25	25	25	25	25	25
Lactose	260	160	60	260	160	60	260	160	210	110
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10	10
Total weight (mg)	650	650	650	650	650	650	650	650	650	650

Evaluation of Precompression Parameter

Table 9: Results of pre-compressional parameters of Ketoconazole

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.34	0.43	20.93	1.26	42°25
F2	0.33	0.42	21.43	1.27	42°25
F3	0.34	0.43	20.93	1.26	41°36
F4	0.35	0.4	12.50	1.14	42°26
F5	0.34	0.43	20.93	1.26	43°15
F6	0.33	0.41	19.51	1.24	43°36
F7	0.34	0.42	19.05	1.24	40°56
F8	0.35	0.43	18.60	1.23	41°26
F9	0.34	0.41	17.07	1.21	40°23
F10	0.31	0.43	17.02	1.20	40°21

Evaluation of post compression Parameter

Table 10: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm²)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.13	0.8217	Passes	1.42	99.41
F2	3.10	0.7262	Passes	1.45	99.77
F3	3.11	0.5314	Passes	1.41	98.53
F4	3.13	0.6425	Passes	1.40	99.41
F5	3.11	0.6346	Passes	1.44	99.33
F6	3.21	0.7114	Passes	1.46	98.51
F7	3.26	0.5612	Passes	1.40	99.57
F8	3.27	0.8554	Passes	1.43	98.33
F9	3.12	0.7377	Passes	1.42	99.65
F10	3.21	0.7114	Passes	1.46	98.51

Method for Preparation of Ketoconazole Floating tablet:

Table 11: Result of Pre-Compression Properties of Ketoconazole Floating Tablets

Material	Angle of repose(Degree)	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
Ketoconazole					
F1	30.31	0.582	0.732	27.33	0.721
F2	29.35	0.581	0.730	28.33	0.723
F3	27.82	0.576	0.728	27.30	0.720
F4	30.69	0.570	0.729	29.30	0.726
F5	28.30	0.580	0.735	30.30	0.730
F6	30.28	0.585	0.732	32.80	0.728
F7	28.46	0.582±	0.742	36.24	0.720
F8	29.49	0.579	0.792	29.72	0.720
F9	30.13	0.584	0.768	28.52	0.739
F10	30.05	0.581	0.759	27.45	0.725

Evaluation of tablets:

All the tablets were evaluated for following different parameters which includes;

Table 12: Results of Post Compression Properties of Ketoconazole Floating tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.53	4.8	300.19	0.58	98.33
F2	3.94	4.4	300.18	0.51	97.20
F3	3.96	4.5	300.33	0.38	99.60
F4	3.95	4.7	300.30	0.16	98.14
F5	3.93	5.2	300.13	0.31	97.21
F6	4.03	5.3	300.16	0.27	97.50
F7	4.05	4.8	300.18	0.29	98.34
F8	3.98	4.5	300.04	0.34	98.31
F9	3.69	4.9	300.02	0.32	97.83
F10	3.93	5.2	300.13	0.31	97.21

Table 13: Results of *in-vitro* buoyancy study of Ketoconazole floating tablets

Formulation Code	Floating lag times (sec)	Total Floating Time (hrs)
F1	55s	>8
F2	35s	>10
F3	30s	>12
F4	75s	>12
F5	60s	>12
F6	80s	>12
F7	110s	>10
F8	95s	>10
F9	106s	>12
F10	105s	>12

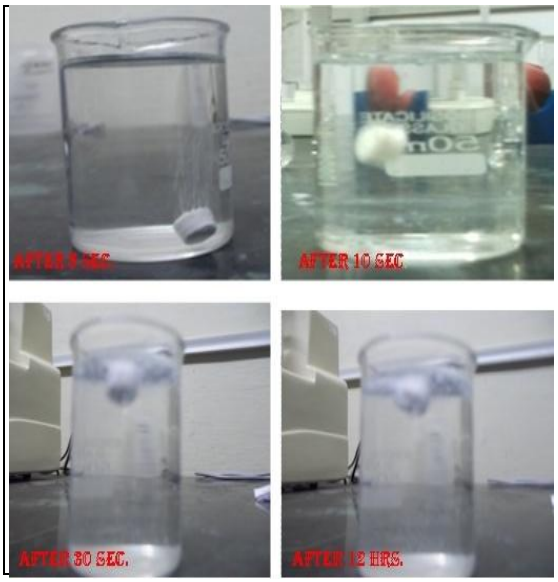

Figure 4: Photographs taken during *in-vitro* floating study of formula F8 in 200 ml 0.1 N HCl at different time intervals.

Dissolution rate studies

Table 14: *In-vitro* Drug Release Study of Ketoconazole Tablets

Time	% Cumulative Drug Release									
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26	07.28	07.45
2	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87	12.56	11.23
3	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28	18.58	38.23
4	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21	40.28	46.32
5	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24	56.98	67.02
6	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12	73.98	88.13
7	82.41	83.43	85.21	82.74	55.62	93.46	91.69	95.43	79.18	95.15
8	82.55	97.13	87.13	83	56	99.13	92	99.25	84.16	99.13
9	83	97.1	94.23	83.21	57.25	99.06	93	99.56	89.26	99.61
10	84.21	97.23	99.26	83.5	57.85	99.81	94.56	99.76	94.56	99.87

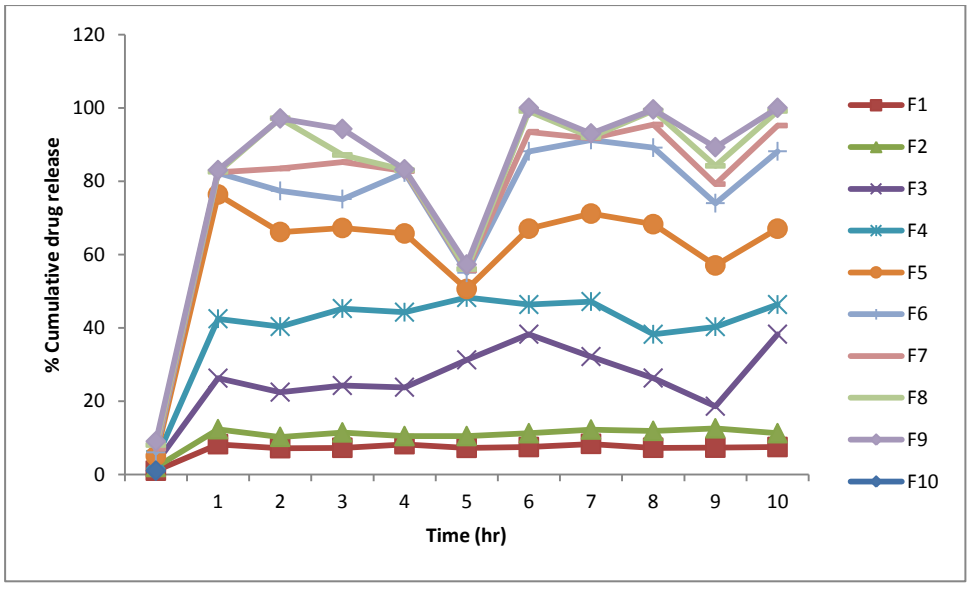

Figure 5: *In vitro* drug release study of Gastro retentive floating tablet

CONCLUSION

Gastro-retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches. This study discusses the preparation of floating tablets of Ketoconazole. HPC, Xantham gum and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. All these results indicated that a low amount of floating agent and high amount of hydrophilic polymer favoured the sustained release of Ketoconazole from gastro retentive tablet formulations. A lesser floating and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The in vitro drug release profiles obtained for tablets (F10) made with combinations of HPC, xathan gum showed a prolonged floating duration (> 12hrs) which was a controlled release characteristic for 12 h.

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