Preparation and evaluation of gastro retentive floating tablets of antifungal drug

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Abstract: Gastroretentive drug delivery system (GRDDS) is one of the novel approaches in the area of oral sustained release dosage forms. Gastro retentive dosage forms has traditional significant interest in the past few decades as they can improve the limitation of conventional and oral controlled release drug delivery system related to fast gastric emptying time. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half lives are eliminated quickly from the systemic circulation require frequent dosing to achieve suitable therapeutic activity. The development of oral sustain release floating solid dosage forms able to attempt release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in controlled manner so, that the drug could be supplied continuously to its absorption sited in the GIT.

Keywords: Gastro retentive drug delivery system, Floating tablet, Antifungal drug, Polysaccharide polymers, Itraconazole

Introduction: The drug delivery systems are used for maximizing therapeutic index and reduction in the side effects of the drug, oral route remains the preferred, promising and effective route for the administration of therapeutic agents. Because, low cost of therapy, ease of administration, flexibility in formulation and handling leads to higher level of patient compliance [1-2]. The novel design of an oral controlled drug delivery system during last two decades, it has limited success in case of drugs with a poor absorption

window throughout the GIT (Gastro Intestinal Tract). This approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [3-4]. Drug delivery system that float immediately upon contact with gastric fluids present promising approach for increasing the bioavailability of drugs with absorption window in the upper small intestine. Gastro retentive systems can stay in the gastric area for several hours, considerably extending the duration medications spend in the stomach. Prolonged stomach retention enhances bioavailability, minimizes drug waste, and improves solubility for medicines that are less soluble at high pH [5]. Gastro retentive systems (GRDDS) are intended to constrain and localize the drug delivery device in the stomach or upper sections of the small intestine until all of the medication is delivered, based on delayed gastric emptying and controlled principles. Flotation or buoyancy (floating systems), mucoadhesion (bioadhesive systems), sedimentation (high-density systems), swelling and expanding (swelling and expanding systems), and geometry are some of the methods (approaches) for establishing gastric retention (modified shaped systems) [6-7]. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [8]. Floating systems are the most often utilized approach for gastric retention among the methods listed above. Because floating systems are less thick than gastric fluid, they stay buoyant in the stomach for longer periods of time. The medicine is gently delivered at the desired pace while the system is floating over the stomach contents [9]. As a result, the gastro retention duration increases and the variability in plasma drug concentration decreases. Two unique technologies have been used in the creation of FDDS, based on the mechanism of buoyancy: A. Effervescent System, and B. Non-Effervescent System. Effervescent systems utilize gas-generating agents, carbonates (such as sodium bicarbonate), and other organic acids (such as citric acid and tartaric

acid) in the formulation to create carbon dioxide (CO2) gas, lowering the system density and allowing it to float atop the stomach fluid. Non-effervescent FDDS is based on the process of polymer swelling or bioadhesion to the mucosal layer of the GI tract. Gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene, and bioadhesive polymer such as chitosan and carbopol are the most often utilised excipients in non-effervescent FDDS [10]. Floating tablets are a sort of sustained release drug delivery device that floats on stomach fluids for a longer time by producing CO 2 gas or swelling and releasing the medicine for a longer duration. Various polymers, such as various grades of HPMC, Eudragit, chitosan, carbopol, guar gum, and xanthum gum 2, can be used to prolong drug release. Drugs that are easily absorbed from the stomach and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing [11-12]. The objective of the present investigation was to develop gastroretentive floating pulsatile formulation of itraconazole for treatment of fungal disease mainly at gastric part of GIT. The proposed formulations will be able to improve gastric residence time and increase bioavailability. A major problem in gastric delivery is the attainment of an optimal concentration at site of action with maximum bioavailability of drugs. The problem is associated with the conventional dosage form for peptic ulcer diseases is frequent dosing due to the low half life. The bioavailability of an instilled compound is generally low from 1.5 – 3.0 h and low solubility, with only a small fraction reaching the target site. In the present study an attempt was made to develop buoyant tablet of itraconazole with variation in polysaccharide polymeric combination with different ratios to increase floating behaviouir at gastric medium, which increase the gastric residence time, thus increase the bioavailability.

Material and Methods

Analysis for absorption maxima (λ_{max}): The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer. The calibration curve of drug samples was prepared in 0.1N HCl by accurately weighed 50 mg of drug sample was soluble in 50 ml of simulated gastric fluid containing 0.1 N HCl in 50 ml volumetric flask. The mixture was again with concentration of 2 µg / ml, 4 µg / ml, 6 µg / ml, upto 20 µg / ml respectively. The absorbance of each solution was measured separately at 245 nm for 0.1 N HCl.

Preparation of floating tablets: The tablets were prepared by direct compression method. Itraconazole, HPMC, dicalcium phosphate and citric acid were sieved through #30 sieves. $NaHCO_3$, Magnesium stearte and MCC were sieved through #60 sieves before the use. All the materials were accurately weighed and blended using hand blender and directly compressed on a manual single punch tablet compression machine into 100mg tablets using flat-faced, round punches 8 mm in diameter. 9 batches of the formulation were prepared using combination of HPMC, citric acd and $NaHCO_3$, with the ratio of drug to polymer (Table 1) [13].

Characterization: Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blend.

Flow properties: Flow properties depend on particle size, shape, porosity and density of the bulk powder. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\Theta = h/r$

Where h=height of pile, r = radius of the base of the pile, Θ=angle of repose.

Other characterization parameters were such as,

Weight variation: The average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches and allowed to rotate for 100 revolutions. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation by using Vernier caliper.

in-vitro buoyancy lag time: The Buoyancy lag time and total floating time were determined by immersion of tablets of different formulation in 0.1 N HCL at 37±.5°C [14].

Percent Drug content estimation: Crushed 10 tablets from all batches in pestle-mortar and weighed equivalent 150 mg as drug dose using for single tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 263nm.

in-vitro **dissolution study:** In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 245 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported [15].

in-vitro drug release kinetic study: The drug release and mechanism it follows to release can be determined by matching the data with various release models like Higuchi, Korsmeyer-Peppas, zero order and first order plots. The kinetics of drug release was studied in various kinetic models by plotting the data obtained from in vitro drug release study. The zero order kinetics was studied by plotting cumulative amount of drug released versus time. Whereas first order kinetics was studied by plotting log cumulative percentage of drug remain versus time. Higuchi's model of kinetics was studied by plotting cumulative percentage of drug released versus square root of time. The mechanism of drug release from the formulation was confirmed by fitting the in vitro drug release data with the Korsmeyer–Peppas model by plotting log cumulative percentages of drug release versus log time. The release exponent 'n' and 'k' values were calculated from the Y intercept and slope of a straight line respectively [16].

Result and Discussion

UV spectrophotometric study: The maximum absorption (λ-max) of drug sample itraconazole in 0.1 N HCl solutions were found to be at 245 nm. The calibration curves in 0.1 N HCl were prepared with drug solutions of known concentrations. The absorbance was measured and plotted against drug concentration. The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99.

Characterization of floating tablets: Floating tablets were prepared by the direct compression method, using HPMC as polymer with citric acid and sodium bicarbonate as floating agent. The effect of the nature of polymers was studied by preparing various formulations of floating tablets. In all these formulations, a constant amount of drug (100 mg) was maintained and it was initially characterized for flow properties and all other parameters. The different characterization as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio includes angle of repose (26.71), bulk density (0.274 g/cm^3), tapped density (0.273 g/cm^3), Carr's index (26.31 %) and Hausners ratio was found to be (1.58). The other characterization includes thickness, hardness, friability, weight variation, drug content, buoyancy lag time and in-vitro drug release. The thickness of all the tablets was in the range of 4.01 to 4.09 mm. The average weights of the entire prepared tablet were 240.17 mg to 240.71 mg which was within the specified limit. The hardness of all the formulated tablets was found to be in the range of 5.04 to 5.36 kg/cm^2. Friability was found to be 0.31 to 0.38 %. Citric acid and sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium resulted in immediate tablet floatation with a lag time in between 140 to 180 seconds. Total buoyancy time of all the prepared formulation was found between 1.12 h to 1.31 h. The swelling Index for all tablets was found in the range of 150.23 % to 159.55 %. The drug content of the entire prepared tablet was found to be 98.65 to 101.32 %. The mucoadhesive strength was found to be in the range of 20.17 to 31.02 gm. The results of the present research work indicated the successful formulation of buoyant bioadhesive tablet with excellent ex-vivo bioadhesive properties and drug release profile. From the in vitro drug release studies, it was found that in formulations F4 showed best sustained release profile. The retarded drug release was found to be in the following order: IFT4>IFT5>IFT7>IFT6>IFT3>IFT8>IFT2>IFT1>IFT9. Cumulative drug release of all the prepared formulation was found to be in between 95.5% to 99% in 12 h. Among the nine formulations (IFT1 to IFT9) prepared formulations F4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

Summary and Conclusion: In the present study an attempt was made to develop a floating tablet of itraconazole with variation in HPMC combination with different ratios to increase citric acid and Na2CO3 floating action materials at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability. A major problem in gastric delivery is the attainment of an optimal concentration at site of action with maximum bioavailability of drugs. The problem is associated with the conventional dosage form for peptic ulcer diseases is frequent dosing due to the low half life. The bioavailability of an instilled compound is generally low from 1.5 – 3.0 h and low solubility, with only a small fraction reaching the target site. The preliminary and screening studies were performed using different polymers and the polymers HPMC promised excellent properties for controlled release with adhesion on surface. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, in-vitro dissolution study. The formulation IFT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

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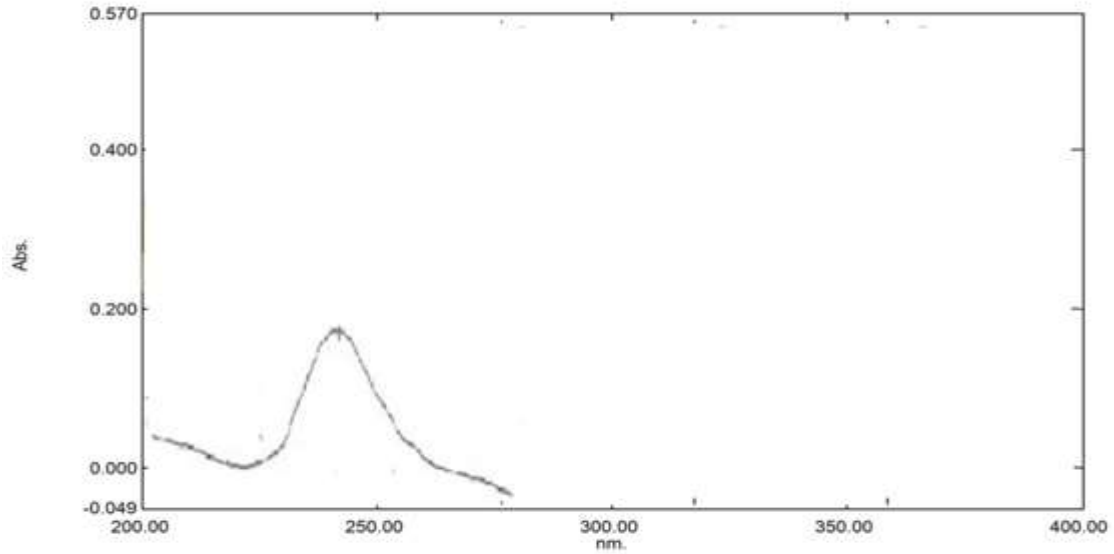

Figure 1: Maximum Absorption wavelength (λ-max) of drug in 0.1N HCl solution (10 µg/ml)

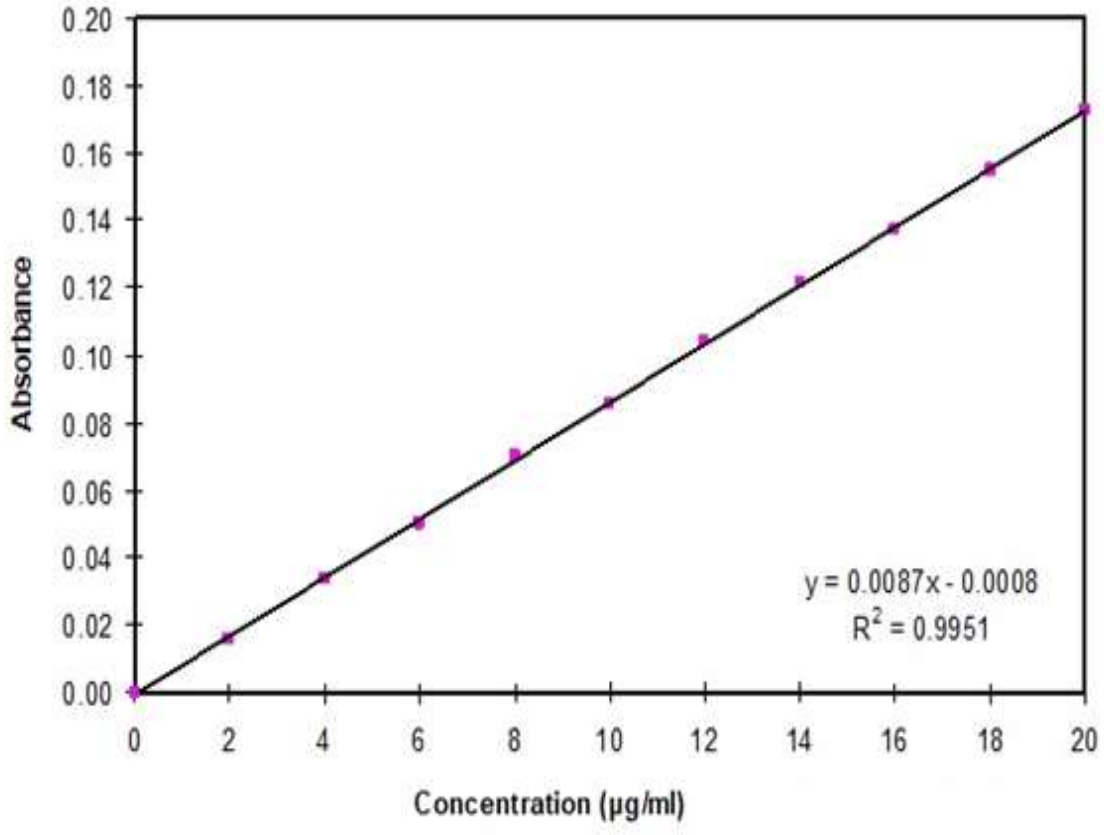

Figure 2: Standard curve of itraconazole in 0.1N HCl solution (245 nm)

Table 1: Various composition of floating tablets

F. Code	Drug (mg)	HPMC (mg)	Dicalcium phosphate (mg)	Citric acid	$NaHCO_3$ (mg)	Magnesium stearate (mg)	MCC (mg)
IFT1	100	55	120	10	5	5	15
IFT2	100	50	125	10	5	5	15
IFT3	100	45	135	10	5	5	15
IFT4	100	55	120	7.5	7.5	5	15
IFT5	100	50	125	7.5	7.5	5	15
IFT6	100	45	135	7.5	7.5	5	15
IFT7	100	55	120	5	10	5	15
IFT8	100	50	125	5	10	5	15
IFT9	100	45	135	5	10	5	15

Table 2: Flow properties of various floating tablets

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner Ratio	Angle of Repose
IFT1	0.252	0.233	19.32	1.10	26.71
IFT2	0.263	0.257	20.33	1.17	22.33
IFT3	0.285	0.271	23.21	1.12	26.12
IFT4	0.243	0.237	22.51	1.17	24.81
IFT5	0.262	0.265	22.24	1.21	21.25
IFT6	0.274	0.220	23.21	1.31	27.24
IFT7	0.291	0.273	26.31	1.58	22.22
IFT8	0.243	0.212	23.21	1.16	25.15
IFT9	0.231	0.222	23.30	1.16	26.14

Table 3: The various characterization of floating tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Total floating & bioadhesion time (h)	Percent Drug content
IFT1	241.21±.49	4.09±.01	5.51±.11	0.36±.13	1.19±0.2	99.52±0.26
IFT2	240.17±.01	4.01±.02	5.54±.12	0.31±.16	1.15±0.3	99.08±0.18
IFT3	241.12±.02	4.06±.01	5.31±.13	0.38±.11	1.25±0.7	99.29±0.98
IFT4	240.19±.04	4.04±.01	5.04±.18	0.32±19	1.13±0.1	99.15±0.15
IFT5	241.21±.01	4.03±.03	5.14±.11	0.34±.17	1.17±0.1	98.65±0.14
IFT6	240.15±.05	4.01±.02	5.36±.10	0.38±.16	1.19±0.2	99.91±0.32
IFT7	241.11±.01	4.06±.03	5.25±.44	0.35±.17	1.21±0.4	99.16±0.44
IFT8	241.73±.03	4.09±.03	5.11±.27	0.32±.13	1.12±0.2	99.14±0.08
IFT9	240.21±.06	4.06±.02	5.10±.21	0.34±.13	1.31±0.3	101.32±0.16

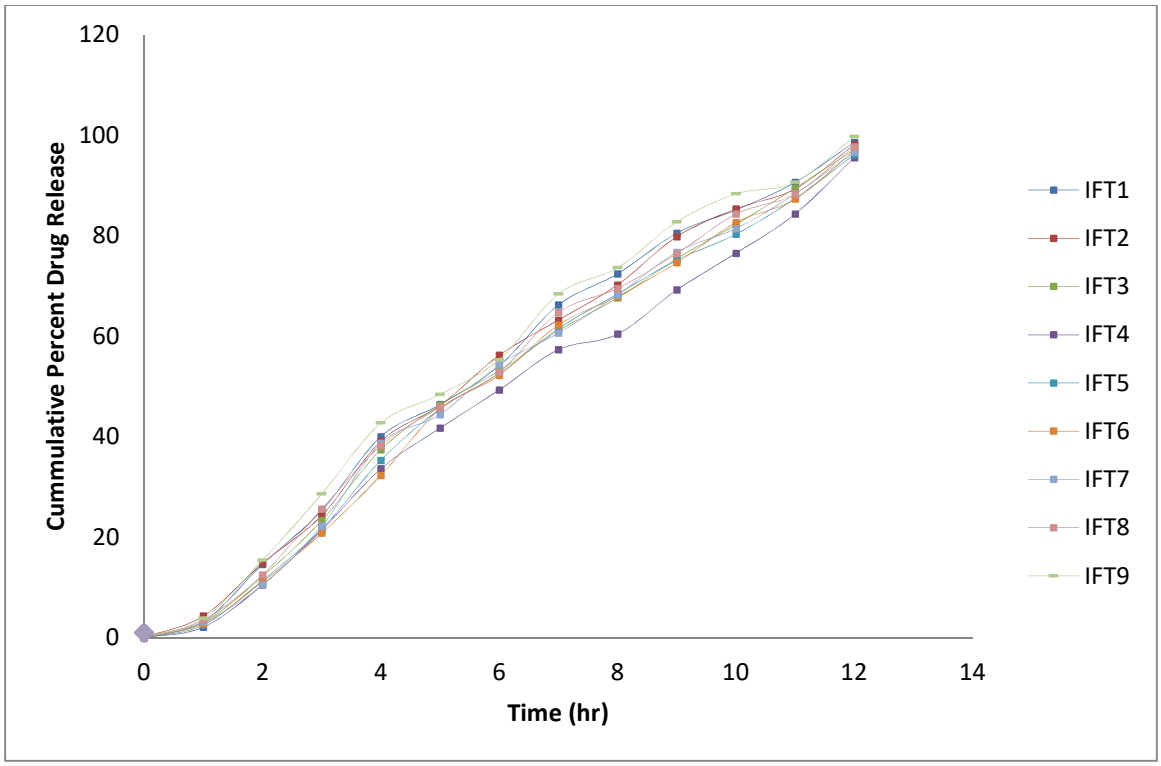

Figure 3: Zero-order kinetic plot of prepared floating tablets