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Development And Characterization Of Floating Drug Delivery System For Antiretroviral Drug: Ritonavir.

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ABSTRACT

This work is an attempt to increase the therapeutic efficacy, reduction of the frequency of dose, improvement of bioavailability and patient compliance by designing the controlled release Ritonavir floating drug delivery system & enhancement in gastric retention time (GRT). Wet granulation method was adopted to prepare controlled release floating tablets of Ritonavir by using different ratios of HPMC K4M, K15M, K100M along with using PVP K30, Magnesium state, talc, sodium bicarbonate, citric acid, lactose, xanthan gum, sodium alginate & Cross carmellous sodium. Post compression study was conducted for the prepared tablets, such as hardness, weight variation, thickness, diameter, drug content, lag time, buoyancy time & invitro dissolution studies. As per ICH guidelines stability studies was conducted. Hardness test indicated good mechanical resistance in all prepared formulations. Sodium bicarbonate was added as a gas generating agent, inducing generation of carbon dioxide in presence of 0.1N HCl as dissolution medium. The combination of sodium bicarbonate & citric acid produced desired floating ability; therefore, this combination was selected for the formulations. The results suggested that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism & invitro release data were also subjected to Higuchi's equation the r values of all the formulations were 0.9526 and above, indicated that the drug released was by Higuchi's mechanism. The formulations were also treated to Peppa's plots, found to be fairly linear and the regression values of all the formulations indicating a dissolution behavior controlled by Non Fickain Diffusion. From this study it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence improve the therapeutic effect of the drug by increasing its bioavailability.

Keywords: Ritonavir, HPMC, GRT, floating drug delivery system.

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INTRODUCTION

Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups [1]. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time. Dosage form with prolonged gastric residence time or gastro-retentive dosage form (GRDF) provides an important option. Under certain circumstances prolonging the gastro-retentive of a delivery system is desirable for achieving greater therapeutic benefits of the drug substance. Drugs which are absorbed in the proximal part of GI tract and drugs that are less soluble may benefit from prolonged gastric retention. Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability.

Oral ingestion is the most convenient and commonly used method of drug delivery [2]. Oral route has some drawbacks also, short residence time in GIT, gastric empting & degradation of the drug, which makes drug delivery system uncertain. Formulating FDDS will increase gastric retention time of drug delivery system. After release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of the fluctuations in plasma drug concentration [3, 4].

Advantage of FDDS [5-8]

- Controlled delivery of drugs.
- Improve drug absorption, because of increased gastro retentive and more time spent by the dosage form at its absorption site.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux
- Ease of administration and better patient compliance.
- Site-specific drug delivery.

Limitations of FDDS [9-12]

- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- High variability in gastric emptying time due to its all or non-emptying process.
- Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore, patients should not be dosed with floating forms just before going to bed.

Drugs that are required to be formulated into gastro retentive dosage forms include [13]

- Drugs acting locally in the stomach.
- Drugs that are primarily absorbed in the stomach.
- Drugs those are poorly soluble at alkaline pH.
- Drugs with a narrow window of absorption.
- Drugs rapidly absorbed from the GI tract and
- Drugs that degrade in the colon.

In the design and development of Hydrodynamically Balanced Systems (HBS), anatomical and physiological factors of the stomach play an important role.

Anatomy Of Stomach

The stomach is divided into three anatomical regions: fundus, body and pylorus or antrum (Figure-1). The proximal stomach consists of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying [14]. The fundus adjusts to increased volume during eating

by relaxation of fundal muscle fibres. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach. To pass through the pyloric wall into the small intestine, particles should be of the order of 1-2mm.

Physiology Of Stomach

Factors such as pH, nature and volume of gastric secretions, and gastric mucosa play an important role in drug release and absorption.

pH: Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2, and in fed condition usually it is 2 to 6 [15].

Volume: The resting volume of the stomach is about 25-50 ml [16]. Gastric volume is important for dissolution of dosage forms in vivo.

Gastric Mucosa: Simple columnar epithelial cells line the entire mucosal surface of the stomach [14]. Mucous, parietal and peptic cells are present in the body of stomach. These cells are associated with different functions. The parietal cells secrete acid whereas the peptic cells secrete precursor for pepsin. The surface mucosal cells secrete mucus and bicarbonate. They protect the stomach from digestion by pepsin and from adverse effects of hydrochloric acid. As mucus has a lubricating effect, it allows chyme to move freely through the digestive system.

Gastric Secretion: Acid, pepsin, gastrin, mucus and some other enzymes are the secretions of the stomach [14]. Normal adults produce a basal secretion up to 16 ml with approximately 4 mmol of hydrogen ions every hour. The volume of this secretion can go beyond 200 ml and 15 to 50 mmol of hydrogen ions when stimulated. Pure parietal secretions is a mixture of hydrochloric acid and potassium chloride. Histamine stimulates acid secretions through the H_2 receptors located on gastric mucosa. Another potent stimulator of gastric acid is the hormone gastrin. Peptides, amino acids, and distention of stomach stimulate its release. The absorption of vitamin B_{12} from the ileum requires the intrinsic factor, which is continuously secreted by the stomach. The mean thickness of mucus in human stomach is 140 μm. It is continuously digested from surface. Generally, it takes 4 to 5 hours for mucus turnover. It protects the gastric mucosa from pepsin and acid in the stomach.

Factors Affecting Gastric Retention

Gastric retention time (GRT) is affected by several factors which include [16, 17]

- Size and shape of the dosage form
- Density
- Concaminant intake of food and drugs
- Biological factors like age, gender, posture, body weight and disease states.

MATERIALS AND METHODS

Ritonavir was obtained as a gift sample from Hetero drugs limited (unit-IX) Vishakhapatnam A.P and other chemicals & reagents were of SD fine chemicals provided by college.

Method Of Preparation

Preparation of Floating tablets of Ritonavir [18, 19]

According to the present invention, the FDDS includes a swelling agent PVP, gas generating component generated by sodium bicarbonate, swelling controlled by xanthan gum, which acts both as swellability and a release controlling agent. The gas generating component sodium bicarbonate interacts with an acid source citric acid by contact with gastric fluid to generate carbon dioxide that gets entrapped within the hydrated gel matrix of the swelling composition. HPMC is used for rate of release of the drug from the tablets. Sodium bicarbonate ($NaHCO_3$) was incorporated in the formulation in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form. Lactose was included in formulation as

hydrophilic agent, showed appropriate release and floating time. Magnesium stearate and talc as lubricant and glidant, all the formulations shown in table 1.

RESULTS AND DISCUSSION

Pre-Compressional Parameters

The characteristics of granules are most important to formulation therefore most universally measured. These basic measurements of the granulations have been utilized to develop the manufacture of many successful pharmaceutical dosage forms. Table 2 shows the powder blend properties of Ritonavir floating tablets.

Bulk density depends on particle size, shape and tendency of particles to adhere together, may influence compressibility, porosity, dissolution and other properties.

The bulk density and tapped density of powder blend was found between 0.588 ± 0.02 to 0.790 ± 0.05 gm/cm3 and 0.665 ± 0.05 to 0.931 ± 0.03 gm/cm^3, which indicates good packing capacity of powder blend. For inter particulate cohesive property, Carr's index was evaluated with angle of repose measurements and studied for the effects of geometry of packing solids with bulk and tapped density. Values of Carr's index below 15% usually show good flow characteristics and above 25% indicate poor flow ability. Carr's index was found to be between 13.73 ± 0.02 to 29.30 ± 0.10. Hausner's ratio method used to evaluate stability of powder column and to estimate the flow properties, it was found between 1.09 ± 0.05 to 1.31 ± 0.02. Low range observed of Hausner's ratio which indicates good flow ability. The angle of repose of all the formulations were found to be within the range of 23.90 ± 0.14 to 31.43 ± 0.17 which showed that, granules were of good flow properties.

Evaluation Of Post-Compressional Parameters Of Tablet Characteristics

Ritonavir floating tablets were prepared by direct compression method and were evaluated for average weight, thickness, hardness, friability and drug content.

Tablet Thickness, Diameter And Hardness

All the formulations were evaluated for various parameters like thickness; diameter and hardness. All the prepared tablets formulations F1 to F12 shown in Table 3, it was found that there was no much variation in thickness of tablets. Thickness and diameter of tablets of all formulations were measured by vernier calliper and there will be no any change in thickness and diameter of tablets respectively. Thickness was in range of 4.1 ± 0.03 to 4.4 ± 0.08. The hardness of tablets was measured by Pfizer hardness tester. The hardness was in range of 7.1 to 8.8 Kg/cm^2.

Weight Variation

The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation. The results are showed in table 3.

Friability Of Tablet

The present study of tablets is within the limit and the slight variation in seen in friability because of the variation in compression force applied and its total weight. The friability of tablets also depends on type of filler and moisture contents present in it. The friability was found to be in the range of 0.23 ± 0.014 to 0.69 ± 0.021 shown in Table 3.

Drug Content And Swelling Index (Water Up Take) Study

The drug content and swelling index (water up take) studies were carried out for all the prepared formulations, the results are shown in Table 4.

Drug Content

Drug content was in range of 97.66 ± 0.20 to 99.58 ± 0.32, which reflects good drug content uniformity in all the prepared formulations. The reading complies as per I P. which indicates drug was uniformly distributed throughout the tablet compressed.

Swelling Index (Water Uptake Study)

Swelling of tablet is also a vital & important factor to ensure floating. To obtain floating balance between swelling and water acceptance must be restored [20]. Tablets composed of polymeric matrices, when they come in contact with water, build a layer of gel around the tablets core. This gel layer governs the release of drug. Swelling is important because the gel barrier is formed by water permeation.

Swelling index results study showed that, the order of swelling in these polymers indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 24 hrs and then gradually decreased due to erosion. The swelling of polymers used in these tablets (HPMC K4M, crosscarmellose sodium, sodium alginate) could be determined by water uptake of the tablets. The complete swelling was achieved by the end of 24 hrs. The % of swelling of F5 and F12 were higher due to increase in the concentration. The swelling index was in range 52.60 ± 0.55 to 71.20 ± 0.56. F6 formulation has higher swelling index. The reason for higher swelling index values are due channelling agent, allows more permeation of water into the gel layer and it enhances the water retention property also. This could be the reason for more moisture uptake by formulations of F6, F7 and F11 values are given in Table 4.

***In-vitro* Buoyancy And Lag Time Study**

The floating lag time (Figure-2) for all the formulations were found to be less than 90 minutes, the floating time duration (Figure-2) was found to be up to 24 hrs in all formulations.

The tablet floated with less lag time due to high concentration of gas generating agent. It was observed that paddle speed affected the floating properties of tablet. However, some results revealed that, as the concentration HPMC K4M increased, total floating time increased, this is because of increased gel strength of matrices, which prevents escape of evolved carbon dioxide from matrices ,leading to decreased density of the formulations. The outermost hydrophilic polymer hydrates and swells and a gel barrier were formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results concluded that linear relationship exists between swelling process and viscosity of polymer. So the presence of optimum amount of HPMC K4, $NaHCO_3$, and citric acid is important in achieving good floating time and minimum floating lag time. Incorporation of sodium bicarbonate helps to produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float. As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and at the same time floating lags time decreases. The results are in Table 5.

***In-vitro* Dissolution Study**

Study was conducted for 24 hours by using 0.1N HCl as dissolution medium, all the formulations showed good drug release rate, whereas formulation F3 showed 98.11±0.32% drug release at 10 hours. Results are in table 6 & 7 and release data in figure 3 & 4. Depending upon the release data F3 formulation was considered as promising formulations among all.

Stability Studies

The most promised formulations were selected stability studies. Three month stability studies were performed as per ICH guidelines at a temperature of $45^0 \pm 1^0$ C over a period of three month on the promising Floating tablet formulation F3. Sufficient number of tablets (10) were packed in aluminium packing and kept in stability chamber maintained at $45^0 \pm 1^0$ C / 75 ± 5 % RH for 3 months. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test

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and *in-vitro* floating studies were performed to determine the drug release profiles, the estimation of drug contents and data of dissolution and *in-vitro* floating studies are shown in table 8 and *in-vitro* release data of the stability in Figure-5.

Table 1: Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ritonavir	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
HPMC K4m	-	-	-	-	-	-	-	-	50 mg	50 mg	100 mg	100 mg
HPMC K100m	200 mg	150 mg	100 mg	50 mg	-	-	-	-	-	-	-	-
PVP K30	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Mg Stearate	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Talc	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Sod Bicarbonate	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Citric acid	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Lactose	10 mg	60 mg	110 mg	160 mg	85 mg	135 mg	185 mg	235 mg	120 mg	70 mg	70 mg	20 mg
Xanthan gum	-	-	-	-	200 mg	150 mg	100 mg	50 mg	50 mg	100 mg	50 mg	100 mg
Sod Alginate	-	-	-	-	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg
Cross carmellous sod (2%)	-	-	-	-	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg
Total weight	**650 mg**	**650 mg**	**650 mg**	**650 mg**	**765 mg**	**765 mg**	**765 mg**	**765 mg**	**700 mg**	**700 mg**	**700 mg**	**700 mg**

Table 2: Pre-compressional parameters of all the Formulations

Formulations	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index	Hausner Ratio	Angle of repose (θ)
F1	0.649 ± 0.05	0.790 ± 0.04	29.30 ± 0.10	1.22 ± 0.02	25.12 ± 0.17
F2	0.754 ± 0.06	0.877 ± 0.02	22.13 ± 0.05	1.31 ± 0.02	30.12 ± 0.15
F3	0.588 ± 0.02	0.931 ± 0.03	22.38 ± 0.07	1.21 ± 0.04	26.33 ± 0.11
F4	0.678 ± 0.04	0.665 ± 0.05	23.31 ± 0.09	1.18 ± 0.02	24.90 ± 0.11
F5	0.710 ± 0.09	0.901 ± 0.08	13.73 ± 0.02	1.22 ± 0.02	25.37 ± 0.17
F6	0.670 ± 0.02	0.699 ± 0.01	25.90 ± 0.03	1.13 ± 0.04	30.11 ± 0.13
F7	0.759 ± 0.02	0.721 ± 0.03	20.17 ± 0.13	1.28 ± 0.09	31.43 ± 0.17
F8	0.712 ± 0.04	0.834 ± 0.05	23.70 ± 0.11	1.22 ± 0.11	29.56 ± 0.15
F9	0.790 ± 0.05	0.642 ± 0.05	21.44 ± 0.10	1.18 ± 0.01	30.44 ± 0.10
F10	0.701 ± 0.08	0.686 ± 0.01	14.99 ± 0.09	1.09 ± 0.05	23.90 ± 0.14
F11	0.699 ± 0.09	0.834 ± 0.04	16.18 ± 0.13	1.24 ± 0.03	29.37 ± 0.13
F12	0.700 ± 0.03	0.742 ± 0.04	24.55 ± 0.11	1.23 ± 0.06	25.35 ± 0.11

*The values represent mean ± S.D; n=3,

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Table 3: Post-Compressional properties of Ritonavir tablets

Formulations	Average weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)
F1	643 ± 0.03	4.4± 0.08	11.8 ± 0.02	7.6 ± 0.06	0.41 ± 0.038
F2	652 ± 0.03	4.1 ± 0.03	11.9 ± 0.03	7.1 ± 0.07	0.69 ± 0.021
F3	646 ± 0.03	4.2 ± 0.01	11.7 ± 0.07	7.3 ± 0.07	0.29 ± 0.087
F4	648 ± 0.03	4.2 ± 0.02	12.9 ± 0.01	8.7 ± 0.03	0.24 ± 0.056
F5	770 ± 0.03	4.4 ± 0.02	12.8 ± 0.04	8.8 ± 0.02	0.29 ± 0.023
F6	768 ± 0.06	4.4 ± 0.03	12.6 ± 0.02	8.1 ± 0.08	0.27 ± 0.067
F7	764 ± 0.03	4.3 ± 0.06	12.4 ± 0.03	8.3 ± 0.05	0.76 ± 0.087
F8	746 ± 0.03	4.3 ± 0.04	12.7 ± 0.09	8.5 ± 0.03	0.23 ± 0.014
F9	701 ± 0.03	4.3 ± 0.02	12.3 ± 0.08	7.5 ± 0.01	0.25 ± 0.086
F10	698 ± 0.02	4.1 ± 0.03	12.7 ± 0.03	7.9 ± 0.06	0.38 ± 0.021
F11	699 ± 0.03	4.2 ± 0.04	12.9 ± 0.04	7.8 ± 0.07	0.27 ± 0.044
F12	695 ± 0.03	4.2 ± 0.02	12.5 ± 0.06	8.2 ± 0.03	0.38±0.051

Table 4: Physico-chemical properties of Ritonavir tablets

Formulations	Drug content (%)	Swelling index
F1	98.89 ± 0.19	61.00 ± 0.36
F2	98.87 ± 0.21	58.35 ± 0.12
F3	99.25 ±0.12	52.60 ± 0.55
F4	97.66 ± 0.20	65.40 ± 0.65
F5	98.51 ± 0.22	69.01 ± 0.34
F6	97.79 ± 0.11	71.20 ± 0.56
F7	99.50 ± 0.15	70.80 ± 0.41
F8	97.50 ± 0.24	68.50 ± 0.50
F9	98.45 ± 0.27	69.38±0.47
F10	97.90 ± 0.08	68.80 ± 0.22
F11	99.33 ±0.20	69.99 ± 0.56
F12	99.58 ±0.32	68.50 ± 0.12

Table 5: Floating ability of various Ritonavir tablets

Formulation codes	Floating lag time (sec/min /hrs)	Floating time (hrs)
F1	125 min	24
F2	60 min	24
F3	82 min	24
F4	75 min	24
F5	45 min	24
F6	50 min	24
F7	55 min	24
F8	85 min	24
F9	70 min	24
F10	60 min	24
F11	85 min	24
F12	90 min	24

*The values represent mean ± S.D; n=3

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Table 6: *In-vitro* Release Study of FDDS of Ritonavir Tablets: F1 to F6

Timings	F1	F2	F3	F4	F5	F6
30min	12.12±0.12	11.20±0.77	12.89±0.34	13.67±0.15	10.22 ± 0.87	12.45 ± 0.21
1 hr	18.97±0.78	25.15±0.85	28.86±0.85	28.44±0.55	14.34 ± 0.23	16.01 ± 0.88
2 hr	23.56±0.76	32.56±0.46	46.31±0.44	39.00±0.90	16.89 ± 0.67	18.12 ± 0.10
3 hr	32.34±0.55	43.78±0.23	52.41±0.27	48.90±0.72	18.99 ± 0.49	20.01 ± 0.32
4 hr	41.12±0.50	48.77±0.55	61.13±0.36	59.11±0.10	22.76 ± 0.54	26.00 ± 0.43
5 hr	46.21±0.80	63.45±0.61	66.76±0.22	66.46±0.13	25.90 ± 0.51	29.78 ± 0.44
6 hr	49.20±0.21	71.37±0.50	70.44±0.10	71.77±0.43	29.00 ± 0.10	33.34 ± 0.65
7 hr	53.56±0.34	75.65±0.83	77.33±0.23	78.90±0.11	32.87 ± 0.89	35.61 ± 0.67
8 hr	57.41±0.87	79.67±0.47	88.61±0.99	87.32±0.29	39.46 ± 0.12	41.28 ± 0.12
9 hr	61.22±0.58	83.40±0.69	97.22±0.45	95.10±0.35	44.78 ± 0.67	45.55 ± 0.78
10 hr	66.54±0.33	88.85±0.15	98.11±0.32	97.90±0.82	48.92 ± 0.90	49.90 ± 0.98
11 hr	74.01±0.10	91.25±0.33	-	-	53.11 ± 0.13	54.89 ± 0.23
12 hr	76.90±0.55	94.02±0.20	-	-	58.23 ± 0.67	58.00 ± 0.19
13 hr	80.88±0.81	95.62±0.83	-	-	66.50 ± 0.78	62.90 ± 0.16
14 hr	84.76±0.90	97.55±0.10	-	-	71.89 ± 0.98	67.88 ± 0.21
15 hr	89.77±0.91	-	-	-	78.10 ± 0.10	73.45 ± 0.43
16 hr	91.20±0.41	-	-	-	83.27 ± 0.54	80.21 ± 0.81
17 hr	93.44±0.87	-	-	-	88.70 ± 0.20	88.63 ± 0.32
18 hr	-	-	-	-	96.35 ± 0.45	93.66 ± 0.91
19 hr			-	-	97.58 ± 0.10	-

*Average of three determinations

Table 7: *In-vitro* Release Study of FDDS of Ritonavir Tablets: F7 to F12

Timings	F7	F8	F9	F10	F11	F12
30min	14.22 ± 0.63	14.68 ± 0.77	4.14 ± 0.24	10.89 ±0.57	9.13 ±0.68	11.43 ±0.44
1 hr	18.44 ± 0.23	19.68 ± 0.25	9.23 ± 0.88	24.14±0.45	27.00±1.33	25.30±0.94
2 hr	19.98 ± 0.83	21.17 ± 0.34	16.89 ± 0.77	32.37±0.33	32.83±1.30	34.56±0.26
3 hr	20.78 ± 0.30	26.82 ± 0.50	27.67 ± 0.43	46.58±0.31	40.95±0.80	41.93±0.80
4 hr	25.80 ± 0.41	32.90 ± 0.63	34.62 ± 0.90	48.06±0.85	46.03±0.68	44.31±0.83
5 hr	28.33 ± 0.44	35.57 ± 0.41	44.14 ± 0.38	57.49±0.49	51.48±0.71	47.29±0.58
6 hr	34.12 ± 0.78	38.90 ± 0.65	49.35 ± 0.12	60.21±0.53	60.67±0.42	53.66±0.44
7 hr	36.89 ± 0.43	43.59 ± 0.76	53.31 ± 0.28	64.45±0.82	66.94±0.71	57.49±0.32
8 hr	43.33 ± 0.51	49.00 ± 0.49	57.17 ± 0.21	67.37±0.73	75.40±0.67	62.46±0.83
9 hr	47.67 ± 0.77	54.16 ± 0.38	63.78 ± 0.67	75.83±0.45	78.65±0.80	65.43±0.57
10 hr	52.54 ± 0.17	58.20 ± 0.59	68.22 ± 0.98	79.40±0.78	81.49±0.66	70.76±0.34
11 hr	57.32 ± 0.53	62.79 ± 0.90	73.66 ± 0.26	85.20±0.35	88.36±0.65	75.39±0.69
12 hr	64.91 ± 0.55	68.90 ± 0.14	77.97 ± 0.24	88.93±0.22	91.41±0.96	79.42±0.78
13 hr	69.72 ± 0.65	73.39 ± 0.90	81.00 ± 0.28	92.30±0.65	93.10±0.13	81.89±0.65
14 hr	74.83 ± 0.54	77.79 ± 0.10	85.35 ± 0.24	94.15±0.95	94.21±0.63	84.66±0.34
15 hr	79.11 ± 0.51	82.40 ± 0.30	88.69 ± 0.79	-	95.87±0.55	87.30±0.63
16 hr	87.36 ± 0.23	85.91 ± 0.62	91.29 ± 0.32	-	97.06±0.51	89.78±0.93
17 hr	92.11 ± 0.45	91.88 ± 0.55	93.68 ± 0.33	-	-	91.11±0.92
18 hr	-	-	95.01 ± 0.25	-	-	93.30±0.61
19 hr	-	-	97.34 ± 0.17	-	-	-
20 hr	-	-	98.67 ± 0.19	-	-	-
21 hr	-	-	99.00 ± 0.66	-		
22 hr	-	-	99.70 ± 0.62	-		

*Average of three determinations

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Table 8: Stability studies of Formulation F3

Sl. No.	Time in days	Physical changes	Mean ± SD (45±1°C)
1.	01	--	98.26±0.91
2.	30	No Change	100.30±1.22
3.	60	No Change	97.58±1.04
4.	90	No Change	99.13±0.82

Figure 1: Anatomy of stomach

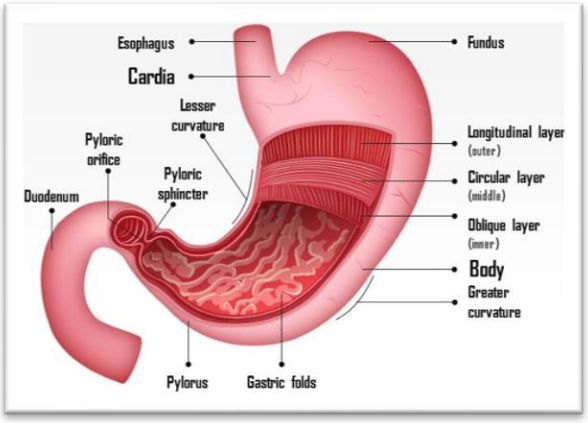

Figure 2: *In-vitro* Buoyancy Study

Side view **Top view**

Figure 3: *Invitro* Release study of FDDS of Ritonavir tablets: F1 to F6.

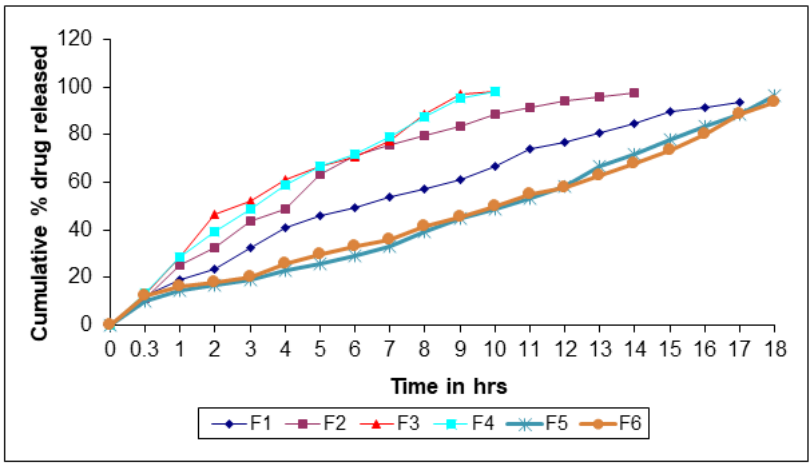

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Figure 4: *Invitro* Release study of FDDS of Ritonavir tablets: F7 to F12

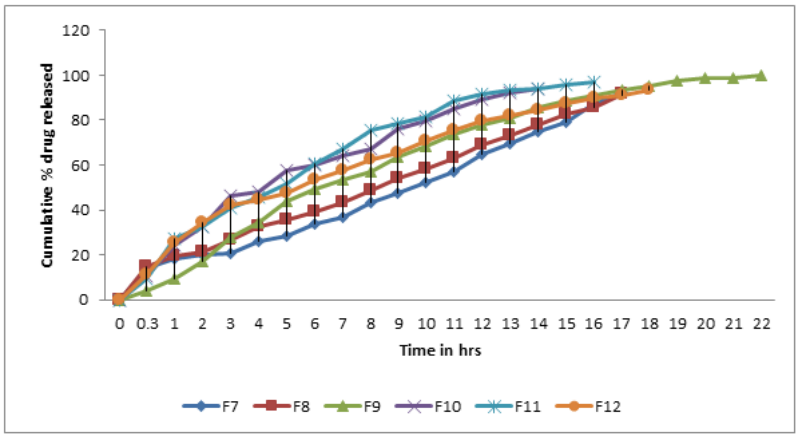
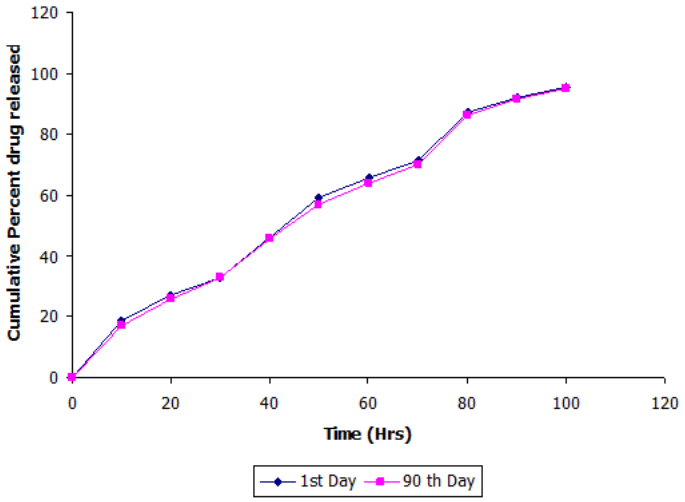


Figure 5: In Vitro release data of the stability formulation F3



CONCLUSIONS

From the present study, the following conclusions can be drawn

- From study it is evident that, floating tablets of Ritonavir can be developed to increase gastric residence time and thereby increasing its bioavailability. Further detailed investigations are required to establish efficacy of these formulations and fix the required dose
- All the prepared tablet formulations were found to be good without capping and chipping.
- Formulated FDDS tablets gave satisfactory results for various post-compressional parameters like hardness, friability, thickness, weight variation and content uniformity.
- As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent (NaHCO3) increases the drugs releases increases and at the same time floating lag time decreases.
- $NaHCO_3$ has predominant effect on the buoyancy lag time, while HPMC K4M, has predominant effect on total floating time and drug release.
- Swelling index has a significant effect on the drug release.
- Sodium alginate and Xanthan gum has given extra adhesion property and helped to maintain the integrity of the tablet.
- Short term stability studies of formulation F3 Indicates there are no significant changes in the drug content and dissolution parameter value at stable at 45^0C and 75% RH for a period of 3 Months.

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