



Research Article

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Formulation and Pharmacokinetic Evaluation of Ritonavir Floating Tablets in the Management of AIDS

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ABSTRACT

In the current study, gastro-retentive tablets of Ritonavir was developed to increase its oral bioavailability using hydrophilic polymers HPMC K 4M, K 15M, and K 100M as release retarding agents. Polyox WSR 303 was chosen as resin, sodium bicarbonate was used as effervescent agents. The tablets were prepared by direct compression method and FTIR studies revealed that there is no interaction between the drug and polymers used for the formulation. Among all the formulations F21 containing HPMC K 100M, Crospovidone, Polyox WSR 303 and sodium bicarbonate, as gas generating agent was chosen as optimized formulation based on the evaluation parameters, floating lag time (33 sec) and total floating time (>24 h) and *in vitro* dissolution studies. From *in vitro* dissolution studies, the optimized formulation F21 and marketed product was shown 98.67% and 95.09 ± 5.01% of drug release respectively. From *in vivo* bioavailability studies, after oral administration of floating tablet containing 100 mg Ritonavir, the C_{max} , T_{max} , and $AUC_{0-\infty}$ of optimized gastroretentive formulation were found to be 30.11 ± 1.16 µg/mL, 8.00 ± 1.23 h and 173 ± 26.34 µg·h/mL, respectively. C_{max} and AUC values of optimized formulation were found to be significantly higher than of marketed product, where longer gastric residence time is an important condition for prolonged or controlled drug release and also for improved bioavailability.

Keywords: Ritonavir AIDS, Floating tablets, Polyox, *In vivo* bioavailability studies.

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INTRODUCTION

Oral route is the most common route of administering the drug owing to the ease of formulation, low cost, convenient for the patient and simple regulatory process. requirement, formulations can be changed from immediate release to

extended release by using several polymers. [1] A GRDDS can be a useful tool in delivery of drugs that are primarily absorbed in the duodenum and upper jejunum or those that have an absorption window in the gastrointestinal tract. [2] Gastro-retentive floating dosage forms are continuously researched and

developed as the stomach is a major absorption zone. The gastric emptying time which varies from 2- 3 hours is a disadvantage for gastro-retentive dosage forms. Based on the formulation type and physiological condition of the patient, the gastric emptying process can vary from a few minutes to 12 hours also. This variation may lead to unpredictable bioavailability and times to achieve peak plasma levels. [3] In addition, the relatively brief gastric emptying time in humans, through the stomach or upper part of the intestine (major absorption zone), can result in incomplete drug release from the drug delivery system, leading to reduced overall efficacy of the drug. Some drugs like Ritonavir exhibit region-specific absorption in different regions of the intestine because of different pH conditions, various enzymes and endogenous components like bile. [4]

There are various approaches to target a specific site in a sustained/controlled release fashion. [5] Some of the common approaches used to increase the gastric residence time of pharmaceutical dosage forms include Floating systems, Swelling and expanding systems, Bioadhesive systems, Unfolding and modified- shape systems, High density systems etc. 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. [6] Whilst the system remains afloat, the drug is released at a desired rate from the system. [7] Following drug release, the residual system gets emptied from the stomach. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal. [8] The present study was aimed on the development of Ritonavir matrix floating tablet by achieving the sustained drug release and determining the pharmacokinetic parameters with *in vivo* bioavailability studies.

MATERIALS AND METHODS

Materials

Ritonavir was procured from MSN Labs Ltd. Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M, and Polyox WSR 303 were obtained from Granules India Ltd, Hyderabad. Sodium bicarbonate, citric acid, PVP K 30, talc and magnesium stearate were procured from SD Fine Ltd, Mumbai and all other chemicals used were of analytical grade.

Methods

Formulation Method

Accurately weighed quantities of polymers were taken in a mortar and mixed geometrically, to this required quantity of Ritonavir was added and mixed slightly with pestle. [9] Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar and

powdered with pestle. The powder is passed through sieve no. 40 and mixed with the drug blend which is also passed through sieve no. 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. [10] To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. [11] The mixture equivalent to 300 mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm² (Table 1, 2 & 3).

Table 1: Composition of floating matrix tablets of Ritonavir with HPMC K4M

Ingredients (Weight in mg)	Formulations						
	F1	F2	F3	F4	F5	F6	F7
Ritonavir	100	100	100	100	100	100	100
HPMC K4M	50	55	60	65	70	75	80
Crospovidone	50	50	50	50	40	25	20
Polyox WSR 303	20	25	30	35	40	45	50
Sodium Bicarbonate	20	22	24	26	28	30	32
Citric acid	10	10	10	10	10	10	10
PVP K-30	46	34	22	10	8	11	4
Talc	2	2	2	2	2	2	2
Mag. Stearate	2	2	2	2	2	2	2
Total Weight	300	300	300	300	300	300	300

Table 2: Composition of floating matrix tablets of Ritonavir with HPMC K15M

Ingredients (Weight in mg)	Formulations						
	F8	F9	F10	F11	F12	F13	F14
Ritonavir	100	100	100	100	100	100	100
HPMC K15M	50	55	60	65	70	75	80
Crospovidone	50	50	50	50	40	25	20
Polyox WSR 303	20	25	30	35	40	45	50
Sodium Bicarbonate	20	22	24	26	28	30	32
Citric acid	10	10	10	10	10	10	10
PVP K-30	46	34	22	10	8	11	4
Talc	2	2	2	2	2	2	2
Mag. Stearate	2	2	2	2	2	2	2
Total Weight	300	300	300	300	300	300	300

Table 3: Composition of floating matrix tablets of Ritonavir with HPMC K100M

Ingredients (Weight in mg)	Formulations						
	F15	F16	F17	F18	F19	F20	F21
Ritonavir	100	100	100	100	100	100	100
HPMC K100M	50	55	60	65	70	75	80
Crospovidone	50	50	50	50	40	25	20
Polyox WSR 303	20	25	30	35	40	45	50
Sodium Bicarbonate	20	22	24	26	28	30	32
Citric acid	10	10	10	10	10	10	10
PVP K-30	46	34	22	10	8	11	4
Talc	2	2	2	2	2	2	2
Mag. Stearate	2	2	2	2	2	2	2
Total Weight	300	300	300	300	300	300	300

Evaluation of Floating Matrix Tablets of Ritonavir

Parameters like Weight Variation, Thickness, Hardness and Friability were evaluated according to the reported method. [12]

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was

determined as floating lag time.^[13] The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time.

Drug content

Twenty tablets were taken, powdered. The powder equivalent to one dose each was transferred to a 100 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 238 nm.^[14]

In vitro drug release studies

The *in vitro* drug release study was performed for the single & multiple-unit tablets using USP Type II dissolution apparatus using 900 ml of 0.1N HCl at a temperature of $37 \pm 0.5^\circ\text{C}$ at 50 rpm. 5 ml of sample was collected at 0, 2, 4, 6, 8, 12, 16, 20, 24 hours and the same volume of fresh media was replenished. The drug content in the samples was estimated using UV visible spectrophotometer at 238 nm.^[15]

Stability studies

Stability testing was conducted at $40 \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ for 3 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60 and 90 days period according to ICH guidelines.^[16] Various *in vitro* parameters like % yield, entrapment efficiency and *in vitro* release studies were evaluated.

In vivo bioavailability studies Ritonavir

Animal Preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C , RH 45% and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water *ad libitum*. The protocol of animal study was approved by the institutional animal ethics committee with No: CPCSEA/1657/IAEC/CMRCP/PhD-15/37.

In vivo Study design

Rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were fed with Ritonavir optimized formulation, group B fed with marketed product with equivalent dose to animal body weight. Blood samples (approximately 0.5 ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24 h post doses. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 minutes to 10 minutes and stored frozen at -20°C until analysis.

Determination of Ritonavir in rabbit plasma by HPLC method

C18 (250 mm×4.6 mm, 5 μ) column at room temperature using Potassium hydrogen phosphate buffer (pH

adjusted to 6.0 ± 0.1 with diluted potassium hydroxide solution), acetonitrile and methanol in the ratio of 50:35:15 v/v and at a flow rate of 1.0 ml/min, while UV detection was performed at 254 nm. The retention time for lopinavir (IS) and ritonavir was found to be 6.0 ± 0.2 and 3.7 ± 0.1 min, respectively.^[17]

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) was prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was resuspended with 1ml of acetonitrile by vortexing for 1 min. After centrifugation (5000-6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a stream of nitrogen at room temperature. Samples were reconstituted in 200 μ L of 50% of acetonitrile and 50% 0.1% orthophosphoric acid was injected for HPLC analysis.

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hours, which was determined by linear trapezoidal rule and $\text{AUC}_{0-\infty}$ refers to the AUC from time at zero hours to infinity. Calculated using the formula $\text{AUC}_{0-t} + [C_{\text{last}}/K]$ where C_{last} is the concentration in $\mu\text{g}/\text{ml}$ at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life ($t_{1/2}$). Volume of distribution (V_d), total clearance (Cl_T) and mean residence time for each subject using a non compartmental pharmacokinetic program. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3[®] pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean $\pm$ SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test. Difference with $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Physico-chemical properties of Ritonavir floating tablets

The Ritonavir floating tablets were prepared and the compositions of different formulations were shown in Table 1, 2, 3. The evaluation parameters like weight variation, thickness, hardness, friability and drug content were found to be within the limits and summarized in Table 4.

In vitro Buoyancy Study

All the prepared Ritonavir dosage forms showed floating lag time of 33 sec (Figure 1) and floated in 0.1N

HCl for more than 12 hours. Sodium bicarbonate content controls the floating behaviour including the lag time. Increased sodium bicarbonate content caused rapid formation and entrapment of CO₂ resulted in reduction of floating lag time. The optimized formulation F21 showed minimum floating lag time of 33 sec and total floating time for the formulations was more than 24 hours.

Table 4: Physicochemical parameters of Ritonavir floating tablets

Formulation Number	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/cm ²)	#Friability (%)	#Content uniformity (%)	Floating Lag time (sec)	Total floating time (hours)
F1	297 ± 0.8	3.21 ± 0.18	4.6 ± 0.46	0.22	96.31 ± 0.45	48	>24
F2	298 ± 0.8	3.54 ± 0.27	4.8 ± 0.48	0.23	95.21 ± 0.35	45	>24
F3	299 ± 0.9	3.46 ± 0.22	5.6 ± 0.53	0.28	94.20 ± 0.35	42	>24
F4	298 ± 0.8	3.81 ± 0.30	5.1 ± 0.50	0.26	96.13 ± 0.45	40	>24
F5	299 ± 0.9	3.90 ± 0.38	4.9 ± 0.48	0.24	95.12 ± 0.35	38	>24
F6	300 ± 0.10	3.85 ± 0.36	4.7 ± 0.46	0.23	94.23 ± 0.35	36	>24
F7	298 ± 0.7	3.84 ± 0.36	4.6 ± 0.46	0.24	92.15 ± 0.19	34	>24
F8	299 ± 0.9	3.98 ± 0.45	4.8 ± 0.48	0.22	94.65 ± 0.35	46	>24
F9	301 ± 0.5	3.67 ± 0.32	4.7 ± 0.46	0.19	96.31 ± 0.45	44	>24
F10	300 ± 0.5	3.35 ± 0.18	4.9 ± 0.48	0.18	90.24 ± 0.15	41	>24
F11	297 ± 0.8	3.29 ± 0.15	4.8 ± 0.48	0.21	97.23 ± 0.60	39	>24
F12	299 ± 0.8	3.38 ± 0.18	4.6 ± 0.46	0.23	95.61 ± 0.35	37	>24
F13	300 ± 0.10	3.40 ± 0.21	4.8 ± 0.48	0.25	94.28 ± 0.35	36	>24
F14	298 ± 0.8	3.28 ± 0.15	4.9 ± 0.48	0.26	93.46 ± 0.19	34	>24
F15	297 ± 0.8	3.35 ± 0.18	5.5 ± 0.43	0.28	92.15 ± 0.19	47	>24
F16	299 ± 0.9	3.23 ± 0.15	5.3 ± 0.42	0.24	97.32 ± 0.60	46	>24
F17	300 ± 0.10	3.18 ± 0.09	5.0 ± 0.49	0.25	91.26 ± 0.18	43	>24
F18	298 ± 0.8	3.20 ± 0.18	4.9 ± 0.48	0.20	90.74 ± 0.20	40	>24
F19	300 ± 0.8	3.42 ± 0.20	4.7 ± 0.46	0.19	94.67 ± 0.35	38	>24
F20	299 ± 0.9	3.23 ± 0.15	4.9 ± 0.48	0.18	96.12 ± 0.45	36	>24
F21	302 ± 0.10	3.11 ± 0.08	4.5 ± 0.45	0.15	98.36 ± 0.68	33	>24

*Values are expressed in mean ± SD: (n=20) #Values are expressed in mean ± SD: (n=3)

In vitro dissolution studies

From the results it can be observed that the polymer HPMC K 100M has controlling effect on the release of drug from the floating matrix tablet of Ritonavir compared to HPMC K15 M and HPMC K 4M. The concentration of polymer was added in increasing order to check its drug release retarding ability and F21 was considered as best one among the all the formulations, and the drug release was 98.67±5.40, when compared with marketed product of 91.46±5.02 within 24 hours (Figure 2, 3 & 4).

Stability Studies

There were no changes observed in % drug content, *in vitro* drug release studies and floating lag time during

storage of the optimized formulation. Hence the optimized formulation was found to be stable.

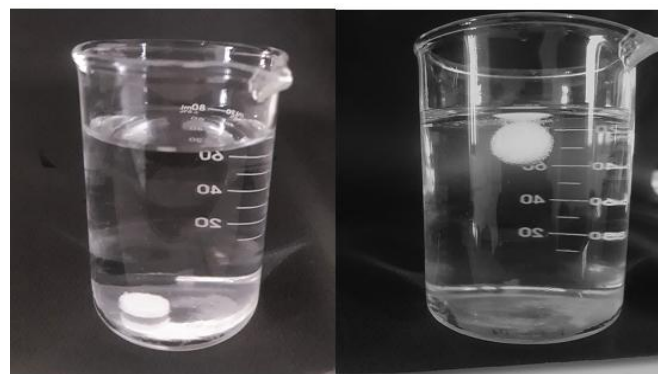


Fig. 1: Pictorial representation of floating lag time of ritonavir optimized formulation (F21)

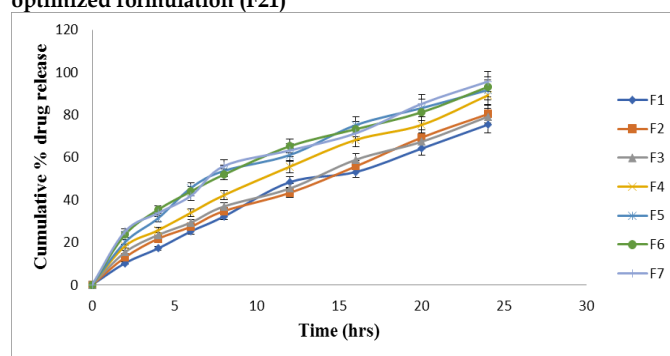


Fig. 2: In vitro drug release profile of ritonavir floating tablets F1-F7

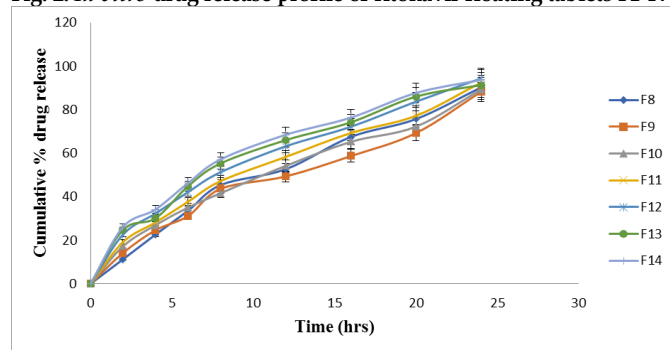


Fig. 3: In vitro drug release profile of ritonavir floating tablets F8-F14

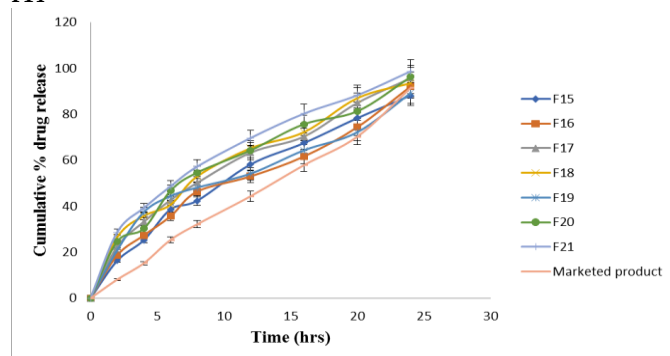


Fig. 4: In vitro drug release profile of ritonavir floating tablets F15-F21

Bioavailability parameters

Mean plasma concentration profiles of prepared Ritonavir optimized formulation and marketed product are presented in Figure 5. Ritonavir optimized formulation exhibited as sustained release *in vivo* when compared with marketed tablet. All the

pharmacokinetics parameters displayed in Table 5. From *in vivo* bioavailability studies, after oral administration of floating tablet containing 100mg Ritonavir, the C_{max} , T_{max} , and $AUC_{0-\infty}$ of optimized gastroretentive formulation were found to be $30.11 \pm 1.16 \mu\text{g/mL}$, $8.00 \pm 1.23 \text{ h}$ and $173 \pm 26.34 \mu\text{g/mL/h}$, respectively. C_{max} and AUC values of optimized formulation were found to be significantly higher than of marketed product, where longer gastric residence time is an important condition for prolonged or controlled drug release and also for improved bioavailability.

Table 5: Comparison of pharmacokinetic parameters of Ritonavir optimized formulation and Marketed Product

Parameters	Ritonavir Optimized formulation	Marketed Product
$C_{max}(\mu\text{g/mL})$	30.11 ± 1.16	22.11 ± 2.13
$AUC_{0-t}(\mu\text{g}^*\text{h/mL})$	173 ± 26.34	137 ± 24.16
$AUC_{0-\infty}(\mu\text{g}^*\text{h/mL})$	205 ± 27.24	156.35 ± 28.2
$T_{max}(\text{h})$	8.00 ± 1.23	6.00 ± 0.24
$t_{1/2}(\text{h})$	11.03 ± 0.5	8.64 ± 0.01
$K_{el}(\text{h}^{-1})$	0.062 ± 0.01	0.085 ± 0.01

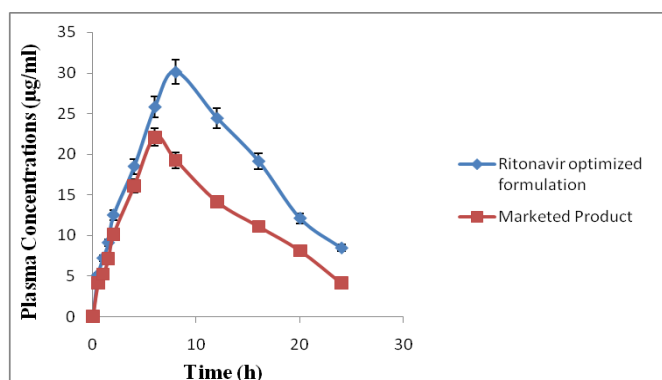


Fig. 5: Plasma concentrations at different time intervals for ritonavir optimized formulation and marketed product

The results indicated that the test formulation could increase the bioavailability of Ritonavir in rabbits effectively. In this study, the Ritonavir floating tablet produce higher bioavailability than that of a marketed product, this overall increase in bioavailability and increased gastric residence time, caused by flotation of dosage form in the stomach.

In the present work, it can be concluded that the Ritonavir floating tablets can be an innovative and promising approach for the delivery and the treatment of HIV. The optimized formulation F21 contains HPMC K100M, Polyox WSR 303 and gas generating agent. *In vitro* release profile of Ritonavir and marketed product when compared, the optimized formulation F21 showed drug release of $98.67 \pm 5.40\%$, whereas $91.46 \pm 5.02\%$ of the drug was released from the marketed product within 24 hours. From *in vivo* bioavailability

studies, after oral administration of floating tablet containing 100 mg Ritonavir, the C_{max} , T_{max} , and $AUC_{0-\infty}$ of optimized gastroretentive formulation were found to be $30.11 \pm 1.16 \mu\text{g/mL}$, $8.00 \pm 1.23 \text{ h}$ and $173 \pm 26.34 \mu\text{g}^*\text{h/mL}$, respectively. C_{max} and AUC values of optimized formulation were found to be significantly higher than of marketed product, where longer gastric residence time is an important condition for prolonged or controlled drug release and also for improved bioavailability.

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