DEVELOPMENT AND *IN VITRO–IN VIVO* EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF AN ANTIRETROVIRAL AGENT RITONAVIR

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ABSTRACT

Objective: The present research work concerns the development of the extended release of Ritonavir floating matrix tablets, designed to prolong the gastric residence time, increase the drug bioavailability, and diminish the side effects of irritating drugs.

Methods: The floating tablets of Ritonavir were prepared by direct compression method using different grades of hydroxypropyl methylcellulose (HPMC), crospovidone, Polyox WSR 303, and sodium bicarbonate, as gas generating agent. Evaluation parameters and *in vivo* radiographic studies were conducted in suitable model.

Results: Among all formulations, F21 was chosen as optimized formulation based on evaluation parameters such as floating lag time (33 s), total floating time (>24 h), and *in vitro* dissolution studies. From *in vitro* dissolution studies, the optimized formulation F21 and marketed product were shown 98.67% and 91.46±5.02% of drug release, respectively. The main appliance of medication discharge follows zero-order kinetics and non-Fickian transport by coupled diffusion and erosion. *In vivo* experiments maintained the potentials in extending the gastric residence time in the fasted state in beagle dogs. The mean gastric residence time of the optimized formulation found to be 330 min±40 in the stomach, where longer gastric residence time is an important condition for prolonged or controlled drug release and also for enhanced bioavailability.

Conclusion: From *in vitro* and *in vivo* radiographic studies, Ritonavir floating tablets estimated to provide novel choice for harmless, inexpensive, and extended release for the effective management of AIDS.

Keywords: Ritonavir AIDS, Floating tablets, Hydroxypropyl methylcellulose, Radiographic studies.

INTRODUCTION

Oral route is foremost common route of administering the drug due to the ease of formulation, low-cost, convenient for the patient, and simple regulatory approval process. Based on the requirement, formulations can be changed from immediate release to extended release using several polymers [1]. Gastroretentive drug delivery systems can valuable in the transport of medications that remain mainly engrossed in the duodenum and upper jejunum/those that need an absorption window in the gastrointestinal tract [2]. Gastroretentive floating dosage forms remain constantly researched and advanced stomach is a main absorption zone [3]. In accumulation, relatively brief gastric emptying time in humans, through the stomach/upper part of the intestine (major absorption zone), can result in incomplete medication release from drug delivery system, leading to reduced generally ability drug. Some drugs like Ritonavir demonstrates region-specific absorption in different regions of the intestine because of different pH conditions, various enzymes and endogenous constituents like bile [4].

There exist numerous methodologies toward target an exact site sustained/controlled release fashion [5]. Some common methodologies used toward increased gastric residence time of pharmaceutical dosage forms include floating systems, swelling and expanding systems, bioadhesive systems, unfolding and modified shape systems, and high-density systems. Floating drug delivery systems have bulk density (BD) lower than gastric fluids and so remain buoyant in the stomach without distressing gastric emptying rate for a prolonged period of time [6]. While system remains afloat, drug released the desired rate from system [7]. Following drug release, residual system gets emptied from the stomach.

However, besides a minimal gastric content needed to allow proper achievement buoyancy retention principle, minimal equal of floating force is also required keep dosage form reliably buoyant on surface meal [8].

MATERIALS AND METHODS

Materials
Ritonavir was procured from MSN Labs Ltd., Hyderabad. Hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M, HPMC K100M, and Polyox WSR 303 existed were obtained from Granules India Ltd., Hyderabad. Sodium bicarbonate, citric acid, PVP K 30, talc, and magnesium stearate existed were procured from S D Fine-Chem Ltd., Mumbai, and all other chemicals used existed were of analytical grade.

Methods

Micromeritic properties of final blend
Final blend of all preparations was evaluated for BD, tapped density (TD), compressibility index (CI), Hausner ratio, and angle of repose [9].

Formulation method
Accurately weighed amounts of polymers were in a mortar and mixed geometrically, and the required quantity of Ritonavir was added to the polymers. Sodium bicarbonate was taken separately, and the powder passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 min. Magnesium stearate added and mixed for 5 min, and later, Talc was added and mixed for 2 min [10-12]. The mixture equivalent to 300 mg was compressed into tablets with 10 mm round concave punches, and the composition is shown in Tables 1-3.

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
Magnesium stearate	2	2	2	2	2	2	2
Total weight	300	300	300	300	300	300	300

HPMC: Hydroxypropyl methylcellulose

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
Magnesium stearate	2	2	2	2	2	2	2
Total weight	300	300	300	300	300	300	300

HPMC: Hydroxypropyl methylcellulose

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
Magnesium stearate	2	2	2	2	2	2	2
Total weight	300	300	300	300	300	300	300

HPMC: Hydroxypropyl methylcellulose

Evaluation of floating matrix tablets of Ritonavir
Parameters such as weight variation, thickness, hardness, and ability were evaluated according to the reported method [13].

In vitro buoyancy studies
The *in vitro* buoyancy was determined by floating lag time. The tablets existed placed in a 100 ml beaker containing 0.1 N hydrochloric acid (N HCl). Time required for tablet to rise to surface and float was determined as floating lag time [14].

Drug content
Twenty tablets were taken and powdered. Powder equivalent to one dose each transferred to a 100 ml volumetric flask and 0.1 N HCl was added; volume was then made up to mark with 0.1 N HCl. Solution was filtered and diluted suitably and drug content in samples was estimated using ultraviolet (UV)-spectrophotometer at 238 nm [15].

In vitro drug release studies
In vitro drug release study was performed for prepared tablets using USP Type II dissolution apparatus using 900 ml of 0.1 N HCl at a temperature of 37±0.5°C at 50 rpm. 5 ml of sample was collected at 0, 2, 4, 6, 8, 12, 16, 20, and 24 h and the same volume of fresh media was replenished. Drug content in samples was estimated using UV visible spectrophotometer at 238 nm [16].

Release order kinetics Ritonavir tablets
In vitro release data from several formulations containing Ritonavir were determined kinetically using different mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas model [17].

Drug-excipient compatibility studies

Fourier-transform infrared spectroscopy (FTIR)
The spectral analysis can be used to identify the functional groups in the pure drug and drug-excipient compatibility. Pure Ritonavir FTIR spectra, physical mixtures, and optimized formulation were recorded using FTIR (SHIMADZU) [18].

Differential scanning calorimetry (DSC)
DSC studies carried out using DSC 60, having TA60 Software, Shimadzu, Japan. DSC thermograms were recorded for pure drug and optimized formulations. Accurately weighed samples were placed on aluminum plate, sealed with aluminum lids, and heated at a constant rate of 5°C/min, over a temperature range of 0–250°C.

Scanning electron microscopy (SEM) studies
The surface and shape characteristics of pellets were determined by SEM (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

Stability studies
Stability testing was conducted at 40°C±2°C/75% RH±5% RH 3 months using stability chamber (ThermoLab, Mumbai). Samples were withdrawn at predetermined intervals of 0, 30, 60, and 90 days' period according to the ICH guidelines [19]. Various *in vitro* parameters such as percentage yield, entrapment efficiency, and *in vitro* release studies were evaluated.

Tablet preparation for *in vivo* radiographic studies
Ritonavir tablets of 300 mg in weight existed were prepared for *in vivo* radiographic studies in beagle dogs. To make tablets X-ray opaque incorporation of BaSO4 necessary. For *in vivo* radiographic studies, 40 mg of Ritonavir and 5 mg of PVP K 30 were replaced with BaSO$_4$ to ensure visibility by X-ray. Amount of X-ray opaque material in these tablets sufficient to ensure visibility by X-ray. Analyses confirmed that these tablets like tablets for *in vitro* testing, i.e. mechanical strength, floating properties, controlled drug release [20].

Ritonavir *in vivo* radiographic studies
Three healthy beagle dogs, weighing approximately 16 kg, existed were used throughout the study. In each experiment, an unanesthetized animal was fasted for 24 h and first radiograph was made to ensure the absence of radiopaque material in the stomach. Dogs swallowed one of the tablets and immediately afterward drank 100 ml of water. During experiment, dogs were not allowed to eat, but water existed available *ad libitum*. The study protocol was approved by the institutional animal ethics committee with No. CPCSEA/1657/IAEC/CMRCP/PhD-15/37. For radiographic imaging, animal was positioned in a right lateral or ventrodorsally recumbency, and after determined time intervals, the radiographs of the abdomen were taken using an X-ray machine (General Electric Corporation, USA). Distance between the source of X-rays and the object was maintained similar for all images [21]. This allowed us to see tablet in the body of the stomach. At different time intervals of 0.5, 3, 4, and 6 h post-administration of tablets, dogs were exposed to abdominal X-ray imaging [22].

Table 4: Micromeretic properties of prepared powder blends of Ritonavir

Formulation	BD (g/cc)	TD (g/cc)	Angle of repose (Θ)	Carr's index (%)	Hausner ratio
F1	0.53±0.11	0.57±0.18	24°.63±0.03	11.90	1.11
F2	0.52±0.11	0.59±0.21	26°.21±0.05	12.67	1.14
F3	0.53±0.11	0.60±0.21	25°.30±0.03	11.64	1.20
F4	0.51±0.10	0.62±0.22	26°.80±0.05	12.90	1.13
F5	0.54±0.12	0.61±0.21	24°.47±0.03	14.64	1.14
F6	0.52±0.11	0.62±0.22	25°.98±0.03	13.90	1.16
F7	0.51±0.10	0.61±0.21	27°.67±0.05	15.38	1.17
F8	0.51±0.10	0.60±0.21	25°.60±0.03	14.56	1.19
F9	0.50±0.09	0.60±0.21	26°.31±0.05	15.33	1.25
F10	0.50±0.09	0.59±0.20	24°.98±0.03	12.38	1.24
F11	0.49±0.08	0.58±0.18	23°.46±0.03	14.56	1.26
F12	0.53±0.11	0.62±0.22	26°.38±0.05	14.23	1.25
F13	0.52±0.11	0.61±0.21	24°.60±0.03	13.67	1.26
F14	0.51±0.10	0.60±0.21	25°.67±0.03	12.45	1.24
F15	0.51±0.10	0.60±0.21	21°.56±0.02	11.98	1.23
F16	0.52±0.11	0.59±0.20	24°.30±0.03	12.03	1.20
F17	0.53±0.11	0.58±0.18	23°.67±0.03	12.65	1.17
F18	0.51±0.10	0.59±0.20	22°.74±0.02	11.08	1.18
F19	0.52±0.10	0.57±0.18	22°.48±0.02	11.01	1.14
F20	0.49±0.08	0.58±0.18	22°.03±0.02	11.21	1.11
F21	0.48±0.08	0.56±0.15	20°.01±0.01	10.01	1.10

Above parameters are communicated as average±standard deviation; (n=3), BD: Bulk density, TD: Tapped density

Table 5: Evaluation parameters of Ritonavir floating tablets

Formulation number	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm²)	#Friability (%)	#Content uniformity (%)	Floating lag time (s)	Total floating time (h)
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	35	>24
F7	298±0.7	3.84±0.36	4.6±0.46	0.24	92.15±0.19	32	>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	35	>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)

RESULTS AND DISCUSSION

Micromeritic properties of prepared powder blend Ritonavir
The results of BD formulations bearing F1 to F21 were reported in the range of 0.48±0.08 g/cc–0.54±0.12 g/cc. The findings of TD formulations F1 to F21 were reported in the range of 0.56±0.15 g/cc–0.62±0.22 g/cc. The angle of repose of all the formulations was found to be satisfactory. The formulation F21 was having an angle of repose value of 20.01±0.01, and CI values existed found to be in range of 10.01–15.38%. These findings indicated that all batches of formulations exhibited good flow properties. Hausner's ratio values were in the range of 1.10–1.26% and values are shown in Table 4.

Physicochemical properties of Ritonavir floating tablets
The Ritonavir floating tablets were prepared, and the compositions of different formulations existed are shown in Tables 1-3 and the tablets are shown in Fig 1.

Figure 1: Ritonavir floating tablets

Table 6: Release order kinetics of F21 and marketed product

Formulation code	Zero order	First order	Higuchi	Korsmeyer–Peppas	n
F1	0.9798	0.8081	0.933	0.892	0.76
F2	0.968	0.7063	0.932	0.911	0.709
F3	0.9704	0.7353	0.916	0.927	0.77
F4	0.9783	0.7142	0.9597	0.921	0.795
F5	0.9329	0.6417	0.957	0.856	0.773
F6	0.9354	0.7068	0.9557	0.8617	0.702
F7	0.9399	0.6355	0.9603	0.8993	0.658
F8	0.973	0.7628	0.96	0.9242	0.782
F9	0.968	0.709	0.9558	0.9174	0.764
F10	0.972	0.805	0.960	0.9073	0.773
F11	0.9614	0.785	0.901	0.892	0.777
F12	0.9457	0.752	0.947	0.896	0.71
F13	0.9348	0.812	0.924	0.874	0.657
F14	0.9225	0.855	0.937	0.896	0.701
F15	0.970	0.845	0.916	0.875	0.711
F16	0.9633	0.855	0.938	0.887	0.721
F17	0.9487	0.871	0.943	0.894	0.651
F18	0.9363	0.895	0.951	0.913	0.611
F19	0.9358	0.894	0.936	0.908	0.632
F20	0.9562	0.903	0.942	0.901	0.732
F21	0.990	0.917	0.961	0.923	0.62
Marketed	0.958	0.893	0.946	0.929	0.59

Table 7: Parameters after accelerated stability study of optimized formulation F21

Parameters	Temperature maintained at 40±2°C RH maintained at 75%±5%RH			
	Initial	After 1 month	After 3 months	After 6 months
Drug content (%)	98.36±0.68	97.24±0.65	97.02±0.65	96.34±0.62
In vitro drug release (%)	98.67±5.40	98.21±5.39	98.02±5.25	97.36±5.15
Floating lag time	33	34	35	35

RH: Relative humidity

The micromeritic parameters and evaluation parameters such as weight variation, thickness, hardness, friability, and drug content existed were found to be within limits and summarized in Tables 4 and 5, respectively.

In vitro buoyancy study

All the prepared Ritonavir dosage forms showed floating lag time of <1 min and floated in 0.1N HCl intended for additional than 12 h (Fig. 2). Sodium bicarbonate content controls the floating behavior including the lag time. Increased sodium bicarbonate content caused rapid formation and entrapment of CO_2 resulted in reduction floating lag time. Optimized formulation F21 showed minimum floating lag time of 33 s and total floating time for formulations >24 h (Fig 3).

In vitro dissolution studies

From the results, it can be observed that the polymer HPMC K 100M has a controlling effect on release drug from 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, drug release was found to be higher 98.67±5.40, when compared with marketed product of 91.46±5.02 within 24 h (Figs. 4-6).

Mathematical modeling of optimized formula (F21) of Ritonavir floating tablets

From the results, it is apparent that the regression coefficient value closer to unity in case of zero-order plot, i.e., 0.990 indicates that drug release follows zero-order mechanism. The drug release mechanism of optimized Ritonavir tablets F21 was best fitting to zero-order and Higuchi model because of the regression coefficient, thus, mechanism of drug release by diffusion. Further, the *n* value obtained from the Korsmeyer–Peppas plots, i.e., 0.62 indicates non-Fickian (anomalous) transport. Thus, active ingredient is being released by coupled diffusion and erosion. The reference standard (marketed product) regression coefficient value is closer to unity in case of zero-order plot, i.e., 0.958,
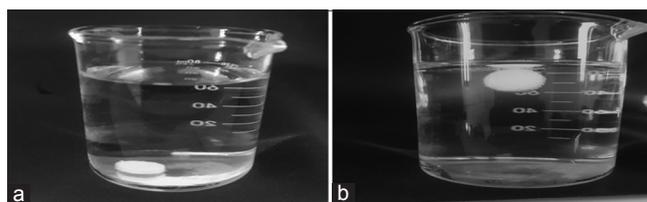
Figure 2: Pictorial representation of floating lag time of Ritonavir optimized formulation (F21). (a) time interval: 0 s. (b) time interval: 33

Figure 3: Ritonavir floating tablets after 24 h

specifying that drug release follows zero-order mechanism. These data indicate lesser amount linearity once plotted by the first-order equation. Hence, it can be concluded that, in case of marketed product also, the major mechanism of drug release follows zero-order kinetics. However, the linearity of the optimized formulation is more when compared to a marketed product. Results are summarized in Table 6 and graphs are depicted in Fig. 7-14.
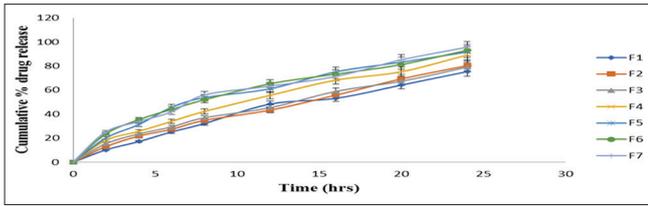
Figure 4: *In vitro* drug release profile of Ritonavir floating tablets F1–F7
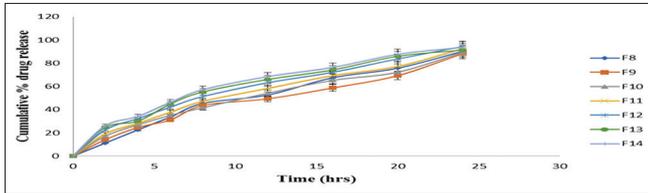
Figure 5: *In vitro* drug release profile of Ritonavir floating tablets F8–F14
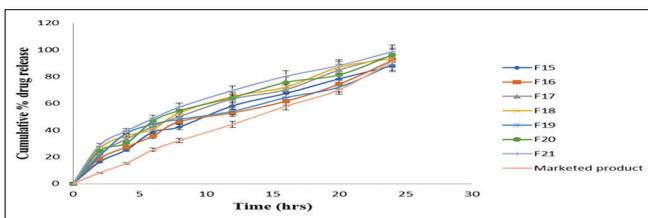
Figure 6: *In vitro* drug release profile of Ritonavir floating tablets F15–F21
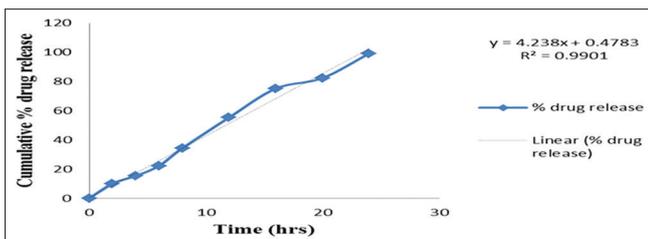
Figure 7: Zero-order plots for the optimized formulation (F21)
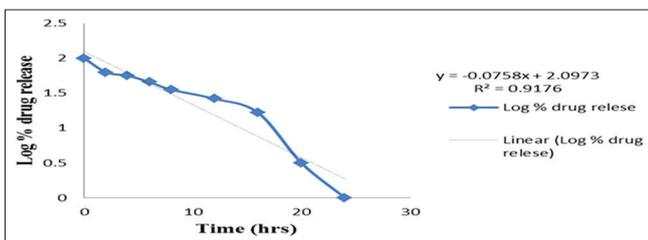
Figure 8: First-order plots for the optimized formulation (F21)
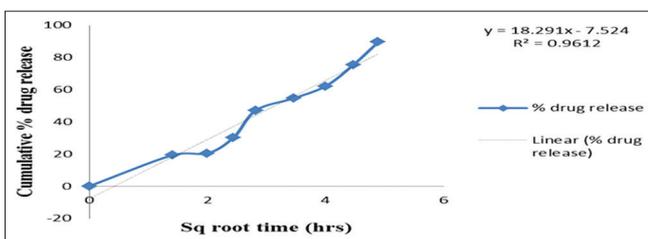
Figure 9: Higuchi plots for the optimized formulation (F21)
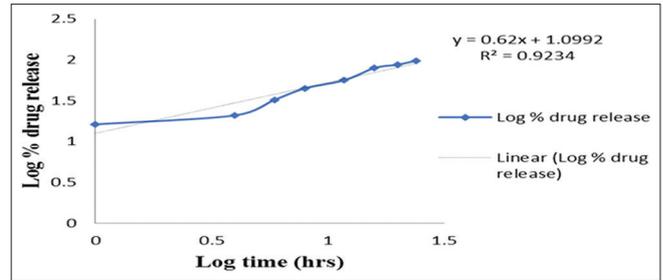
Figure 10: Korsmeyer–Peppas plots for the optimized formulation (F21)*. In vitro* drug release order kinetics for marketed product
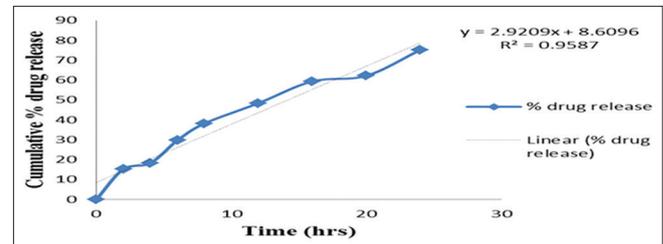
Figure 11: Zero-order plots for the marketed product
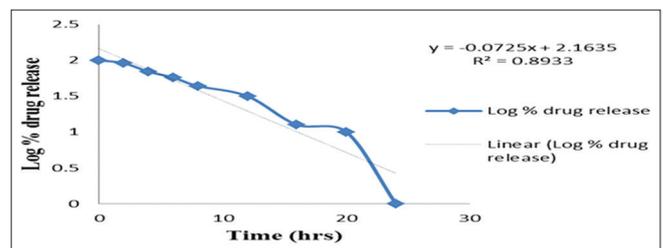
Figure 12: First-order plot for the marketed product
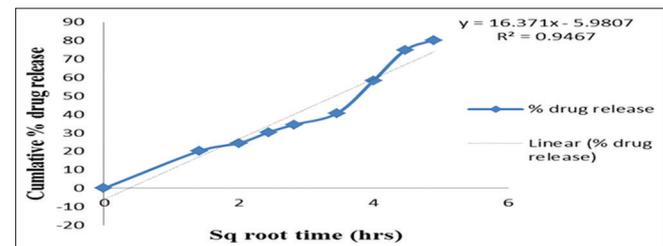
Figure 13: Higuchi plot for the marketed formulation
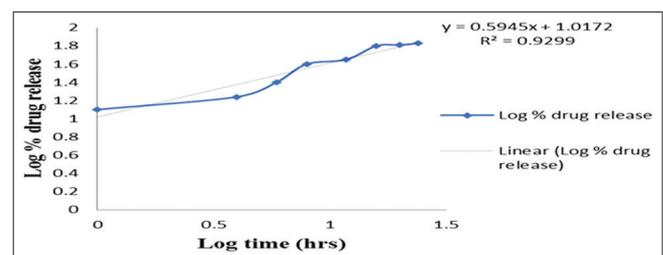
Figure 14: Korsmeyer–Peppas plot for the marketed product

Drug-excipient compatibility studies

There is no alteration in the peaks of Ritonavir pure drug and optimized formulation, suggesting that there was no interaction takes place between drug and excipients and the spectrums are depicted in Figs. 15-17.
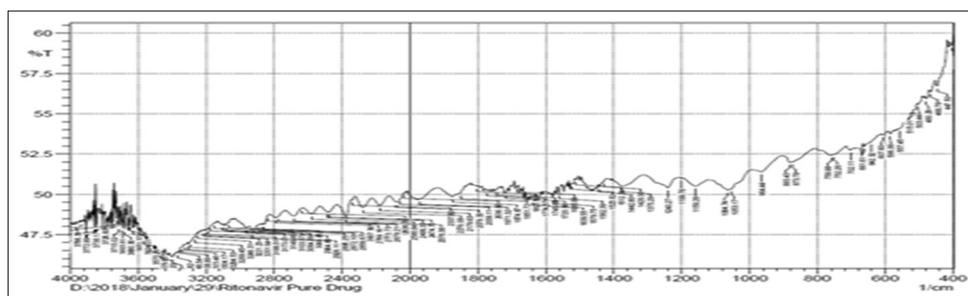
Figure 15: Fourier-transform infrared spectroscopy of pure drug Ritonavir
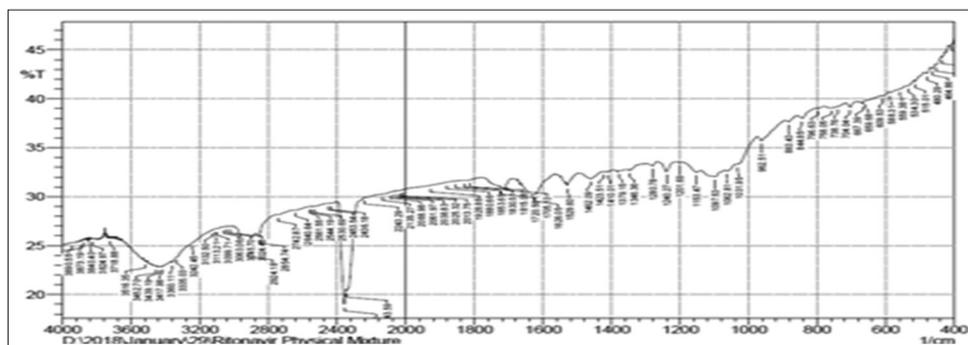
Figure 16: Fourier-transform infrared spectroscopy of Ritonavir physical mixture
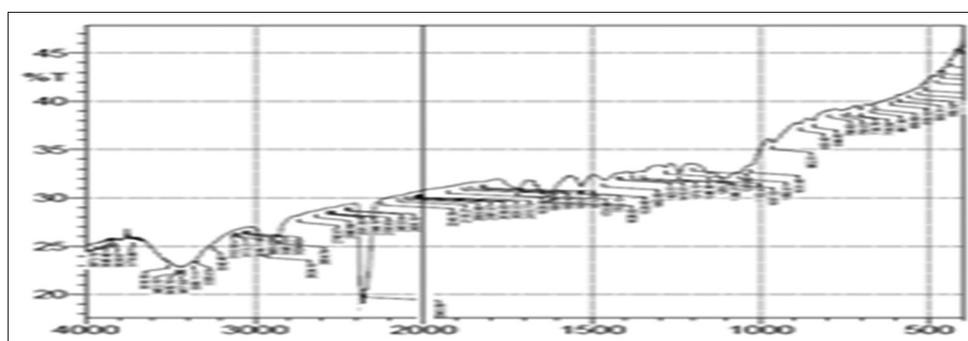
Figure 17: Fourier-transform infrared spectroscopy of Ritonavir optimized formulation
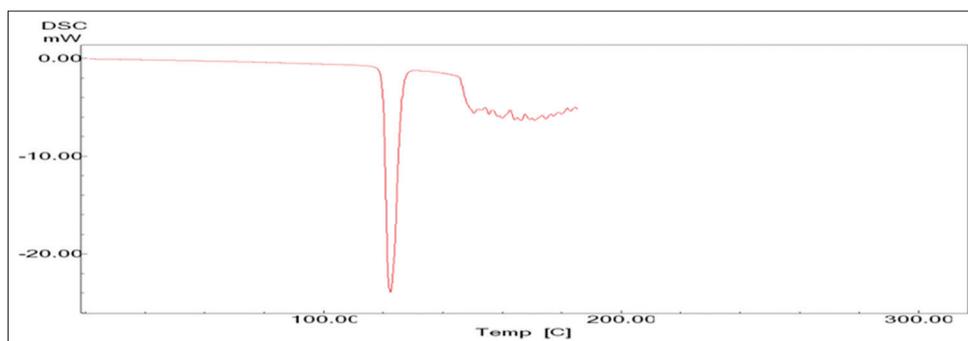
Figure 18: Differential scanning calorimetry thermogram of Ritonavir pure drug

DSC studies

Pure powdered Ritonavir showed melting endotherm at 122.10°C. DSC thermogram of floating tablet showed melting peak drug at 119.36°C. There was no significant difference in melting point of drug and optimized formulation. It is compatible with excipients present in the tablet and there was no major interaction of the drug with the excipients; it is depicted in Figs. 18-21.

SEM studies of Ritonavir floating tablets

The SEM of optimized floating tablet shows a rough surface morphology and dented surface structure, but they showed good floating ability on medium, indicating that intact surface it is shown in Fig. 22. The shell of tablet also showed some porous structure and it may be due to the release of carbon dioxide.
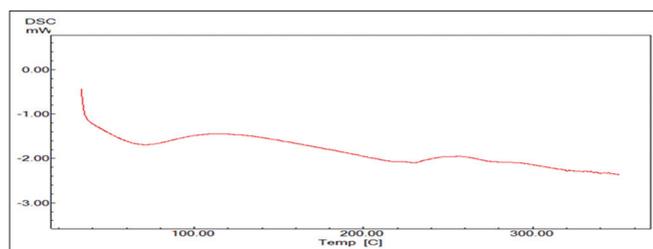
Figure 19: Differential scanning calorimetry thermogram of hydroxypropyl methylcellulose K15M
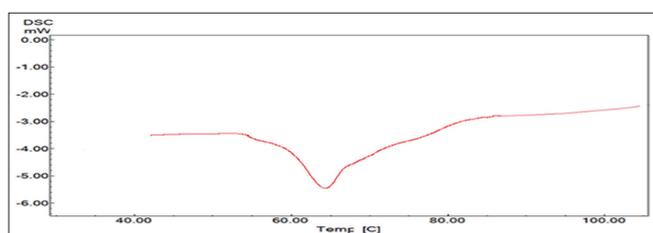
Figure 20: Differential scanning calorimetry thermogram of WSR 303
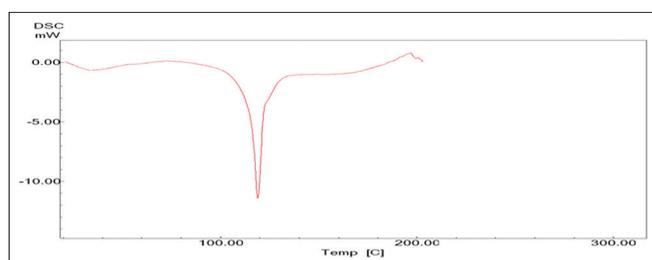
Figure 21: Differential scanning calorimetry thermogram of optimized formulation

Stability studies

There were no changes observed in percentage drug content, *in vitro* drug release studies, and floating lag time during storage of the optimized formulation, and the results are tabulated in Table 7. Hence, the optimized formulation was found to be stable.

In vivo radiographic studies of Ritonavir optimized formulation (F21)

The behavior of the tablet in the dog stomach was observed in real time using a radiographic imaging technique. On radiographic images made 0.5 h after the administration, the tablets were observed in the animal's stomach. In the next picture taken at 1.5 h, significant changes were detected, and the tablet had altered its position and turned around. This provided evidence that the tablets did not adhere to the gastric mucus but, on the contrary, floated on the gastric fluid. In addition, the swelling of the tablet is visualized very well together with the white dry core and translucent swelling layer around it. As the swelling continued, the results have shown, in Fig. 23, that the mean gastric residence time for the developed floating tablets was 330 min±40. The comparison of gastric motility and stomach emptying between humans and dogs shows no big differences. Therefore, it might be speculated that experimentally proven increased GRT in beagle dogs can be compared to known literature data for humans.

CONCLUSION

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
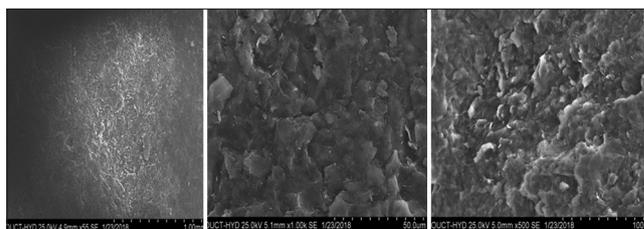
Figure 22: Scanning electron micrographs of optimized Ritonavir floating matrix tablets
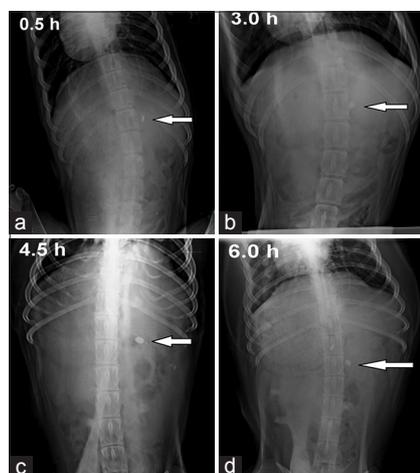
Figure 23: Intragastric behavior of the BaSO$_4$-loaded optimized Ritonavir floating tablets (F21) represented by typical radiographic images after definite time intervals (The tablet is pointed by arrow). (a) after 0.5 h (b) after 3 h (c) after 4.5 h, and (d) after 6 h of tablet administration

the optimized formulation F21 showed drug release of 98.67±5.40%, whereas 91.46±5.02% of the drug was released from the marketed product within 24 h. The major mechanism of drug release follows zero-order kinetics and non-Fickian transport by coupled diffusion and erosion. This means that water diffusion and the polymer rearrangement have an essential role in the drug release. The release rate constant of optimized formulation F21 was low enough prolonging drug delivery. *In vivo* experiments supported the expectations in prolonging the gastric residence time in the fasted state in beagle dogs. The mean gastric residence time for the tested tablets was 330 min±40. This result is encouraging because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the prolonged or controlled release dosage form.

AUTHORS' CONTRIBUTIONS

R. Shireesh Kiran: Drafted the complete manuscript. B. Chandra Shekar: Supervisor of the research work, provided the guidance in the research work. B. Nagendra Babu: Advised the scholar to get quality of work.

CONFLICTS OF INTEREST

No conflicts of interest were raised by the authors.

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