DEVELOPMENT AND CHARACTERIZATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM FOR RITONAVIR TABLETS USING NATURAL POLYMERS

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ABSTRACT

Objective: This study involves preparation and evaluation of floating tablets of ritonavir (RN) for improving the drug bioavailability by prolongation of gastric residence time. RN is an antiretroviral agent used in the treatment of HIV and viral diseases have been taken as a model drug in this investigation because of its low biological half-life (3-5 hrs). Moreover, it is primarily absorbed from stomach.

Methods: RN floating tablets were prepared by the dry granulation technique, using guar gum and xanthan gum as polymers, sodium bicarbonate as effervescent agent, polyvinylpyrrolidone as binding agent, Dicalcium phosphate as diluents, crospovidone as swelling agent and magnesium stearate as lubricant. The prepared tablets were evaluated for various physicochemical parameters.

Results: Drug-excipient interaction studies were conducted by Fourier transform infrared spectroscopy and differential scanning calorimetry. The results suggested that there was no incompatibility between the drug and polymers. The prepared tablets were evaluated for their physical characteristics. All the parameters were within the pharmacopoeial limits. Further, tablets were also studied for their floating properties and *in vitro* drug release characteristics. The tablets exhibited controlled and prolonged drug release profiles. The developed formulation was found to be stable.

Conclusion: The developed floating tablets of RN exhibit prolonged release up to 12 hrs, and thus may improve bioavailability and minimize fluctuations in plasma drug concentrations.

Keywords: Ritonavir, Floating tablets, Gastric residence time, Gastroretentive drug delivery system.

INTRODUCTION

For the last three decades, oral controlled release dosage forms have been developed due to their important therapeutic advantages. By the introduction of a variety of controlled delivery systems, the inconvenience of conventional tablets or capsules was overcome. This controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time. However, this benefit had not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, or (iv) exhibit low solubilities at high pH values [1-3]. These limits promoted the development of gastroretentive drug delivery systems (GRDDS). GRDDS are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from the upper gastrointestinal tract.

Various approaches have been proposed to achieve gastric retention and includes co-administration of drugs or pharmaceutical excipients that influence the gastric motility pattern and thereby delay gastric emptying [4], magnetic systems [5], mucoadhesive systems [6], swelling or unfolding [7], density-controlled systems that either float on gastric contents [8] or sediment and combination systems [9].

Ritonavir (RN) is a protease inhibitor widely prescribed in antiretroviral regimen. It blocks the HIV protease, thereby reducing the viral load in the infected individual [10]. This drug is mainly suffers with low oral bioavailability due to degradation of RN by the cytochrome P450-3A4 (CYP3A4) isoenzymes in the distal intestine [11], efflux of the absorbed drug by counter transporter proteins (mainly P-glycoprotein) present in the distal intestine [12,13] and is unstable at alkaline pH [14]. It shows pH-dependent solubility and solution stability [15]. Moreover, it is primarily absorbed from stomach [16] and having short half-life (~3-5 hrs). Due to these characteristics, it was selected for the development of GRDDS.

METHODS

RN was obtained as a gift sample from Novartis, Hyderabad. Guar gum, xanthan gum was purchased from Colorcon Asia Private Limited, India. Sodium bicarbonate, crospovidone, Dicalcium phosphate, magnesium stearate, and polyvinylpyrrolidone (PVP) k-30 were purchased from S. D. Fine-Chem. Ltd., Mumbai, India.

Procedure for preparation of RN floating tablets

Accurately weighed quantities (Table 1) of polymer and Dicalcium phosphate, crospovidone were taken in a mortar and mixed geometrically. To this required quantity of RN was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder was passed through sieve No. 40 and mixed with the drug blend which was also passed through sieve No. 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this PVP K30 was added and mixed for 2 minutes. The mixture equivalent to 300 mg was compressed into tablets with 10 mm flat punches at a hardness of 5 kg/cm^2. The composition of the different formulations is shown in Table 1.

Solubility studies

The equilibrium solubility of RN was measured in 0.1 M hydrochloric acid (pH of 1.2), phosphate buffer of pH 6.8, and pH 7.4 to determine its solubility. Excess amounts of the drug were added to 50 ml-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5°C

for 24 hrs, in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, and Staufen, Germany). After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 μm pore syringe filter). Then, the filtered samples were diluted with an appropriate amount of dissolution medium and assayed by ultraviolet (UV)-spectrophotometer at 210 nm for RN.

Drug-excipient interaction study: Differential scanning calorimetry (DSC)

DSC thermo grams were recorded on a DSC (Perkin-Elmer, New York, NY). The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (20-300°C) at a constant scanning speed (10°C/minutes) in sealed aluminum pans, using nitrogen purged gas.

Fourier-transform infrared (FTIR) spectroscopy

Drug-polymer compatibility studies were conducted using FTIR spectrophotometer (Schimadzu) by KBr pellet technique. IR spectrum of pure drug and polymers were seen in between 4000 and 400 cm^{-1}.

Evaluation of physicochemical properties

The prepared tablets were evaluated for parameters such as hardness, friability, weight variation, thickness, *in vitro* drug release, floating lag time (FLT), total buoyancy time, and stability study.

Wight variation

A total of 20 tablets were randomly selected and were weighed using an electronic balance (Shimadzu BL-22OH, Japan). Results are expressed as mean value and standard deviation (SD).

Hardness test

The hardness tests of the tablets were determined using Monsanto hardness tester (Campbell Electronics, India). For each formulation, the hardness of six tablets was determined. Hardness values are reported in kg/cm^2. Mean and SD values were also calculated.

Thickness

The thickness of the tablets was determined by using vernier calipers (Mitutoyo, Japan). 10 tablets from each batch were used. Mean and SD values were also calculated.

Friability

About 10 tablets were weighed and subjected for this test by using Roche friabilator (Erection instrument and engineering, Ahmadabad, India).

Drug content

About 10 tablets from each batch were taken and triturated, powder equivalent to its average weight and were transferred into a 100 ml volumetric flask, to this 50 ml of 0.1N HCl was added then shaken for 5 minutes and make the final volume with 0.1N HCl up to 100 ml. Then the solution was sonicated for 15 minutes and filtered, then absorbance was determined at 210 nm using UV/visible spectrophotometer (Elico, SL 159, India) against 0.1N HCl blank.

Floating behavior

The buoyancy property was determined by the FLT and total floating time (TFT) by placing the tablet in a 250 ml beaker containing 0.1N HCl and was observed visually.

In vitro dissolution studies

In vitro drug release studies were conducted for a period of 12 hrs using USP XXIV type-II (Paddle) dissolution apparatus (Lab India, India) at 37±0.5°C at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. 5 ml of sample was withdrawn in predetermined time intervals from the dissolution medium and replaced with fresh medium to maintain the sink condition. Then, the samples were analyzed for RN by UV/visible spectrophotometer (Elico, SL 159, India) at 210 nm.

Kinetic modeling of drug release profiles

The dissolution profiles of all formulae in 0.1 N HCl were fitted to zero-order, first-order, Higuchi [17] and Korsmeyer–Peppas kinetic models [18]. The model with the highest correlation coefficient was considered to be the best fitting one.

Physical stability studies

Physical stability studies were conducted according to International Conference on Harmonization guidelines [19]. One of the optimized formulations was placed in a desiccator containing saturated sodium chloride solution (75% Rh). The desiccator was stored at 40°C for 3 months. At predetermined time intervals, the tablets were examined for hardness, FLT, TFT, drug content, and drug release.

RESULTS AND DISCUSSION

RN exhibited a pH dependent solubility phenomenon in different buffers. It shows maximum solubility in 0.1N HCl, while the solubility was decreased as the pH increased.

Drug-excipients interaction study

DSC studies indicated a sharp endothermic peak at 120-125°C corresponding to its melting point, for pure RN (Fig. 1). No significant change in the position of this peak or broadening of peak in the thermogram of drug and excipient mixture was observed with respect to the thermogram of pure drug (Fig. 2). Hence, it can be concluded that the drug and excipients do not interact with each other.

Drug-polymer interactions were studied by fourier transform-infrared spectroscopy analysis. Fig. 3 showed the IR spectra of pure RN. The characteristic CH stretching, NH stretching of secondary amine, C=C stretching, and C=O stretching of pure drug was observed at 2964.47 cm^{-1}, 3357.73 cm^{-1}, 3025.35 cm^{-1}, and 1714.67 cm^{-1}. The characteristic peaks confirmed the structure of RN. The same peaks were also reported in the physical mixture (Fig. 4). Hence, it indicates the stable nature of drug in all formulations.

Physical properties of tablets

The tablets of RN were prepared by direct compression method using natural polymers (xanthan gum, guar gum). The data of physical parameters

Table 1: Composition of the ritonavir floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ritonavir	100	100	100	100	100	100	100	100	100	100
Guar gum	20	40	60	80	100	-	-	-	-	-
Xanthan gum	-	-	-	-	-	20	40	60	80	100
NaHCO$_3$	40	40	40	40	40	40	40	40	40	40
DCP	90	70	50	30	10	90	70	50	30	10
Crospovidone	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
PVP K-30	15	15	15	15	15	15	15	15	15	15
Total tablet weight	300	300	300	300	300	300	300	300	300	300

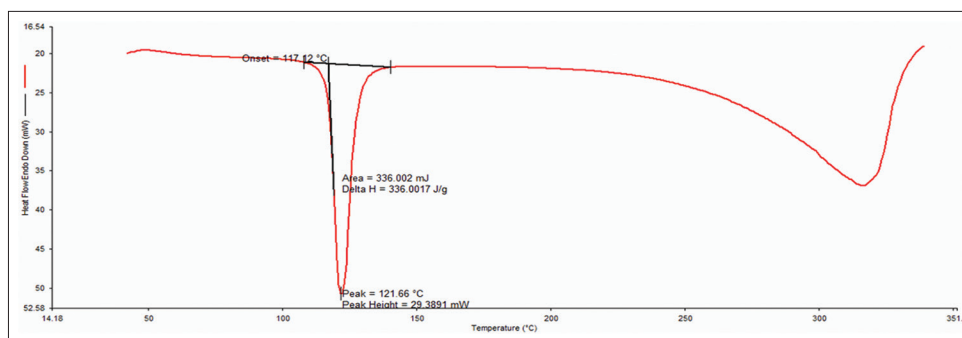DCP: Di calcium phosphate, PVP: Polyvinylpyrrolidone

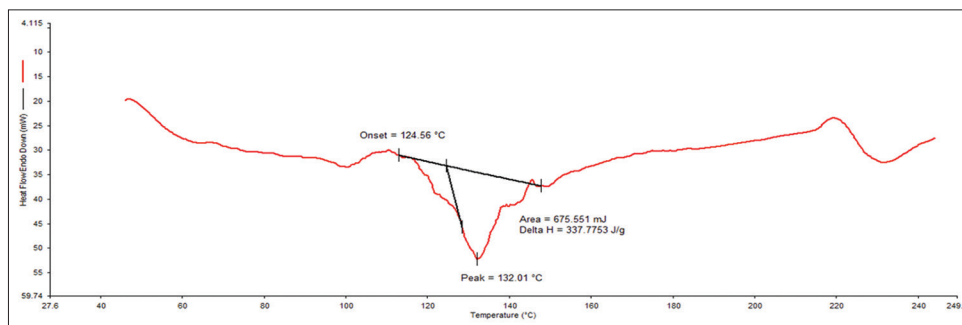**Fig. 1: Differential scanning calorimetry spectra for pure drug**

Fig. 2: Differential scanning calorimetry spectra for drug+excipients
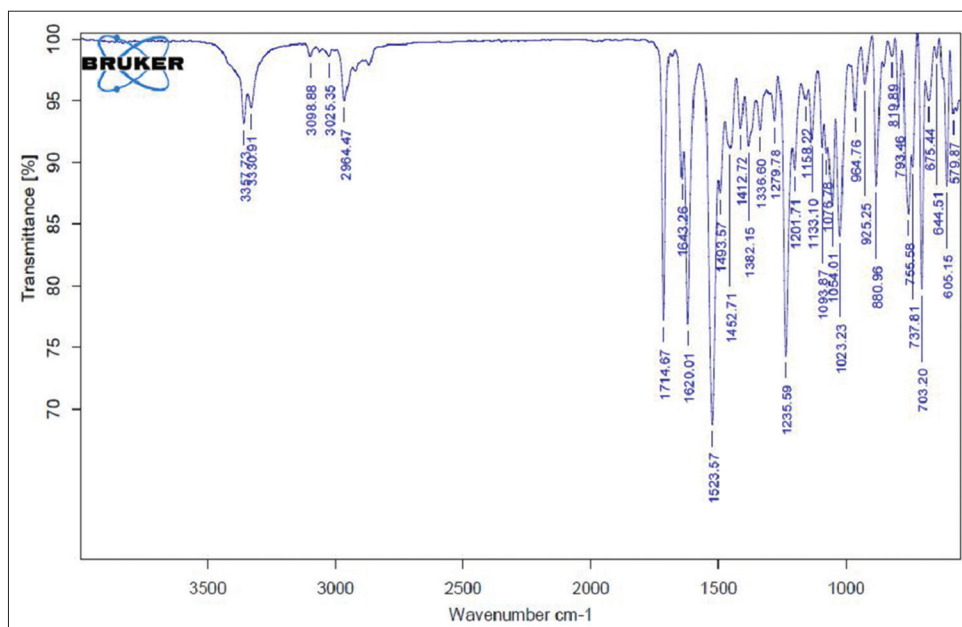

Fig. 3: Fourier-transform infrared spectra for pure drug

were presented in Table 2. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability [20]. The physical evaluation of the tablets revealed uniform thickness and weight for all the tablets (evident from low SD values). The hardness values between 5 and 5.3 kg/cm^2 and low friability values (below 0.45%) across all formulations indicated that the tablets had sufficient mechanical strength. The drug content uniformity studies revealed that drug content between 96.33±2.3% and 98.91±2.8% is acceptable.

FLT and TFT

In this study, sodium bicarbonate was used as a gas-generating agent to aid floating of tablets. The *in vitro* testing revealed the ability of

most formulations to maintain buoyant for more than 12 hrs (Table 2 and Fig. 5). As shown in Table 2, all the formulations floated with a lag time of < 1 minute. The FLT of the formulations F1-F5 prepared with different concentrations of guar gum with constant sodium bicarbonate ratio, ranged from 15 to 35 seconds and that of formulations F6-F10, prepared with xanthan gum, ranged from 37 to 62 seconds had no significant effect. In all the formulations, as the concentration of sodium bicarbonate increased, the FLT was decreased [21] and TFT increased, but the difference in FLT was not statistically significant.

In vitro release studies

In vitro dissolution studies of all the formulations of RN tablets were conducted in 0.1 N HCl (pH 1.2). Formulations (F1-F5) were prepared

Table 2: Physical parameters of gastroretentive tablets of ritonavir

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	FLT (seconds)	TFT (hrs)	Drug release (%)
F1	302	5.1±0.115	3.5±0.05	0.22	98.28	15±1	>12	99.56
F2	300	5.3±0.2	3.5±0.08	0.36	99.52	23±3	>12	97.95
F3	297	5.2±0.305	3.5±0.05	0.25	99.04	27±5	>12	80.05
F4	301	5.0±0.230	3.5±0.08	0.33	99.56	18±4	>12	99.96
F5	299	5.1±0.115	3.5±0.05	0.26	99.41	35±2	>12	97.98
F6	296	5.0±0.23	3.5±0.05	0.37	99.84	45±7	>12	89.20
F7	298	5.0±0.101	3.5±0.01	0.12	98.28	47±8	>12	70.98
F8	300	5.1±0.2	3.5±0.03	0.14	99.52	62±2	>12	66.65
F9	301	5.3±0.215	3.5±0.04	0.19	99.04	37±4	>12	98.32
F10	302	5.20±0.23	3.5±0.08	0.28	98.56	49±9	>12	84.19

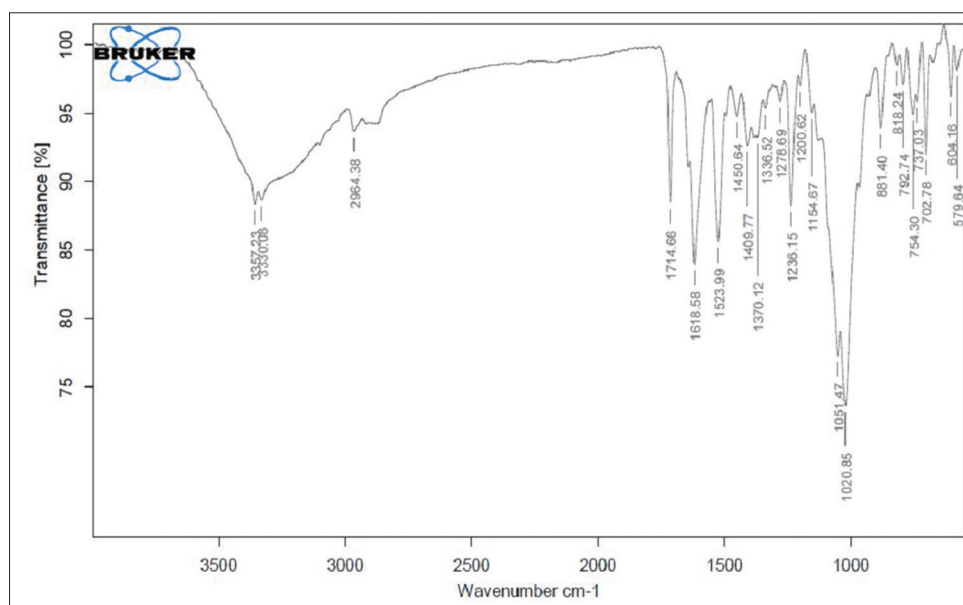FLT: Floating lag time, TFT: Total floating time

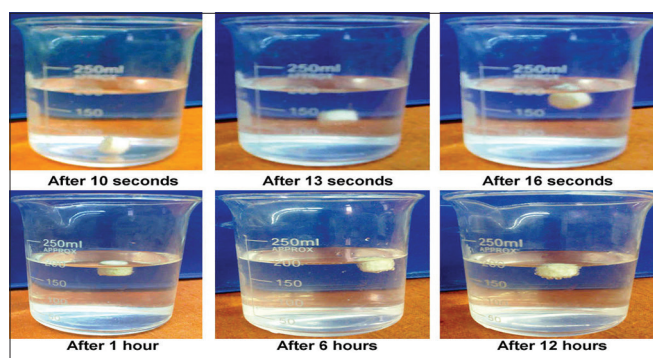**Fig. 4: Fourier-transform infrared spectra for pure drug+physical mixture**

Fig. 5: Floating characteristics of ritonavir floating tablet

with varying concentrations of guar gum, and F6-F10 were prepared with varying concentrations of xanthan gum. The drug release profiles of the formulations, F1-F5 prepared with guar gum shown in Fig. 6. The effect of guar gum concentration on drug release was evaluated. As the concentration of guar gum was increased, the drug release from the floating tablets was significantly decreased [22]. The differences in the release might be due to the amount of gel layer formed on the surface of the tablets. If the polymer concentration is too low, a complete gel layer may not form resulting in a significant amount of drug being released too quickly or tablet may disintegrate [23].

The *in vitro* drug release studies revealed that formulations F1, F2, and F3 showed a release of 92.4, 95.2, and 96.7%, respectively, in 6, 8, and 10 hrs (Fig. 7). Formulation F4 showed maximum drug release of 98.5% in 12 hrs. The variation in drug release was due to different polymer concentrations in all the formulations. Formulations (F1-F3) were unable to sustain the drug release desired period of time. Formulation F4 met the needed theoretical drug release profile and floated with a lag time of 18 seconds. Formulation F5 failed to release the required drug profile. For these reasons, F4 was considered as the best formulation among all the five formulations of this series. The results were shown in Fig. 6. Drug release profiles of formulations F6-F10, composed of xanthan gum, are shown in Fig. 6.

The percentage of drug released from formulations F6, F7, and F8 was 86.8, 84.3, and 87.3, respectively, in 6, 8, and 10 hrs. This variation was considered to be due to different polymer concentrations in formulations. Further, these three formulations failed to meet the required theoretical drug release profile. Formulation F9 met the needed theoretical drug release profile and floated with a lag time of 37 seconds. Formulation F10 failed to release the required drug profile. For these reasons, F9 was considered as the best formulation among all the five formulations of this series. The results were shown in (Fig. 6). Data of the *in vitro* release of the optimized formulation were fit into different kinetic models to explain the release kinetics of RN from the floating tablets. The kinetic models used were a zero-order equation, first-order equation, Higuchi and Korsmeyer–Peppas models (Table 3). Optimized formulation follows Higuchi
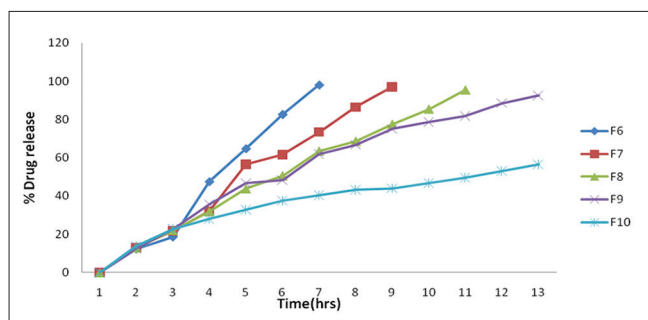
Fig. 6: Drug release profiles of ritonavir floating tablets composed of xanthan gum
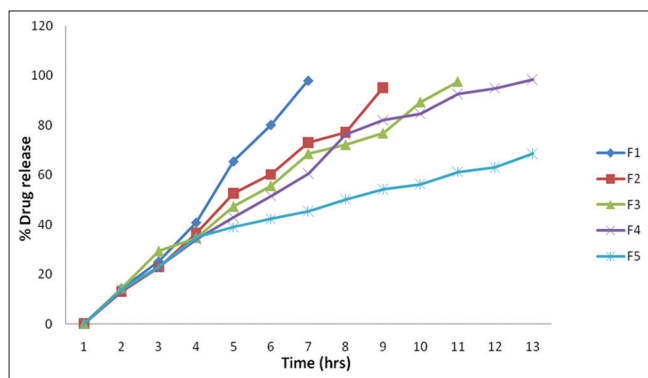

Fig. 7: Drug release profiles of ritonavir floating tablets composed of guar gum

Table 3: The correlation coefficient (R^2) values for optimized formulation

Zero-order	First-order	Higuchi	Peppas
0.9815	0.7027	0.9953	0.8928

Table 4: Stability studies optimized batch

Parameters	Storage conditions		
	At 2-8°C	Room temperature	At 40°C
% cumulative drug release	95.10	96.82	94.73
Drug content uniformity (%)	99.13	99.35	98.46
Color change	No	No	No

model compared to all other models. Optimized formulation (F4) was selected for stability study based on physical characters and *in vitro* drug release. The stability study was conducted for 3 months. No significant change was observed in the tablet hardness, FLT, TFT, and drug content or *in vitro* dissolution (Table 4). Hence that, it can be concluded that the formulation F4 was stable for 3 months under different storage conditions

CONCLUSION

RN floating tablets were successfully formulated by floating technique. The optimized formulation (F4) was selected on the basis of *in vitro* buoyancy and *in vitro* drug release. The addition of gel forming agent and gas generating agent was essential to achieve *in vitro* buoyancy. The results of the *in vitro* drug release and *in vitro* buoyancy study showed that the optimized formulation (F4) sustained the drug release (98.47±0.71%) up to 12 hrs and remained buoyant for >12 hrs. Optimized formulation (F4) does not show any significant change in

physical appearance, floating properties and drug release after storage at 40°C/75% RH and stable for 3 months.

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