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FORMULATION AND EVALUATION OF BUOYANT TABLETS OF KETOCONAZOLE

GHOSH T.*, S. BHARATH, NAIK R., B. V. BASAVARAJ, R. DEVESWARAN

Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, Karnataka
Email: tanmoy.ps.ph@msruas.ac.in

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ABSTRACT

Objective: The primary objective of the present work was to formulate the gastro-retentive delivery system of ketoconazole (ktz) for its extensive absorption in the stomach.

Methods: The solubility and dissolution of antifungal ktz were reported to be higher in the stomach than in the intestinal pH conditions because of its dibasic pKa values 6.51 and 2.94. Thus the development of target buoyant tablets using Hydroxy Propyl Cellulose (HPC) and Xanthan gum (Xg) as polymers along with the effect of citric acid and sodium bicarbonate as an effervescent causing agent of floatation properties and drug release profile was investigated. The formulation optimization was carried out by using a central composite design using Design Expert software by taking HPC, Xanthan gum and sodium bicarbonate as independent variables and floating lag time, *in vitro* drug release profile as dependent variables respectively.

Results: The optimized formulation of ktz buoyant tablets could be developed. The amount of HPC and Xg was found to significantly influence all *in vitro* response parameters. The results of pre-compression and post-compression parameters of all the formulations were found to be within the standard limits. The optimized formulation exhibited floating lag time of 160 secs with sustained drug release over a period of 12 h in simulated stomach pH condition.

Conclusion: Buoyant tablets of ktz with sustained drug release over a period of 12 h in simulated stomach conditions for enhanced drug absorption could be successfully developed.

Keywords: Buoyancy, Gastro-retentive drug delivery, Ketoconazole, Optimization design

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INTRODUCTION

ktz is a broad-spectrum anti-mycotic drug having two pKa values(6.51 and 2.94) with poor water solubility and short elimination half-life of 2 h [1]. It is a drug of choice for treatment of candidiasis, oral thrush, candiduria and paracoccidioidomycosis. It has been reported that the solubility and dissolution of ktz have found to be increased in the stomach pH than in the intestinal pH conditions. Thus in the present study, an attempt has been made to formulate ketoconazole into a floating drug delivery system to prolong its gastric residence time with an increase in its dissolution and absorption. As for reliable retention behavior in the stomach, the design of dosage form, food effects and the complex motility of the stomach poses a major challenge to the formulator [2]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion [3, 4] flotation, sedimentation [5, 6] expansion, modified shape systems [7, 8] or by the simultaneous administration of pharmacological agents [9, 10] that delay gastric emptying.

The floating drug delivery system (FDDS) have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* with effervescent and without effervescent systems have been used in the development of FDDS. The effervescent system uses matrices prepared with swellable polymers and effervescent components *e. g.* sodium bicarbonate and citric acid or tartaric acid. In non-effervescent FDDS, the drug mixes with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [11].

In the present investigation, an attempt to increase the dissolution was made by developing gastro-retentive floating tablets of ktz using HPC, Xg as a gel-forming agent and also release retardant agent with citric acid-sodium bicarbonate as effervescent components.

MATERIALS AND METHODS

ktz and Xg were purchased from Yarrow chem. Product, Mumbai. HPC was purchased from Himedia Laboratories Pvt. Ltd, Mumbai. All other ingredients, reagents and solvents were of analytical/ laboratory grade.

Design of formulations

Formulations were developed using a central composite design after results obtained through conducted pre-formulation trials. The Design-Expert Software (version 8.0.1, Stat-Ease Inc., Minneapolis, USA) suggested eight model formulations as shown in table 1 considering the concentration of HPC, Xanthan gum and sodium bicarbonate as independent variables with the percentage drug release, floating lag time as dependent variables.

Table 1: Central composite design response for three factors

Run	Formulation code	Type	Factor 1: A HPC	Factor 2: B xanthan gum	Factor 2: B sodium bicarbonate
1	OFT-1	Factorial	50	50	50
2	OFT-2	Factorial	50	150	50
3	OFT-3	Factorial	150	150	100
4	OFT-4	Factorial	150	150	50
5	OFT-5	Factorial	150	50	100
6	OFT-6	Factorial	150	50	50
7	OFT-7	Factorial	50	150	100
8	OFT-8	Factorial	50	50	100

Formulation development of ketoconazole buoyant tablets

Floating tablets of ktz were prepared using the values given in table 1 by wet granulation technique with a constant concentration of citric acid and varied concentration of sodium bicarbonate as effervescent agents as shown in table 2. Weighed quantities of drug and polymer were mixed homogeneously using mortar and pestle. PVP-K30 (5% w/v) solution in alcohol was used as a granulating agent. Granules were prepared by passing wet coherent mass through a BSS # 12 sieve. The obtained granules were dried at 40^0C temperature for 30 min. The dried granules were sieved through BSS # 16, sodium bicarbonate and citric acid were mixed and blended with magnesium stearate and talc. Lubricated granules were compressed into tablets using ten stations single rotary punching machine (Rimek RSB-4 mini press) using 12 mm punches and die to obtain tablets of desired specifications.

Table 2: Formulation table for trials given in optimization design

Ingredients	Quantity(mg)							
	OFT-1	OFT-2	OFT-3	OFT-4	OFT-5	OFT-6	OFT-7	OFT-8
Ketoconazole	200	200	200	200	200	200	200	200
HPC	150	150	150	50	50	50	50	150
Xanthan Gum	150	50	50	150	50	150	50	150
Sodium bi carbonate	50	50	100	100	50	50	100	100
Citric acid	25	25	25	25	25	25	25	25
Lactose	60	160	110	110	260	160	210	10
Mg stearate	10	10	10	10	10	10	5	5
Purified talc	5	5	5	5	5	5	10	10
Total weight(q. s)	650	650	650	650	650	650	650	650

Evaluation studies

Drug-polymer compatibility studies by FTIR and DSC

The drug and polymer interactions were studied by FTIR spectroscopy using KBr disc method. The spectra were recorded for pure drug, polymers and physical mixture of drug and polymer in the ratio 1:1 at the scanning range of 400-4000 cm^{-1} using FTIR-8400 S, spectrophotometer (SHIMADZU, Japan). DSC studies were also carried out to check the compatibility of the drug with polymers used in formulation design.

Pre-compression studies

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner ratio [12].

Post-compression studies

Six tablets from each batch formulation were randomly selected and organoleptic properties such as color, odor and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. Prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche Friabilator, Koshiash Industries, Mumbai).

Determination of swelling index

The swelling index of tablets was determined in 0.1N Hcl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 5 h. The sample tablet from each batch was weighed and placed in a petri dish containing 10 ml of 0.1N HCl. After each hour the tablet was removed from a petri dish, excess solvent on the surface of the tablet was blotted with the paper gently and weighed again up to 5 h. The percentage of weight gain by the tablet was calculated by using the formula [12].

$$\text{Swelling index (S. I.)} = \{(Wt\text{-}Wo)/Wo\} \times 100$$

Where S. I. = Swelling index,

Wt = Weight of tablet at time t,

Wo = Weight of tablet before immersion.

Drug content

Twenty tablets from each batch were randomly sampled, weighed and powdered. Tablet triturates equivalent to the average weight of the tablets was dissolved in 0.1 N HCl in 100 ml volumetric flask. The sample solution was further diluted and the absorbance was measured at 269 nm using 0.1N HCl as blank and the % drug content was estimated using the following formula [13].

$$\text{Concentration} = \frac{\text{Absorbance}}{\text{Slope}}$$

Drug content (mg) = concentration x dilution factor

$$\%\ \text{Drug content} = \frac{Drug content\ (mg)}{Lable\ claim\ (mg)}\ X\ 100$$

***In vitro* buoyancy studies**

The tablets individually were placed in a 100 ml beakers containing 0.1N HCl. The *in vitro* buoyancy was determined by the floating lag-time (time period between placing the tablet in the medium and the tablet floating). The duration up to which the tablet floats on the dissolution medium was taken as duration of buoyancy. The studies were carried out in triplicate [14].

***In vitro* dissolution study**

In vitro dissolution studies were carried out in 900 ml of 0.1N HCl as the dissolution medium for 12 h using USP type II dissolution apparatus (Shimadzu TDT 08L dissolution tester). The rpm of the paddle was kept at 50 rpm and the temperature was maintained at 37 °C±0.5 °C. A sample (2 ml) of the solution was at regular predetermined time intervals and the volume replaced with fresh dissolution medium. The withdrawn samples were diluted suitably and the absorbance was measured at 269 nm by using UV/Visible Spectrophotometer [15, 16].

Development of optimized RFT formulation

In order to accurately optimize a probable formulation to attain 100% drug release in 12 h, the evaluation results obtained from eight formulation trials were further predicted using Design Expert software. One such response (formulation design) was experimentally tested to check whether the predicted values assumed by the software matches with the experimental results in terms of floating time and dissolution rate as indicated in table 6 and fig. 1.

RESULTS AND DISCUSSION

FTIR studies

The combined IR spectrum of ktz showed the characteristic absorption peaks at 3236, 3062, 1581 and 1265 cm^{-1} denoting stretching vibrations of–NH, aromatic–CH,–NH bending and an aromatic C-O group respectively. In case of HPC a peak was observed at 2885.31 cm^{-1} indicating the presence of the primary alcoholic group present in the molecule. Another prominent peak appeared at 1249.79 cm^{-1} suggesting it as an C-O-C stretch. The FTIR spectra of the pure Xg showed a broad absorption peak at 3637.50 cm^{-1} indicating the hydrogen bond-OH groups,, 2887.24 cm^{-1}indicatingC-H aromatic stretch,1274.86 cm^{-1}indicating an C-O-C stretch, 1730.03 cm^{-1} indicating C=O stretch. The IR spectra of physical mixture drug-

polymer blends showed neither shift nor disappearance of characteristic peaks when compared with IR-spectrum of pure sample suggesting that there was no interaction between drug and polymers as shown in fig. 2.

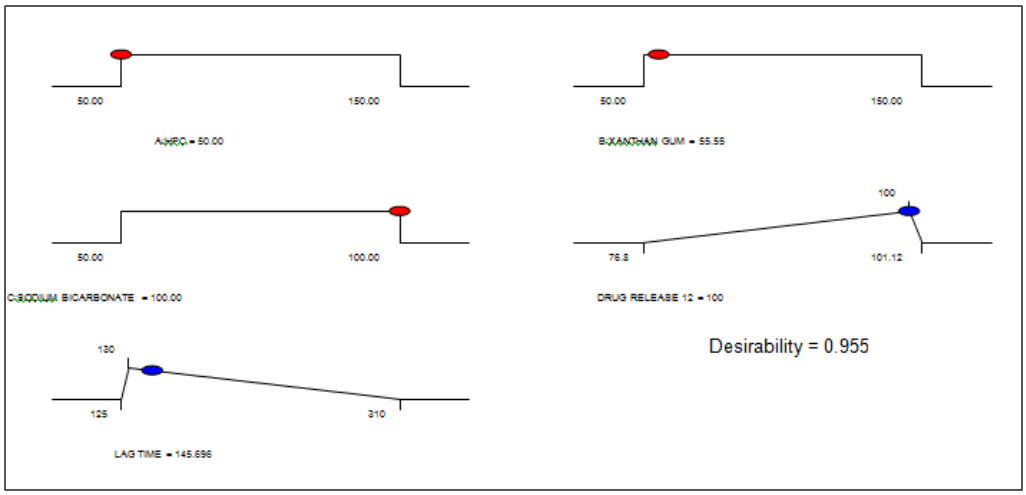

Fig. 1: Parameters suggestions for RFT formulation

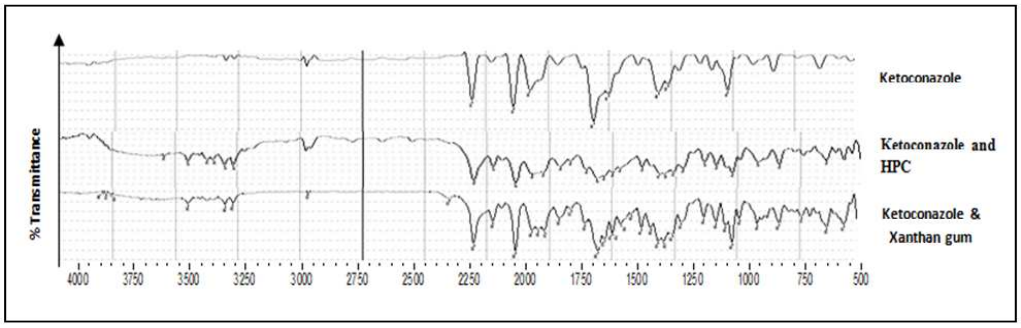

Fig. 2: IR spectra of Ketaconazole, physical mixture of Ketaconazole-HPC and Ketaconazole-Xanthangum

DSC studies

The DSC thermograms of the drug and polymer tested are shown in fig 3. DSC curve of ktz exhibited endothermic peak (150.15 °C) corresponding to the melting point of the drug and immediately followed by sharp symmetric exothermic peak (154 °C) due to its degradation. The physical mixture of drug-polymer blends, ketoconazole with HPC and ketoconazole with xanthan gum exhibited sharp peak of the drug without any changes. Thus the drug was found to be stable with the polymer used in the formulation.

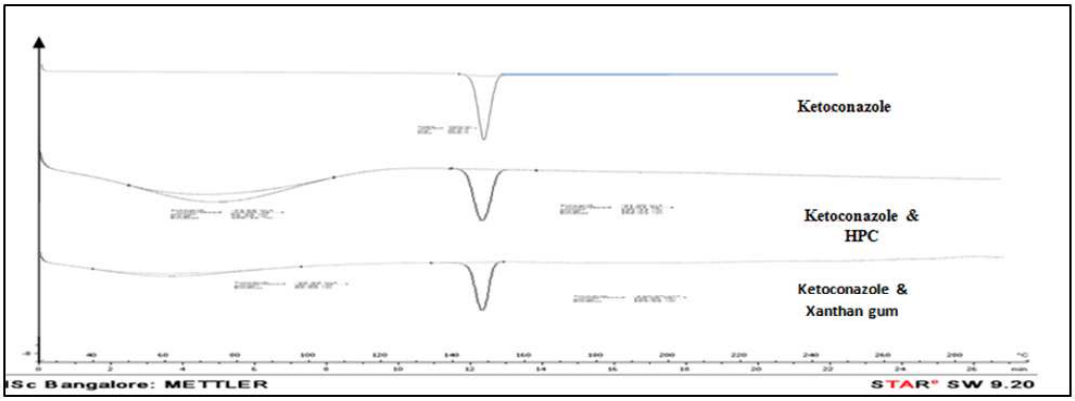

Fig. 3: DSC thermogram of ktz, physical mixture of ktz-HPC and ktz-xanthan gum

Pre-compression evaluation for optimization trials given in the design

The values of bulk density were found to be in the range from 0.344 to 0.506 g/cc; tapped density in the range of 0.389 to 0.590 g/cc, which indicated that the powder blends were having good flow properties. The Hausner's and compressibility index, angle of repose values for the formulations showed good flow properties as indicated in table 3.

Table 3: Pre-compression results for optimization trials given in the design

Batch. code	Bulk density* (g/cc)	Tapped density* (g/cc)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
OFT-1	0.481±0.001	0.56±0.001	27 ° 75′	14.25	1.164
OFT-2	0.387±0.001	0.442±0.0015	28 ° 59′	12.61	1.143
OFT-3	0.441±0.001	0.506±0.001	24 ° 24′	12.47	1.143
OFT-4	0.506±0.001	0.590±0.001	26 ° 41′	14.20	1.165
OFT-5	0.459±0.001	0.536±0.001	24 ° 24′	14.17	1.167
OFT-6	0.487±0.001	0.569±0.001	23 ° 06′	14.37	1.166
OFT-7	0.457±0.001	0.533±0.0015	25 ° 55′	14.39	1.166
OFT-8	0.344±0.001	0.389±0.001	29 ° 54′	12.08	1.123

*Mean valve±SD (n=3)

Post-compression evaluation for optimization trials given in the design

All the tablets were found to be capsulate with no cracks. All the batches prepared (OFT1-OFT8) showed hardness in the range of 5.80 to6.80 kg/cm^{2}with good mechanical strength for the tablets. Further friability values below 1% ensured the same. The formulation batches passed all the official tests for tablets. The floating lag time and total floatation time were recorded between 125-310 secs and 21-24 h respectively as indicated in table 4.

Table 4: Post-compression results for optimization trials given in design

Batch. code	Hardness* (kg/cm^2)	Weight variation*	Friability test (%)	Drug content (%)	Floating lag time (sec)	Total floating time (h)
OFT-1	5.80±0.11	650±3	0.92	98.18±4.30	125	21
OFT-2	6.20±0.3	649±9	0.87	99.16±3.25	150	24
OFT-3	6.40±0.2	650±7	0.93	98.49±5.15	270	23
OFT-4	6.80±0.2	650±5	0.89	99.10±4.25	310	21
OFT-5	5.80±0.2	650±9	0.88	97.65±6.05	245	22
OFT-6	6.40±0.4	650±7	0.89	98.76±5.21	270	24
OFT-7	6.20±0.4	648±8	0.82	99.57±4.14	235	23
OFT-8	6.80±0.3	649±6	0.83	98.64±6.10	145	24

*Mean valve±SD (n=3)

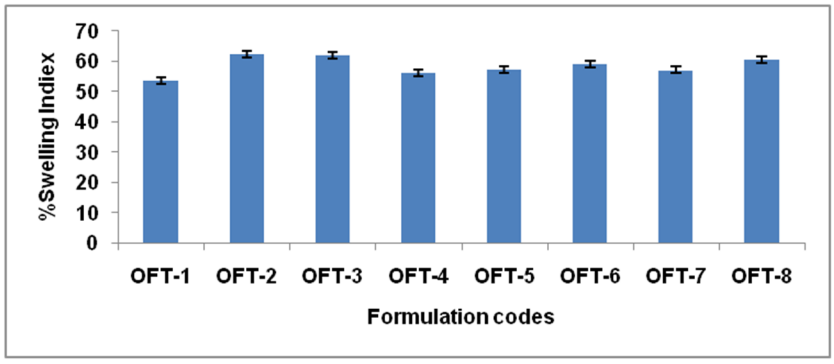

Fig. 4: Comparative bar chart for swelling index of formulations, mean±SD (n=3)

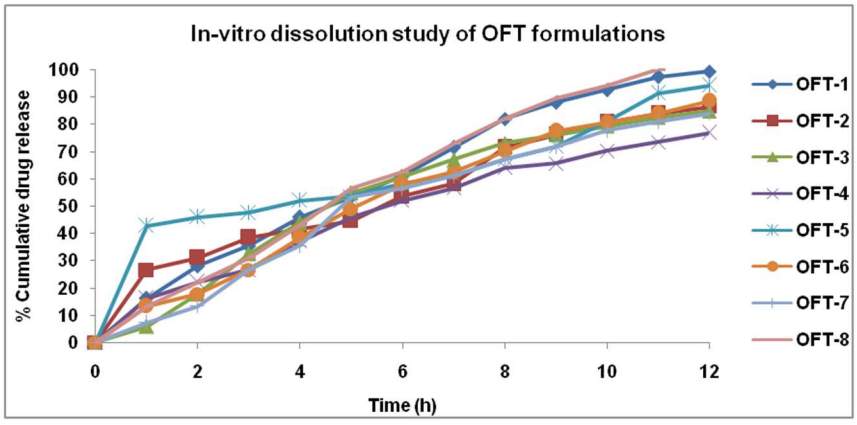

Fig. 5: *In vitro* drug release profile of formulations OFT: 1-8

Swelling index

The swelling index was studied for 5 h in 0.1N HCl and the results indicated in fig. 4. The swelling property was directly proportional to the concentration of the polymer, which may be attributed to the hydrophilic property of the polymer and also to its concentration in the dosage form.

***In vitro* dissolution studies**

The comparative *in vitro* drug release profile for 12 h of all the formulations (fig. 5) OFT-1(98.4%),OFT-2(86.4%),OFT-3(84.8%), OFT-4(76.8%),OFT-5(94.1%),OFT-6 (88.4%), OFT-7(83.9%), OFT-8 (101.1%) showed extended drug release at the end of 12h in the simulated stomach pH conditions.

Drug release kinetic studies

In order to establish the mechanism of drug release, the experimental data were fitted into various kinetic models. It was observed that the highest correlation was found for the first order and Korsmeyer equation which indicated the drug release occurred by diffusion mechanism. Release of drug from matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending upon the concentration [17, 18]. The correlation values of the first-order equation of all formulations were found to be in the range 0.9327 to 0.9957. To confirm the diffusion mechanism, the data were fitted into Korsmeyer equation. All the formulations showed the 'n' value between 0.3 to 1; signifying non-fickian diffusion table 5 i.e.; the drug diffuses partly through the swollen matrix and gradually expanding hydrated matrix with increasing diffusion path length.

Optimized formulation (RFT)

Predicted vs. experimental values of optimized RFT formulation has been reported in table 6. The values of pre-compression and post-compression parameters of the RFT formulation were found to be within the IP limits. The floating lag time and percentage drug release in 12 h. were found to be 160 sec. and 100 % respectively which was comparable with the predicted results obtained from the Design Expert software. The release rate followed the non-fickian diffusion mechanism as its "n" value was found to be 0.5423with best fit model as a matrix type.

Table 5: Formulation drug release kinetics model

Code	Kinetic models										
	Zero-order plot		First-order plot		Matrix plot		Korsmeyer peppas			Hix. crow plot	
	r^2	K	r^2	K	r^2	K	r^2	N	K	r^2	K
OFT-1	0.976	8.006	0.989	-0.148	0.970	-0.148	0.998	0.763	13.417	0.997	-0.0039
OFT-2	0.933	6.957	0.986	-0.110	0.981	20.258	0.973	0.527	18.840	0.979	-0.0313
OFT-3	0.953	7.051	0.992	-0.112	0.961	20.392	0.965	1.055	6.735	0.984	-0.0317
OFT-4	0.958	6.197	0.995	-0.099	0.979	17.965	0.992	0.688	12.172	0.988	-0.0265
OFT-5	0.756	7.365	0.932	-0.122	0.958	21.788	0.911	0.322	30.541	0.907	-0.0339
OFT-6	0.981	6.989	0.995	-0.113	0.958	20.067	0.997	0.853	9.679	0.9923	-0.0317
OFT-7	0.975	6.701	0.994	-0.104	0.948	19.218	0.994	1.044	6.353	0.9926	-0.0297
OFT-8	0.986	8.117	0.981	-0.156	0.955	23.261	0.996	0.883	10.564	0.9955	-0.0407

Table 6: Generalized optimization solution data predicted vs. actual

Number	HPC	Xanthan gum	Sodium bicarbonate	Cumulative %drug release 12h	Floating lag time (sec)
1	50	55.55	100	99.99	145.696
2	50	55.24	98.64	99.95	146.952
3	50	54.49	100	99.99	148.021
4	50	50	88.36	99.96	156.72
5	50	50	74.34	99.066	169.344
RFT (Experimental)	50	55	100	100.55	160

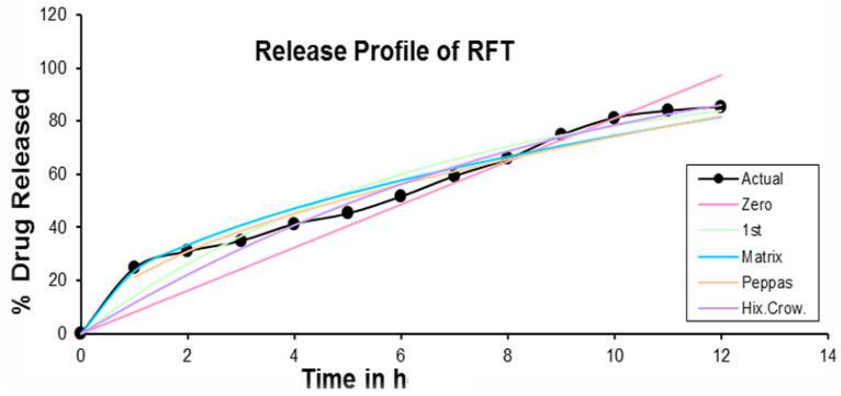

Fig. 6: *In vitro* drug release kinetics of RFT formulation

CONCLUSION

The development of optimized buoyant tablets of ktz with an increase in solubility and dissolution profile with extended drug release for a period of 12 h in simulated stomach pH conditions could be successfully achieved. The results opens a new insight about using the design of formulation softwares by providing polymer manipulations necessary to optimize formulation variables to obtain the desired outcome with respect to drug release, floating time or any other parameters.

The net result of this research work was the formulation of a stable, floating Ktz formulation with 12 h *in vitro* drug release which may be tested for *in vivo* bioavailability studies in suitable animal models.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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