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Formulation and evaluation of atazanavir sulphate floating matrix tablets

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ABSTRACT

Atazanavir Sulphate is a highly selective inhibitor of HIV protease and the 7th protease inhibitor for HIV treatment is formulated as floating matrix tablets, sustained its release for a period of more than 12 hours. Atazanavir Sulphate formulated using three different grades of HPMC polymer such as K4M, 15M, and K100M for retardation and sodium bicarbonate for tablet to remain buoyant for duration of release. A total of 18 formulations were prepared changing concentration of polymers and sodium bicarbonate. Of all formulations, F4 formulation shows optimized results following zero order kinetics and regression values nearer to 1, best fitted with Korsmeyer-Peppas model.

Keywords: Gastric Residence Time (GRT), Narrow Absorption Window (NAW), Gastric Residence Dosage Form (GRDF), Floating Drug Delivery System (FDDS), Gastro-Intestinal Tract (GIT)

INTRODUCTION

The oral route is the predominant and most preferable route for drug delivery, but drug absorption is unsatisfactory and highly variable in the individuals despite excellent in vitro release patterns. The major problem is in the physiological variability such as gastrointestinal transit as well as gastric residence time (GRT); dominate in overall transit of the dosage forms. GRT of the oral controlled release system is always less than 12 h [1].

There are numerous drugs that demonstrate poor efficacy and bioavailability when administered via the oral route. Such drugs include those that a) act locally within the stomach (e.g. amoxicillin), b) are absorbed within the stomach or specific regions of the upper intestine (e.g. furosemide), c) are unstable in intestinal fluids (e.g. captopril) and d) are poorly soluble within the alkaline environment of the intestine (e.g. diazepam). A significant factors leading to the poor bioavailability of numerous drugs is due to their narrow absorption window (NAW), most commonly located in the upper region of the small intestine i.e. the duodenum and jejunum. These segments of the small intestine posses extensive drug absorptive properties and absorption of NAW drugs is limited due to the rapid transport of drug past these regions. Therefore, this has led to researchers exploring the possibilities of extending the gastric residence time (GRT) of the drug and therefore

indirectly prolonging the time, for maximal site-specific absorption [2].

One of the most feasible approaches for gastrointestinal tract (GIT) is to control GRT using Gastric Residence Dosage Form (GRDF) that will provide us with new and important therapeutic options. GRDF are designed on the basis of one of the several approaches like formulating low density dosage form that remain buoyant above the gastric fluid (FDDS) or high density dosage form that is retained at the bottom of the stomach, imparting bio-adhesion to the stomach mucosa, reducing motility of the GIT by concomitant administration of drugs or pharmaceutical excipients, expanding the dosage form by swelling or unfolding to a large size which limits the emptying of the dosage form through the polymeric sphincter, utilizing ion–exchange resin which adheres to mucosa, or using a modified shape system [3, 4].

Floating Systems

The concept of FDDS came into discussion to overcome the difficulty, while swallowing medicinal pills experiencing gagging or choking in patients. These observations suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml so that pill will float on water surface.

Based on the mechanism of buoyancy, two distinctly different technologies, i.e., non effervescent and effervescent systems have been utilized in the development of FDDS.

Atazanavir Sulphate is a highly selective inhibitor of HIV protease and the 7th protease inhibitor approved for HIV treatment. Atazanavir is available as 200mg, 150mg and 100mg twice daily capsules. Oral bioavailability of the drug is 69% at fasting state. Its t1\2 ranges from 5-7hr. As the pH increases, the solubility of Atazanavir Sulphate decreases, leads to poor absorption in the intestine. To improve the absorption of Atazanavir Sulphate, in stomach and to reduce dosing frequency, Atazanavir can be formulated into the floating drug delivery system as matrix tablet formulations of Atazanavir Sulphate using various low-density polymers [5].

MATERIALS & METHODS

Atazanavir Sulphate, a drug, HPMC, a polymer, Sodium bicarbonate and all other chemicals used in formulation obtained from Hetero Labs, Hyderabad, Telanaga.

Methodology

Preparation of Atazanavir Sulphate Floating Matrix Tablets

Atazanavir Sulphate tablets were formulated by direct compression method. The drug powder, polymers (HPMC K4M, HPMC K 15M, HPMC K100M), sodium bicarbonate (20%), lactose were blended thoroughly with mortar and pestle [6]. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. The required amount of the blend was weighed and finally this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 10-mm standard flat-face punches.

Table 1: Formulation Composition for Floating Matrix Tablets of Atazanavir Sulphate

S.No	Formulation	Atazanavir Sulphate	HPMC K4M	HPMC K15M	HPMC K100 M	SBC	Lactose	Talc	Mg Stearate
1	F1	150	52.5			70	70.5	3.5	3.5
2	F2	150	42			70	81	3.5	3.5
3	F3	150	28			70	95	3.5	3.5
4	F4	150	28			80	85	3.5	3.5
5	F5	150	28			90	75	3.5	3.5
6	F6	150	21			70	102	3.5	3.5
7	F7	150	21			80	92	3.5	3.5

8	F8	150	21			90	82	3.5	3.5
9	F9	150	14			70	109	3.5	3.5
10	F10	150		52.5		70	70.5	3.5	3.5
11	F11	150		42		70	81	3.5	3.5
12	F12	150		28		70	95	3.5	3.5
13	F13	150		21		70	102	3.5	3.5
14	F14	150		14		70	109	3.5	3.5
15	F15	150			42	70	81	3.5	3.5
16	F16	150			28	70	95	3.5	3.5
17	F17	150			21	70	102	3.5	3.5
18	F18	150			14	70	109	3.5	3.5

Drug= Atazanavir Sulphate; HPMC= Hydroxy Propyl Methyl Cellulose;
SBC=Sodium Bi-Carbonate; MCC= Microcrystalline cellulose.
Lactose and MCC was used as filler in formulations F1 to F19.
All the numerical values were expressed in mg [6].

Evaluation of Tablets

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Tablet Thickness

The thickness in millimeters (mm) was measured individually for 10 tablets by using vernier calipers. The average thickness and standard deviation were reported.

Weight Variation

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Table 2: Weight Variation Standard Test Values

Average weight (mg)	% Deviation
130 or less	10
130-324	7.5
More than 324	5

Hardness of Tablets

Ten tablets were measured in the hardness examination. Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

Friability of Tablets

Twenty tablets of the formulation were weighed and measured in a Roche Friabilator. The tablets were rotated at 25rpm for 4min, and the samples were then reweighed. The percentage friability was calculated using the equation

$F\% = (W1-W2)/W1 \times 100$

Where F% represents the percentage weight loss;
W1 and W2 are the initial and final tablets weights.

Content Uniformity

Ten tablets were weighed and triturated to fine powder. Weight equivalent to 10 mg of Atazanavir Sulphate was dissolved in 10 ml of 0.1 N HCl and agitated for 15 min, the volume was adjusted to 100 ml using 0.1 N HCl with continuous agitation for

5min. The solution was filtered and suitable dilutions were prepared with 0.1 N HCl. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 301nm by using UV-Visible spectrophotometer [7].

The Floating Lag Time and the Total Floating Time

This test was characterized by floating lag time and total floating time. The test was performed using USP XXIII type II paddle apparatus using 900 ml of 0.1 N HCl at paddle rotation of 50 rpm at 37 ± 0.5o C. The time required for tablet to rise to surface of dissolution medium and duration of time, the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

Water Uptake Studies

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at 37o + 0.5oc, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU)

$\%WU = (W_t - W_o) * 100 / Wo$

Where W_t is the weight of the swollen tablet;

W_o is the initial weight of the tablet [8].

Drug–Excipients Compatibilty Studies

Compatibility of the drug in the formulation, drug–excipient interaction studies was performed. The infrared spectra of pure drug, physical mixture of drug and excipients, were recorded in the range of 4000 to 400 cm^{-1}on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

Dissolution Studies

Apparatus: Dissolution test apparatus (USP XXIII)
Method: USP type 2 apparatus (paddle method)
Dissolution medium: 0.1N HCl
Volume: 900 ml
Temperature: 37 + 0.5 ºC
Speed: 50 rpm

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 30min, 1, 2, 3, 4, 6, 8, 10 and 12h. The volume of dissolution fluid adjusted to 900 ml by replacing, 5ml of dissolution medium after each sampling. The release studies were conducted with 3 tablets & the mean values were plotted against time. Each sample was analyzed at 301 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve [9, 10].

Mechanism of Drug Release

The kinetics of Atazanavir Sulphate tablets formulations were determined by finding the best fit of the release data to zero order, first order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas plots.

Zero Order Release Rate Kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F= K_o.t$

Where ‘F’ is the drug release, ‘K’ is the release rate constant and‘t’ is the release time.

The plot of % drug release versus time is linear.

First Order Release Rate Kinetics

Release rate data are fitted to the following equation

$Log (100-F) = kt$

A plot of log % drug release versus time is linear.

Higuchi Release Model

According to this model, drug release was described as a square root of time-dependent diffusion process based on Fick’s law.

$Qt = KH\ t_{1/2}$

Where KH is Higuchi’s rate constant;

Qt is the amount of drug released at time t.

If a plot of square root of time *vs* cumulative amount of drug released yields a straight line, then the particular dosage form is considered to follow Higuchi kinetics of drug release

Korsmeyer and Peppas Release Model

Korsmeyer and Peppas Release Model is a simple, semi-empirical, relating exponentially the drug release to the lapsed time.

$Qt /Q\infty = K.tn$

Where, Q_t /Q_∞ is the fraction of drug released,

‘K’ is the release constant;

‘t’ is the release time;

‘n’ is diffusion exponent

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the

release is through anomalous diffusion or non-fickian diffusion (Swellable & Cylindrical Matrix).
In this model, a plot of log (Q_t/Q_∞) *vs* log (time) is linear.

In-Vivo Confirmation of Buoyancy by using Radiographic Studies

For this study, the tablets were prepared by replacing half of the amount of drug with barium sulfate. After overnight fasting of three healthy volunteers, they were fed with low calorie food and allowed to take water after these tablets were administered orally. Radiographs were obtained at 0.5, 1, 2, 3, 4 and 6 h. Over these periods, volunteers were allowed to take water [11, 12].

RESULTS & DISCUSSION

The fabricated matrix tablets of Atazanavir Sulphate were evaluated for their physical characteristics such as weight variation, hardness, thickness, friability, drug content, buoyancy. The weight variations of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 324mg (Table 3). Weight of the tablet was fixed at 350 mg and the weight variation for every batch was tested and found within the acceptance limits.

Hardness of the tablet was fixed 4 kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release. The thickness of floating tablets linearly correlated with the weight of the tablets. Friability test of all the formulations was found satisfactory. Drug content uniformity and floating capacity of fabricated tablets in all formulations was calculated and the results are presented in Table 3.

Table 3: Evaluation of Physical Parameters of Floating Tablets

Formula code	Weight variation(mg)	Hardness kg/cm2	Thickness(mm)	Friability (%)	Lag time (sec)	Total floating time (h)	Drug Content (%)
F1	347±2.3	4±0.5	3.21±0.08	0.26	118	>12	97.32±2.3
F2	351±3.8	4±0.5	3.23±0.06	0.23	148	>12	98.56±2.0
F3	356±4.5	4±0.3	3.21±0.06	0.48	290	>12	98.21±1.8
F4	351±8.3	4±0.5	3.22±0.09	0.51	85	>12	95.91±1.5
F5	345±5.3	4±0.2	3.26±0.08	0.22	54	6	97.75±2.3
F6	349±2.3	4±0.5	3.21±0.05	0.41	>300	6	96.25±1.8
F7	353±5.5	4±0.5	3.24±0.05	0.35	139	6	97.48±2.8
F8	344±5.6	4±0.2	3.28±0.02	0.38	103	4	97.69±2.4
F9	348±3.3	4±0.5	3.23±0.02	0.41	-	-	97.35±1.7
F10	346±6.2	4±0.3	3.21±0.16	0.29	98	>12	96.55±2.4
F11	351±4.3	4±0.5	3.28±0.05	0.38	103	>12	94.48±1.8
F12	349±2.3	4±0.4	3.19±0.09	0.41	112	>12	95.42±.09
F13	345±2.9	4±0.5	3.29±0.05	0.52	169	>12	95.99±1.3
F14	348±8.3	4±0.5	3.26±0.02	0.34	-	-	98.91±2.8
F15	353±3.8	4±0.4	3.23±0.02	0.45	52	>12	98.46±3.2
F16	346±4.9	4±0.3	3.27±0.02	0.25	67	>12	97.41±2.1

F17	349±8.3	4±0.1	3.23±0.02	0.28	79	>12	97.97±2.6
F18	347±6.33	4±0.7	3.28±0.02	0.38	>200	6	98.91±2.8

The results of percentage swelling obtained from the water uptake studies of the formulations containing HPMC K4M were shown in table 4 and 5 and HPMC K100M in table 6.

The swelling index of the tablets increases with an increase in the polymer viscosity grades as shown in figure 1-3.

Table 4: Percentage Swelling Index of Formulations with HPMC K4M

Time (Hr)	F1	F2	F3	F4	F5
1	16.97±0.30	14.05±0.69	14.87±0.94	13.87±0.28	13.62±0.86
2	22.47±0.02	21.25±0.38	22.73±0.92	25.01±0.10	23.54±0.31
3	48.34±0.31	47.60±0.66	35.68±0.53	38.21±0.33	35.27±0.15
4	69.19±0.66	60.67±0.82	55.39±0.35	50.08±0.66	53.13±0.35
6	80.83±0.33	74.51±0.33	67.33±0.71	69.86±0.66	60.32±1.18
8	75.59±0.66	71.97±0.98	64.69±0.53	66.87±0.98	21.91±0.15
10	71.20±0.66	71.17±1.02	63.93±0.88	65.28±0.50	
12	70.99±0.82	66.78±0.33	57.29±0.53	59.94±0.83	

Data represents mean ± SD (n=3)

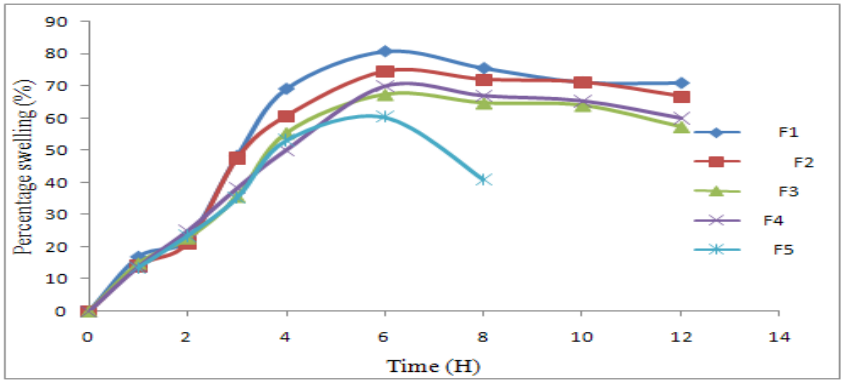

Figure 1: Percentage Swelling of HPMC K4M *Vs* Time

Table 5: Percentage Swelling of Formulations with HPMC K15M

Time(Hr)	F10	F11	F12	F13	F14
1	16.97±0.30	14.05±0.69	14.87±0.94	13.87±0.28	10.62±0.86
2	22.47±0.02	21.25±0.38	19.73±0.92	18.01±0.10	15.54±0.31
3	48.34±0.31	47.60±0.66	44.68±0.53	38.21±0.33	20.27±0.15
4	69.19±0.66	60.67±0.82	58.39±0.35	56.08±0.66	31.13±0.35
6	81.83±0.33	74.51±0.33	70.33±0.71	65.86±0.66	45.32±1.18

8	79.59±0.66	72.97±0.98	68.69±0.53	62.87±0.98
10	76.20±0.66	68.17±1.02	66.93±0.88	61.28±0.50
12	70.99±0.82	64.78±0.33	60.29±0.53	57.94±0.83

Data represents mean ± SD (n=3)

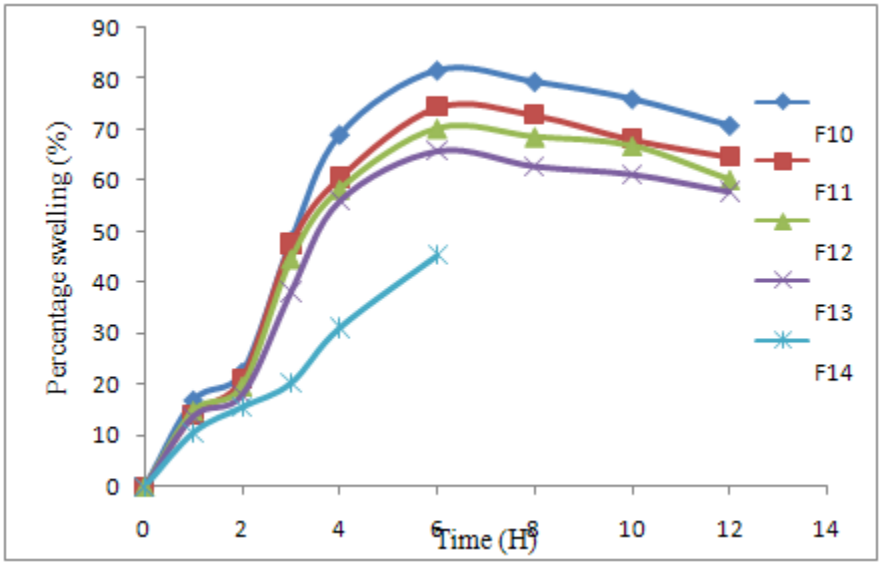

Figure 2: Percentage Swelling of HPMC K15M Vs Time

Table 6: Percentage Swelling of Formulations with HPMC K100M

Time(h)	F15	F16	F17	F18
1	25±0.65	21.50±0.34	18.33±0.90	10.62±0.86
2	36.24±0.34	31.17±0.87	22.17±0.67	15.54±0.31
3	69.50±0.98	64.67±0.71	59.67±1.45	20.27±0.15
4	87.00±0.78	78.17±0.61	66.50±1.56	39.13±0.35
6	96.50±0.65	84.67±0.85	72.83±0.34	48.32±1.18
8	80.17±2.34	76.67±1.45	68.00±0.67	51.91±0.15
10	76.83±0.92	74.50±0.64	68.33±0.81	
12	70.50±1.32	64.50±0.78	62.33±0.64	

Data represents mean ± SD (n=3)

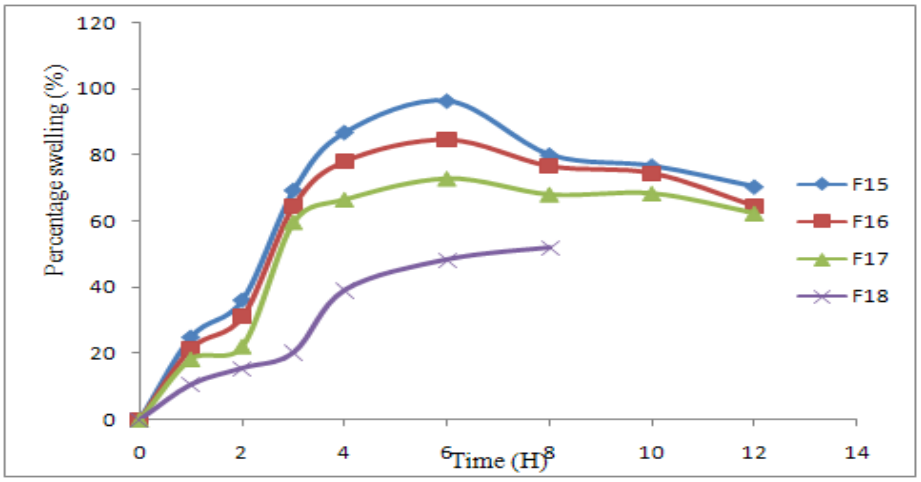

Figure 3: Percentage Swelling of HPMC K100M *Vs* Time

The *in vitro* dissolution testing was performed and the results of the formulations were expressed in tables 7, 8, 9 and10.

In vitro dissolution study of formulations F1, F2, F3 , F4 and F5 were done in 0.1 N HCl and the Percent of drug release from formulations F1, F2, F3, F4 and F5 was 61.79, 69.85, 82.43, 89.43 and 94.07 in 12 hours respectively. The formulations F3, F4 and F5 are formulated by varying the concentrations of sodium bicarbonate. When the sodium bicarbonate concentration was 80 mg (F4), the tablet float immediately and release was good.

Table 7: Percentage Drug Release of Formulations with HPMC K4M

Time(h)	F1	F2	F3	F4	F5
1	5.4±0.30	6.51±0.69	11.28±0.94	9.3±0.28	9.08±0.86
2	10.92±0.02	10.56±0.38	20.96±0.92	13.97±0.10	14.48±0.31
4	17.82±0.66	13.45±0.82	44.82±0.35	21.77±0.66	22.75±0.35
6	22.41±0.33	21.08±0.33	58.81±0.71	40.5±0.66	43.28±1.18
8	39.21±0.66	42.42±0.98	68.87±0.53	61.71±0.98	69.42±0.15
10	50.35±0.66	51±1.02	76.96±0.88	78.43±0.50	85.92±0.35
12	61.71±0.82	69.85±0.33	82.43±0.53	89.43±0.83	94.07±1.18

Data represents mean ± SD (n=3)

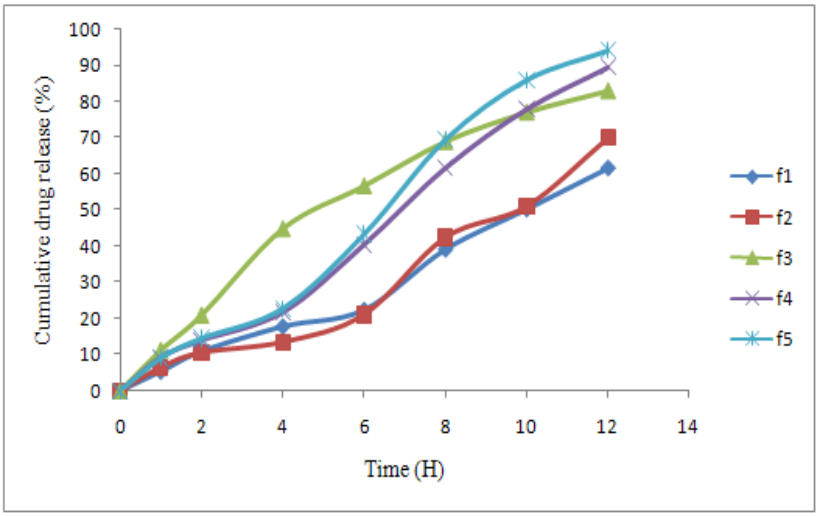

Figure 4: Percent Drug Release of HPMC K4M *Vs* Time

Formulations F6, F7, and F9 are prepared, but the floating tablets could not retain its physical integrity for desired period of time. At higher sodium bicarbonate concentration, formulation F8 shows higher drug release.

Table 8: Percent Drug Release of Formulations with HPMC K4M

Time(H)	F6	F7	F8	F9
1	38.14±0.20	7.2±0.96	11.01±0.49	44.34±0.81
2	56.35±0.80	26.57±0.36	16.28±0.92	57.85±0.10
4	70.78±0.61	49.9±0.84	25.15±0.33	83.5±0.67
6	82±0.39	68.14±0.34	52.28±0.77	85.5±0.63
8	89.35±0.67	76.9±0.99	71.78±0.53	94.7±0.97
10	90±0.69	89.35±1.02	94.71±0.88	96.87±0.50
11	94.07±0.86	94.5±0.33	92.71±0.53	94.07±0.89

Data represents mean ± SD (n=3)

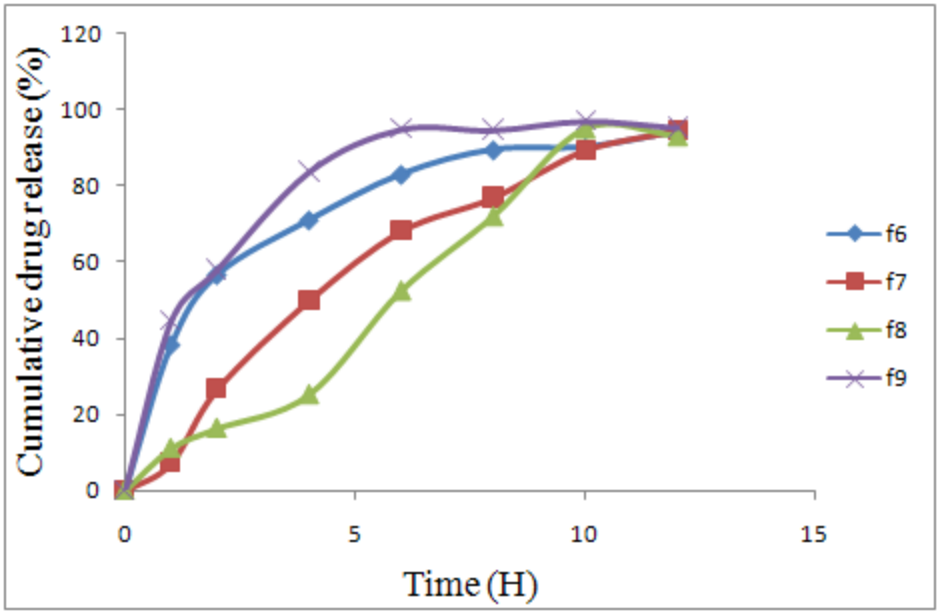

Figure 5-Percentage Drug Release of HPMC K4M Vs Time.

The *in vitro* dissolution studies for the formulations F10, F11, F12, F13 and F14 prepared with HPMC K15M were done in 0.1N HCl and the percent of drug release from formulation F10, F11, F12, F13 was 51.29, 55.97, 74.05, 78.96 in 12 hours respectively (Figure 6). Formulation F13 has shown maximum drug release in 12 hours with floating lag time of 169 seconds.

Table 9: Percentage Drug Release of Formulations with HPMC K15M

Time (h)	F10	F11	F12	F13	F14
1	4.05±0.01	6.64±0.17	9.05±0.45	9.77±0.78	32.77±0.25
2	5.59±0.15	10.77±0.41	12.40±0.46	16.28±0.33	38.48±0.69
4	11.62±2.56	13.73±0.03	22.65±0.30	33.85±0.39	71.68±5.34
6	15.76±0.79	19.61±0.61	37.78±0.65	46.92±0.62	85.64±0.62
8	19.37±3.54	28.09±0.77	53.53±0.70	55.92±0.70	90.29±0.70
10	36.32±0.91	38.26±2.15	64.72±2.5	68.67±2.5	94.10±2.5
12	51.29±1.23	55.97±0.61	74.05±0.78	78.96±0.78	93.67±0.78

Data represents mean ± SD (n=3)

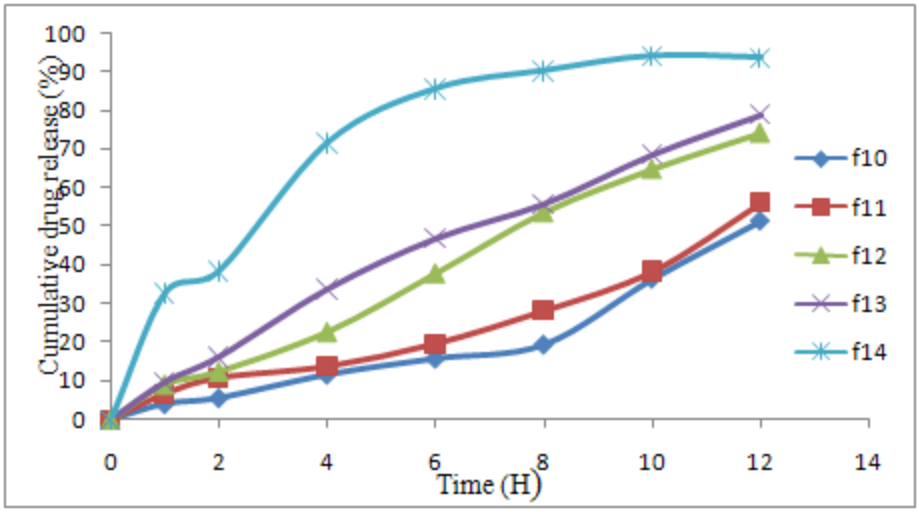

Figure 6: Percentage Drug Release of HPMC K15M Vs Time

The *in vitro* dissolution studies for the formulations F15, F16, F17 and F18 prepared with HPMC K100M were done in 0.1N HCl and the percent of drug release from formulation F15, F16, F17 was 43.3, 51.25, 69.46 in 12 hours respectively (Figure 7). Formulations floated for 12 h. As the concentration of the polymer is decreased, the amount of drug release also increases.

Table 10: Percentage Drug Release of Formulations with HPMC K100M

Time (h)	F15	F16	F17	F18
1	4.3±1.19	6.29±0.66	6.51±0.84	31.70±0.25
2	5.73±0.03	9.16±0.71	11.0±0.61	44.95±0.69
4	9.23±7.57	10.64±1.30	17.64±0.31	72.53±5.34
6	11.39±2.30	13.94±1.40	33.00±0.78	84.04±0.62
8	14.84±0.53	17.41±1.40	45.51±1.09	86.67±0.70
10	24.37±1.69	29.53±2.02	59.53±1.09	92.08±2.5
12	43.3±0.30	51.25±0.27	69.46±0.78	94.69±0.78

Data represents mean ± SD (n=3)

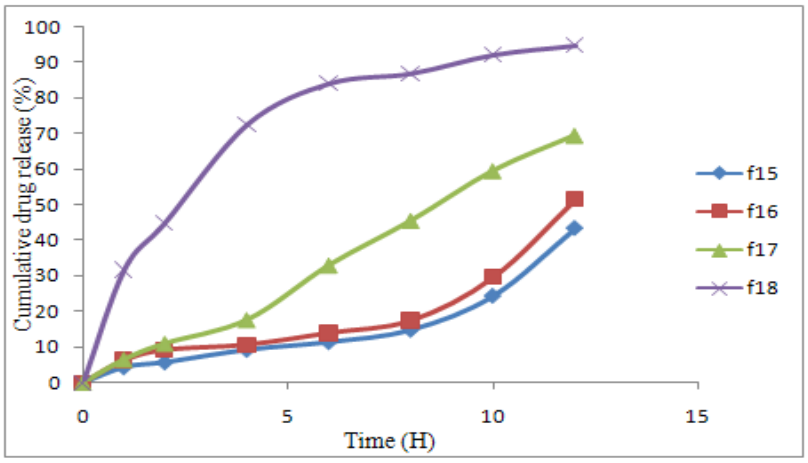

Figure 7: Percentage Drug Release of HPMC K100M Vs Time

The regression coefficient (R^2) values of drug release data of all formulations obtained by curve fitting method for zero order, first-order, and Higuchi and Krosmeyer-Peppas model are reported in Table 11. The n value of optimized formulation F4 is 0.832 by Krosmeyer-Peppas. This indicates that the drug release mechanism is of non-fickian diffusion. The R^2 value for F4 formulation is nearer to 1, which implies the drug release is of zero-order.

Table 11: Release Kinetics of Optimized Formulations

Formulation	Zero order	First order	Higuchi	Krosmeyer & Peppas	Peppas (n)
F4	0.985	0.957	0.940	0.842	0.832
F1	0.991	0.943	0.963	0.941	0.807

The possible chemical interaction of drug with the excipients was analysed by FTIR studies. Figure 8, shows the IR spectra of Atazanavir Sulphate, HPMC K4M, and the F3 formulation. Pure drug shows a characteristic peak at 1699.29, 1674.21, 1651.07 cm^{-1}. HPMC K4M show important bands at 1456.26 and 1417.68 cm-1, respectively.

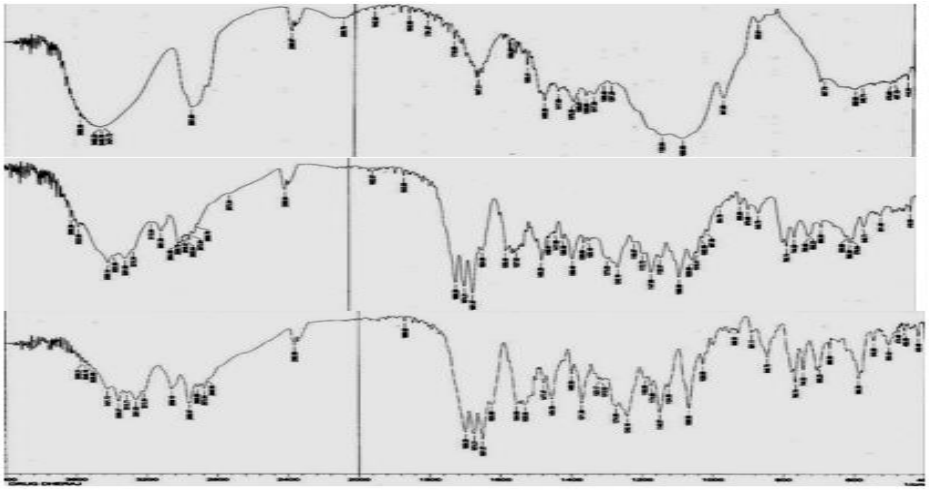

Figure 8: FTIR Studies of Atazanavir Sulphate, Polymer and F4 Formulation

The *in vivo* behavior of the tablets is observed in the radiographic pictures at different time intervals in healthy volunteers, confirm the *in vivo* buoyancy in the stomach is for 300±33.65 min (n=6).

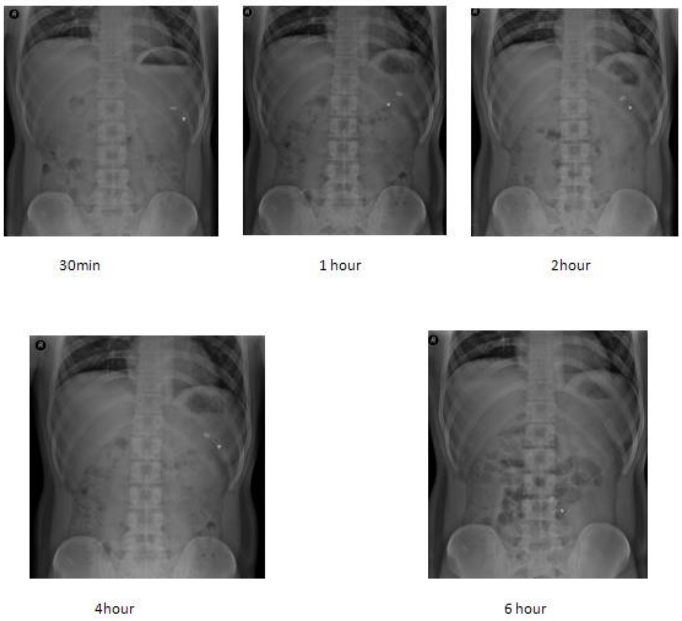

Figure 8: Radiographic Images of Tables at 0.5, 1, 2, 4, 6 hours respectively

CONCLUSION

The Atazanavir Sulphate floating tablets were successfully formulated and evaluated. The addition of gel-forming polymer HPMC (K4M) and gas-generating agent sodium bicarbonate were provided the sustained drug release and buoyancy. The FTIR results showed there were no excipient interactions. The formulated tablets showed uniformity of weight, hardness, friability, drug content were all lying within the limits. The tablets could float within 3min and maintained for more than 12 h. The drug release at 12 h was more than 85%. *in-vivo* studies showed that the tablet was retained in stomach for 6 hours. F4 formulation showed following zero order kinetics and regression values nearer to 1, best fitted with Korsmeyer-Peppas model.

REFERENCES

[1]. Mathiowitz, E., Chickering, De III and Lehr, C.M. Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches, and Development Marcel Dekker, 1999, 477-505. https://www.crcpress.com/Bioadhesive-Drug-Delivery-Systems-Fundamentals-Novel-Approaches-and-Development/Mathiowitz-III-Lehr/p/book/9780824719951

[2]. Benn, A., Cooke, W.T. Intraluminal pH of Duodenum and Jejunum in Fasting Subjects with Normal and Abnormal Gastric or Pancreatic Function. *Scandinavian and Journal of Gastroenterology*, 6, 1971, 313–317. https://www.ncbi.nlm.nih.gov/pubmed/5561176

[3]. Charman, W.N., Porter, J.H., Mithani, S and Dressman, J.B. Physicochemical and Physiological Mechanisms for the Effects of Food on Drug Absorption: The Role of Lipids and pH. *Journal of Pharmaceutical Sciences*, 86 (3), 1997, 269–282. https://doi.org/10.1021/js960085v

[4]. Chen, J., Park, H and Park, K. Synthesis of superporous Hydrogels: Hydrogels with Fast Swelling and Superabsorbent Properties. *Journal of Biomedical Materials Research*, 44, 1999, 53-62. https://doi.org/10.1002/(SICI)1097-4636(199901)44:1<53::AID-JBM6>3.0.CO;2-W.

[5]. Gangadharappa, H.V., Rahamath-Ulla, M., Pramod Kumar, T.M and Shakeel, F Floating Drug Delivery System of Verapamil Hydrochloride using Karaya gum and HPMC. *Journal of Clinical Research and Regulatory Affairs*, 23(1), 2010, 13-20. https://www.tandfonline.com/doi/abs/10.3109/10601331003604762

[6]. Hao, Z., Xuetao, J., Lingshan, K and Shen, G Design and Evaluation of a Dry Coated Drug Delivery System with Floating–Pulsatile Release. *Journal of Pharmaceutical Sciences*, 97, 2008, 263–273. https://doi.org/10.1002/jps.21083

[7]. Gan-Lin, C., Wei-Hua, H *In Vitro* Performance of Floating Sustained-Release Capsule of Verapamil Drug. *Development and Industrial Pharmacy*, 24(1), 1998, 1067-1072.

[8]. Dasharath, M. Patel., Natvarlal, M. Patel., Nitesh, N. Pandya and Pranav, D. Jogani Gastroretentive Drug Delivery System of Carbamazepine: Formulation Optimization using Simplex Lattice Design: A Technical Note. *AAPS PharmSciTech*, 8 (1), 2007, 82-86. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2750446/

[9]. Hilton, A.K., Deasy P.B *in vitro* and *in vivo* evaluation of an oral Sustained-Release Floating Dosage Form of Amoxycillin Trihydrate. *International Journal of Pharmacy*, 86(1), 1992, 79–88. https://doi.org/10.1016/0378-5173 (92), 90033-X

[10]. Ina, K., Roland, B (1999) Floating or Pulsatile Drug Delivery Systems based on Coated Effervescent Cores. *International Journal of Pharmaceutics*, 187, 175–184. https://www.ncbi.nlm.nih.gov/pubmed/10502623

[11]. Jain, S.K., Awasthi, A.M., Jain, N.K and Agrawal, G.P Calcium Silicate based Microspheres of Repaglinide for Gastro Retentive Floating Drug Delivery: Preparation and vitro characterization. *Journal of Control Release*, 107, 2005, 300-309. https://www.ncbi.nlm.nih.gov/pubmed/16095748

[12]. Kalpana, S., Satyanarayan, P., Subrata, M., and Korla Appana, C Influence of Hydroxypropyl Methyl Cellulose on Drug Release Pattern of a Gastroretentive Floating Drug Delivery System using a 3^2 Full Factorial Design. *Pharmaceutical Development and Technology*, 14(2), 2009, 193–198. https://doi.org/10.1080/10837450802498902