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Formulation Development and Characterization of Atazanavir Sulphate Controlled Release Non-Effervescent Floating Matrix Tablets

[1, 2] Someshwar Komati*, [1] Vishali Dasi, [1, 3] Rajendra Kumar Jadi, [4] Narayana Raju Padala

[1] KLR Pharmacy College, Paloncha, Khammam - 507 115, TS, India

[2] Department of Pharmaceutics, University College of Pharmaceutical Sciences, Palamuru University, Bandameedipally, Mahabubnagar – 509 001, TS, India

[3] Department of Pharmaceutics, Anurag Group of Institutions, School of Pharmacy, Venkatapur, Medchal, Hyderabad – 500 088, TS, India

[4] Department of Pharmaceutics, Sri Vasavi Institute of Pharmaceutical Sciences, , Tadepalligudem, West Godavari - 534 101, AP, India.

ABSTRACT

The objective of the present work to develop extended-release floating matrix tablets of Atazanavir (ATZ), which were designed to prolong the gastric residence time and drug release after oral administration. Different grades of ethyl cellulose (i.e. EC N20, EC N22, EC N45, EC N50, EC N100 etc.,) as floating aids and Hydroxypropyl methylcellulose (i.e. HPMC K100M) were used to get the desired floating and prolonged release profile over an extended period. All the formulations extended the drug release up to 24 hours and more and the formulations were optimized based on the all physicochemical properties. The drug release and floating property depended on the floating aid, polymer type, and their proportions.. The formulation prepared with EC and HPMC K100M has more floating time than the formulation prepared with the EC alone. The optimized formulation (F10) prepared with a combination of EC N100 and HPMC K100M was evaluated for *In vivo* radiographic study, which shows the floating property for up to 9 hours. The DSC study shows that there is no drug-polymer interaction. This study gives the preliminary idea about the development of the floating drug delivery systems of Atazanavir without the use of a gas generating agent.

Keywords: Non-effervescent, extended-release, gastric residence time, buoyancy, floating aid.

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***Address for Correspondence:**

Someshwar Komati, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Palamuru University, Bandameedipally, Mahabubnagar- 509 001, TS, India

INTRODUCTION

The oral route is considered as the most promising route of drug delivery[1]. But most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach [2]. This leads to incomplete absorption of drugs having an absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed[3]. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed [4]. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time[5]. To date, their usefulness is limited to systemic administration. So, to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development[6]. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and minimum values, below which the drug is no longer effective [7-11].

The main aim and object of this present work is to formulate non-effervescent extended-release floating matrix tablets using different polymeric concentrations and evaluating all formulations and notifying the optimized formulation.

MATERIAL AND METHODS

MATERIALS

ATZ sulfate was received as a gift sample from Aurobindo Pharma Ltd, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K100M) procured from DOW chemical company, USA. Ethylcellulose (EC) purchased from Aurobindo Pharma Ltd, Hyderabad, India. Magnesium Stearate procured from Himedia Pvt. Ltd., Mumbai and Hydrochloric Acid (HCl) procured from Merck specialties Pvt. Ltd., Mumbai, India.

METHODS

Pre-formulation studies

Pre-formulation is the first step in the rational development of dosage forms. The physical properties of powder mixture were evaluated for the angle of repose (ɵ), Carr's index or compressibility index (%) and Hausner's ratio [12-14].

Table 1: Physicochemical properties of powder blends (F1 to F16)

Formulation code	Angle of repose (ɵ)	Carr's index (%)	Hausner's ratio
F1	27.63±0.35	10.45±0.15	1.08±0.16
F2	26.89±0.28	11.36±0.23	1.20±0.12
F3	23.04±0.61	10.82±0.35	1.06±0.03
F4	25.36±0.29	10.65±0.18	1.04±0.05
F5	24.13±1.30	15.06±0.22	1.03±0.01
F6	26.08±0.83	14.08±0.37	1.02±0.07
F7	25.21±0.64	15.23±0.26	1.03±0.09
F8	28.62±0.48	12.64±0.52	1.05±0.06
F9	30.26±0.09	12.09±0.38	1.08±0.10
F10	29.86±0.73	14.87±0.65	1.16±0.11
F11	27.65±0.91	15.32±0.25	1.12±0.18
F12	26.38±1.30	12.86±0.23	1.06±0.12
F13	25.71±0.83	12.06±0.35	1.23±0.01
F14	24.45±0.64	10.25±0.18	1.06±0.07
F15	28.24±0.09	11.23±0.65	1.05±0.09
F16	26.18±0.73	13.84±0.25	1.02±0.06

Drug excipient compatibility studies

Thermal properties of pure drug and the formulation were evaluated by Differential scanning calorimetry (DSC) using a diamond (DSC) (Mettler Star SW 8.10). The analysis was performed at a rate 5^0C min^{-1} to 200^0C temperature range under a nitrogen flow of 25 ml min^{-1}.

Preparation of ATZ floating matrix tablets

ATZ bisulfate and all other ingredients are accurately weighed and sifted through sieve 44. ATZ sulfate is well mixed with the number of required polymers of different grades (i.e. HPMC and EC) then mixed in geometric proportions. The above powder blend lubricated with magnesium stearate then lubricated blend is subjected to compression by required 8mm circular standard flat-faced punch on a sixteen station Cadmach rotary tablet punching machine.

Evaluation of prepared ATZ floating matrix tablets

The evaluation was performed to assess the physicochemical properties such as tablet thickness (mm), weight variation (mg), tablet hardness (kg/cm^2), friability (%), drug content estimation (%), total floating time (TFT), *in vitro* dissolution studies and kinetics of drug releases[15].

In vitro dissolution studies

The tablet was placed inside the dissolution vessel (USP XXIII) and operated with 50rpm. 5ml of the sample was withdrawn at time intervals of 1hr, 2hr, and 3hr, 4hr, 5hr, 6hr, 7hr up to 24hours. The volume of dissolution fluid adjusted to 900ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 tablets and the mean values were plotted versus time. Each sample was analyzed at 250nm using a double beam UV-Visible spectrophotometer [16].

Drug release kinetics

The cumulative amount of drug released from different matrix tablets (containing different drug and polymer) at different time intervals was fitted to zero-order and first-order kinetics. The data were also subjected to Higuchi's model and diffusion parameters were estimated using Kerseymere's equation[17].

$$M_t/M_\infty = Kt_n$$

In which the value of exponent 'n' is indicative of the mechanism governing the release process of the drug from matrix tablets which are determined by taking log time on the X-axis log % release on the Y-axis

Table 2: Analysis of diffusional drug release

'n' values	Mechanism
0.5	Fickian diffusion
0.5 < n < 1.0	Non – fickian diffusion
1	Case II transport
> 1.0	Super case II transport

RESULTS AND DISCUSSION

Preparation of ATZ standard curve

Initially, the pure ATZ was scanned in the UV-range such as 200-400 nm. The maximum absorbance for ATZ was found at 250nm. A standard concentration of ATZ in the range of 10-70 µg/ml was prepared in 0.1N HCl and the absorbances were measured at 250nm. ATZ is showing good linearity between 10-50 µg/ml with a R^2 of 0.993 (Figure 1).

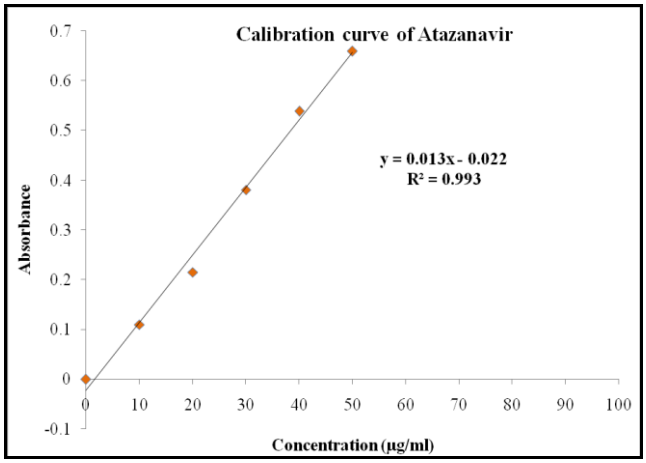


Fig. 1: Standard curve of ATZ sulphate in 0.1N HCl

Prototype formulation development of ATZ floating matrix tablets with EC

The formulation of ATZ with EC was developed with the use of the drug and polymer ratio of (1:1) then pre-lubricated with magnesium stearate. Different grades of the EC used in the above formulations such as EC N20 (F-1), EC N22 (F-2), EC N45 (F-3), EC N50 (F-4) and EC N100 (F-5). To study the floating property, the prepared tablets were placed in 100ml of 0.1N HCl. The tablets were not floated and the tablet remained at the bottom of the glass beaker. This is mainly may be due to the high hardness of the tablets. The tablet was found to be like a tight compact and there are no void spaces for entrapment of the air and water. Based on the above observation, it was decided to reduce the tablet hardness in further formulation. The prepared formulations were evaluated for the floating property. The tablets were found to be floated but it was disintegrated in a short period. That was maybe due to the less hardness of the tablets.

Table 3: Formulation composition of the prepared ATZ Sulphate matrix tablets by the different grades of EC

F CODE	F1	F2	F3	F4	F5
ATZ	100	100	100	100	100
EC N20	100	-	-	-	-
EC N22	-	100	-	-	-
EC N45	-	-	100	-	-
EC N50	-	-	-	100	
EC N100	-	-	-	-	100
Magnesium stearate	2	2	2	2	2
Tablet total weight	202	202	202	202	202

Based on the above observations, further formulations were developed with a combination of EC and HPMC K100M to overcome the above problem. Three different grades were selected based on the viscosity of the polymers such as EC N22, EC N50, and EC N100.

Formulation development of ATZ floating matrix tablets prepared with the combination of different grades of EC and HPMC K100M

Floating matrix tablets of the ATZ were prepared by a combination of different grades of EC (i.e. EC N22, EC N50, and EC N100) and HPMC K100M. The drug and HPMC K100M were mixed and sifted through 44 sieves; the above blend was lubricated with magnesium stearate. The blend was compressed with an 8mm flat-faced punch at hardness around 5-6 kg/cm^2. The tablets were evaluated for various physicochemical parameters and shown in Table 4.

Table 4: Formulation composition of the prepared ATZ floating matrix tablets

F CODE (mg/tablet)	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
ATZ	100	100	100	100	100	100	100	100	100	100	100
EC N22	100	-	-	100	-	-	100	-	-	100	-
EC N50	-	100	-	-	100	-	-	100	-	-	-
EC N100	-	-	100	-	-	100	-	-	100	-	100
HPMC K100 M	25	25	25	50	50	50	75	75	75	40	70
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2
Tablet total weight	227	227	227	252	252	252	277	277	277	242	272

***In vitro* drug release studies of ATZ floating matrix tablets prepared by combination of different grades of EC and HPMC K100M**

The *In vitro* dissolution study shows that the prepared ATZ matrix tablets extend the drug release up to 15 hours. The formulation F6 releases the complete drug in 9 hours. As the EC viscosity increased in the F7 and F8, drug release was extended up to 11-15hrs. The formulation F9 releases the complete drug in 20 hours. As the polymer viscosity increased in the F10, 97% of drug release observed in 24 hours. In formulation F11, prepared by using EC N100, 85% of drug release was observed in 24 hours. In formulation F12, 91% of drug release was observed in 24 hours. As the polymer viscosity increased in the formulation F13, 84% of drug release was observed in 24hrs. Also as the polymer viscosity increased in the formulation F14, 72% of drug release was observed in 24hrs. The *In vitro* dissolution study shows that the prepared matrix tablet extends the drug release up to 24 hours (F15 and F16). As the polymer grade changed in the F16, the drug released was within 24hrs and drug release kinetics of all formulations (F6 to F16) was summarized in table 5.

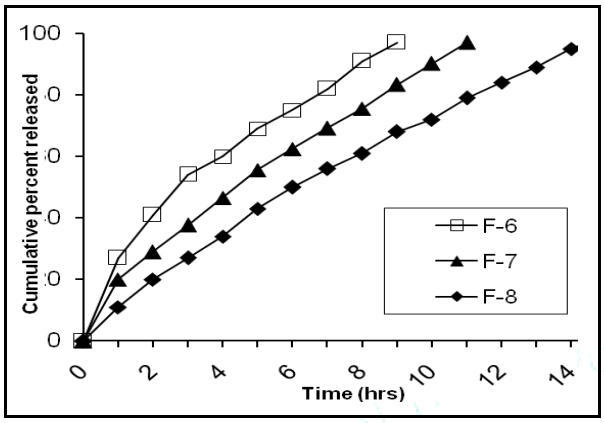


Fig. 2: Dissolution profiles of F6 to F8 formulations

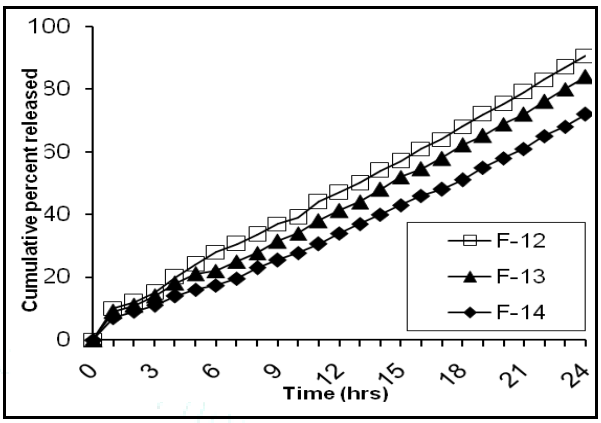


Fig 4: Dissolution profiles of F12 to F14 formulations

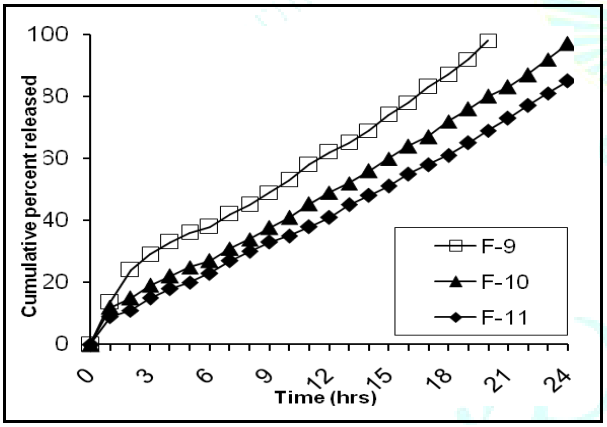


Fig 3: Dissolution profiles of F9 to F11 formulations

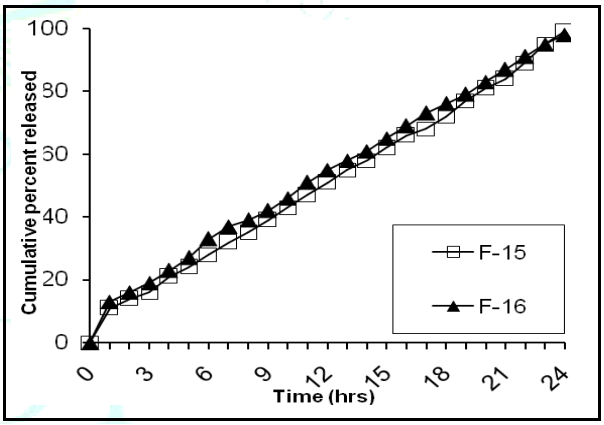


Fig 5: Dissolution profiles of F15 and F16 formulations

Table 5: Release kinetics of formulations prepared with combination of different grades of EC and HPMC K100M

Kinetics	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Zero order (r^2)	0.943	0.982	0.989	0.984	0.996	0.996	0.998	0.997	0.995	0.997	0.996
First order (r^2)	0.895	0.864	0.796	0.778	0.811	0.919	0.905	0.929	0.952	0.722	0.819
Higuchi (r^2)	0.995	0.976	0.997	0.961	0.936	0.932	0.946	0.93	0.919	0.942	0.959
Peppas (n)	0.995	0.671	0.812	0.615	0.71	0.761	0.757	0.766	0.798	0.755	0.7

***In vitro* buoyancy studies**

Based on the *in vitro* drug release and other physicochemical properties F10 formulation was optimized for further study. The tablets were dropped into 100ml of 0.1N HCl taken in 250ml beaker. The tablets were observed for the floating time. Digital photographs were taken at initial, 3 hrs, 6 hrs, 12 hrs, 18 hrs, and 24 hrs. The matrix tablets prepared with the combination of different grades of EC and HPMC K100 M remain floats for about 24hrs and more. Fig. 6 shows the photographs of floating property in the 0.1N HCl.

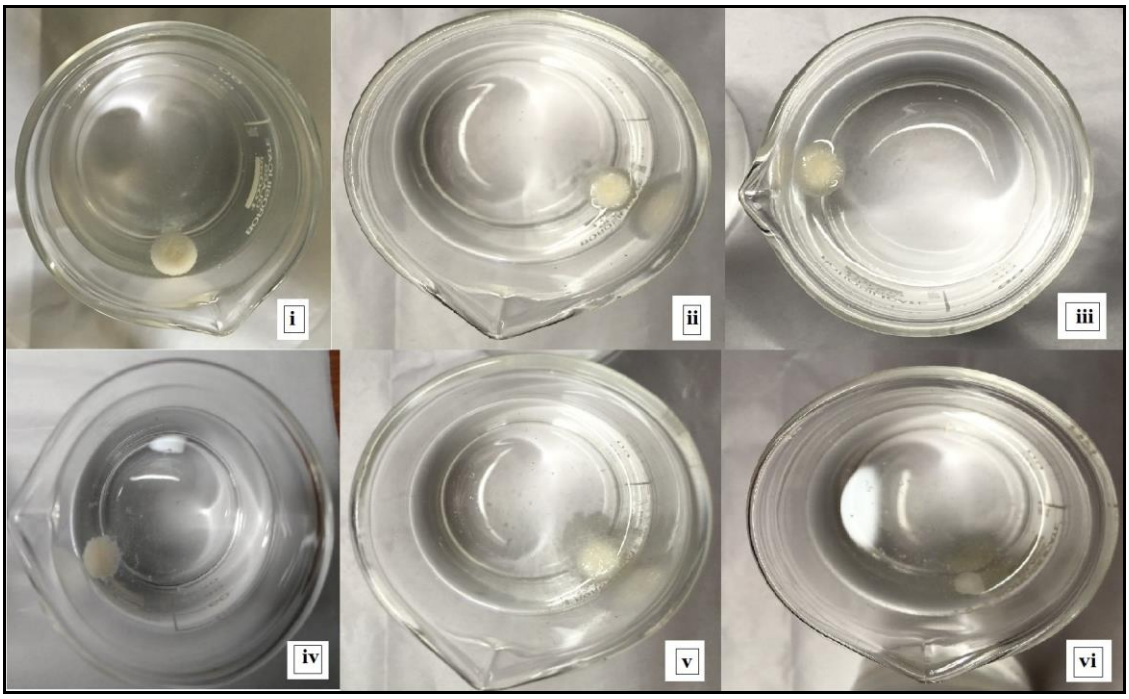


Fig. 6: *In vitro* buoyancy studies of optimized formulation (F10): (i) At initial time; (ii) At 3 hours; (iii) At 6 hours; (iv) At 12 hours; (v) At 18 hours; (vi) At 24 hours;

Differential scanning calorimetric study (DSC)

The DSC study was conducted on the selected formulations. DSC thermogram of pure ATZ shows sharp endothermic peak at 210.1^{0}C (shown in Figure 7) Similar endothermic peaks were obtained at 211.1^{0}C (shown in Figure 8) for the formulation prepared with EC, at 208.3^{0}C (shown in Figure 9) for the physical mixture prepared with HPMC K 100 M, at 210.6^{0}C (shown in Figure 10) for the formulation prepared with combination of EC and HPMC K 100 M. Table 6 summarizes the DSC melting points of different concentrations.

Table 6: DSC melting points of the selected formulations

Formulations	DSC melting points in ^{0}C
Pure ATZ	210.1^{0}C
ATZ-EC	211.1^{0}C
ATZ-HPMC K100 M	208.3^{0}C
ATZ-EC-HPMC K100 M	210.6^{0}C

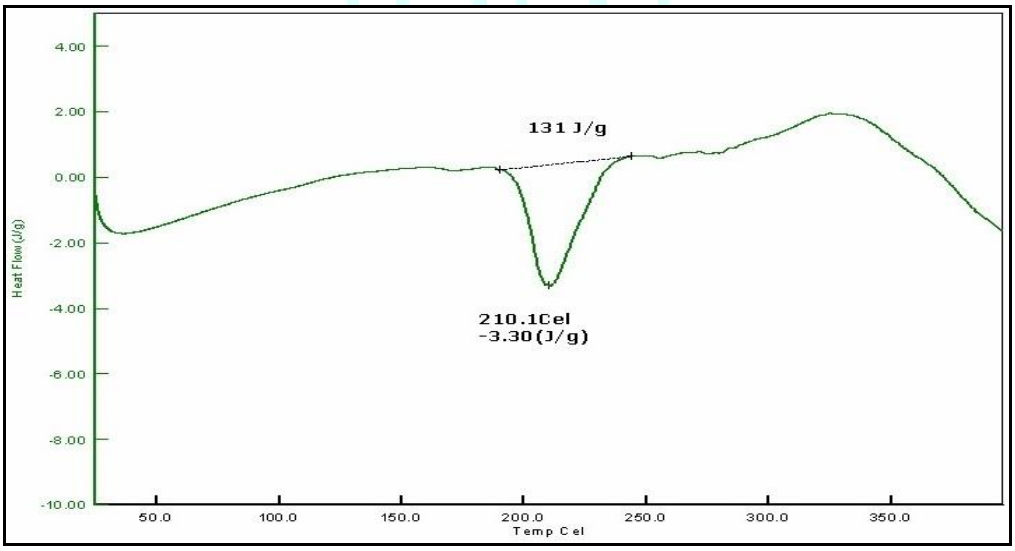


Fig 7: DSC thermograph of the pure ATZ

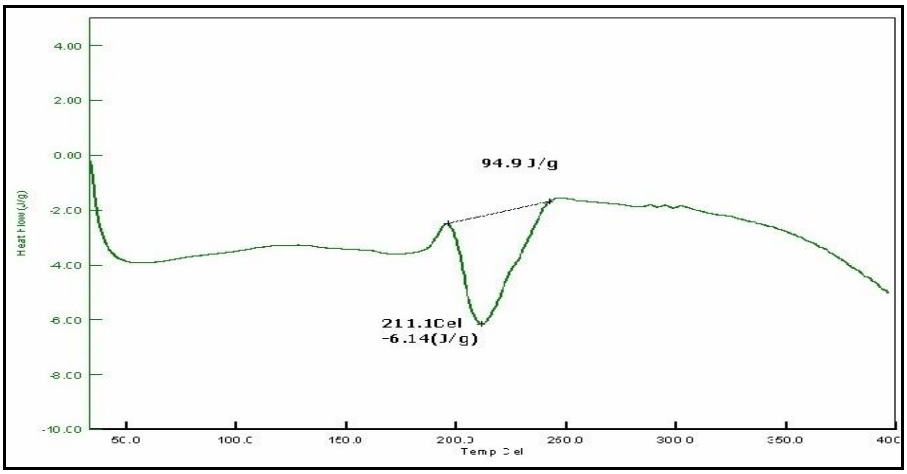


Fig 8: DSC thermograph of the ATZ-EC.

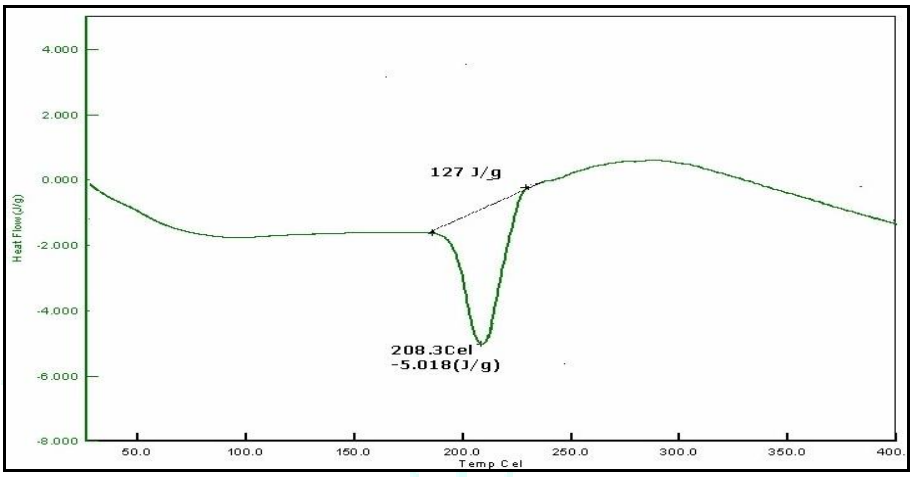


Fig 9: DSC thermograph of the ATZ-HPMC K100 M

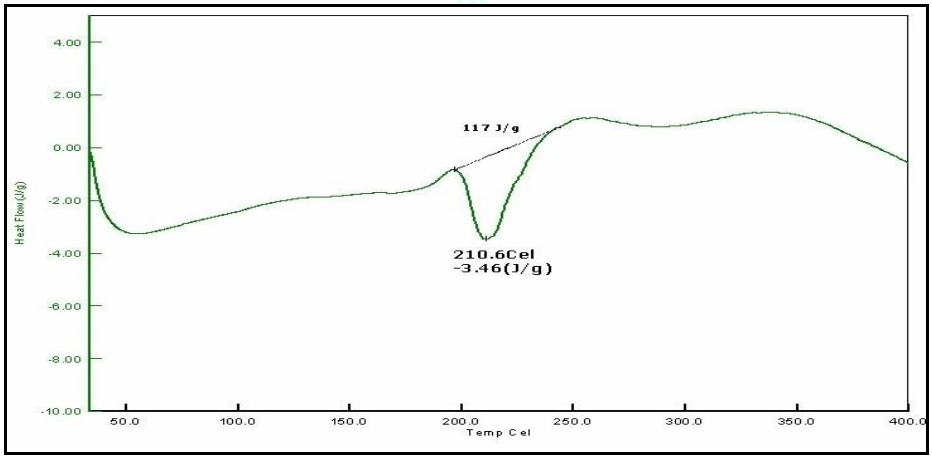


Fig 10: DSC thermograph of the ATZ-EC-HPMC K100M.

In vivo radiographic studies

The tablets were incorporated with 50mg of $BaSO_4$ which was used in the various diagnostic tests. The tablets were given to the volunteers with a glass of water and a standard diet was provided. X-rays were taken at different time intervals such as 5min, 30min, 3hours, 6hours, and 9hours. (i.e.: Protocol number was KLRPC/IHEC/2010-2011/003).

Table 7: Formulation table for X-ray radiographic study (modified F10 formulation).

Ingredients	Modified F10
$BaSO_4$	50
EC N22	-
EC N50	-
EC N100	100
HPMC K100 M	50
MCC	50
Mg stearate	2
Final weight	252

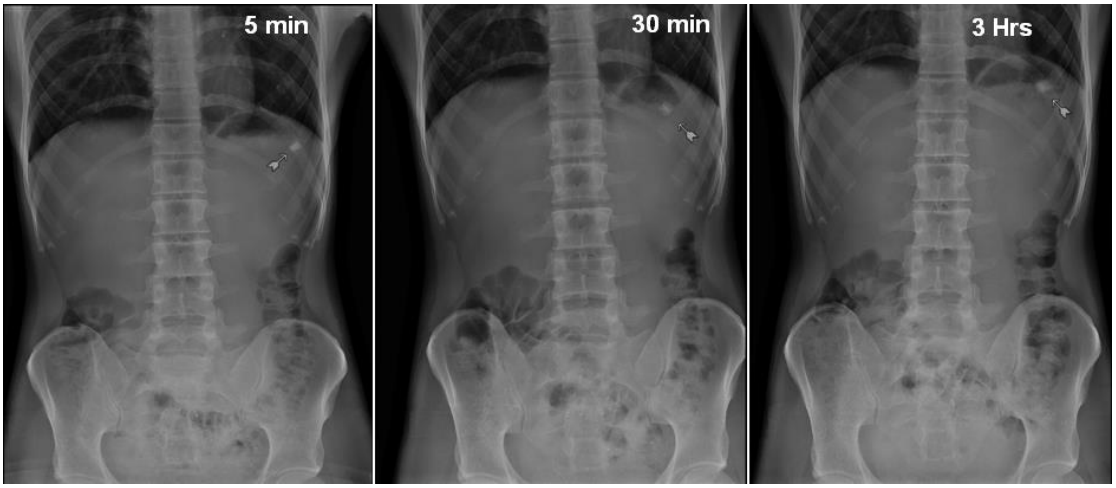


Fig 11: *In vivo* radiographic studies of formulation F10 for with in 5min, 30min and 3hours

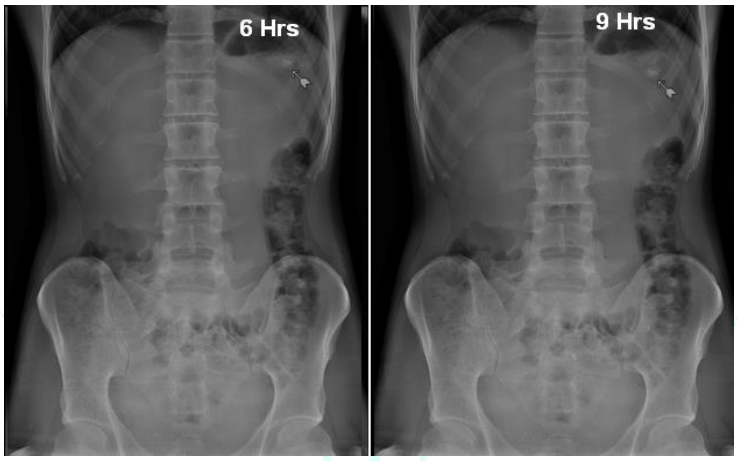


Fig 12: *In vivo* radiographic studies of formulation F10 for 6hours and 9hours

CONCLUSION

In conclusion, HPMC K100M can be successfully employed in the preparation of controlled release floating tablets of ATZ. The formulations were prepared and succeeded without a gas generating agent. A combination of polymers can be successfully employed for better results. The research study provided useful information for the formulation of scientists working on the formulation, characterization during the development of controlled drug delivery systems of ATZ using these polymers.

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