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FORMULATION DEVELOPMENT OPTIMIZATION AND CHARACTERIZATION OF NON-EFFERVESCENT SUSTAINED RELEASE FLOATING MATRIX TABLETS OF ATAZANAVIR SULPHATE

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ABSTRACT

The main objective of the present research was to develop sustained release floating matrix tablets of Atazanavir sulphate (ATZ). This drug has the ability to act as HIV protease inhibitor that exhibits its action by blocking the processing of viral gag-pol proteins in HIV infected cell thereby inhibiting the production of the proteins in HIV infected cell thereby inhibiting the production of the mature virions. ATZ has plasma half-life of about 6.5 hours which needs to be administered frequently for the better therapeutic efficacy. But this frequent administration results in plasma disturbances and also some side effects like cardiac conduction damage, rashes, hyper bilurubinea, nephrolithiasis, nausea, jaundice. ATZ drug shows maximum solubility at pH of acid hence necessary to deliver the drug in stomach is beneficial. ATZ tablets were developed to extend the gastric residence time and to increase drug release after oral administration by utilizing different grades of polymers like MC and HPMC K100M in-order to get the required floating and sustained release over prolonged period of time. All the steps followed in preparation of Atazanavir tablets were extended the drug release up to 24 hours and more and the formulations were optimized to meet the desired release profiles. The drug release and the floating of the drug release depends on the type of polymer and the proportion of polymer used. When the formulation developed using the combination of both the polymers showed

more floating time when compared to the formulation developed with EC alone. In vivo radiography study was conducted on this combinational formulary which revealed floating property of about 8hrs. The DSC and FTIR studies showed that there is no interaction between drug and the polymer used. Besides the approach could be a potential alternative for giving information about the preparation of floating drug release system of Atazanavir without use of gas generating agent. Atazanavir is an azapeptide HIV-1 PI that prevents the formation of mature virions through the potent and selective inhibition of viral Gag and Gag–Pol polyprotein processing in HIV-1-infected cells.[1-2]

1.0 INTRODUCTION

1.1 Introduction to HIV infection and AIDS[3-5]

HIV abbreviates Human Immuno Deficiency virus. This virus attacks human immune system and hence AIDS, is a collection of symptoms developed due to various infections. It suppresses immune system and eventually causes death of infected patient. The causative organism, HIV belongs to Lentivirus a subgroup of Retroviridae family. HIV binds to CD4 receptors on susceptible host cells i.e. T-helper cells, B-lymphocytes, macrophages, monocytes etc.

HIV infection merely has 3 stages. In first stage flu like symptoms occurs, and stage-2 is asymptomatic and in stage-3, CD4 cells count falls below 200cells/mm³. Infection is transmitted from one person to another through sexual contact, parenteral transmission, from mother to her child etc. Two types of genes are present in HIV genome i.e. i) structural genes that include gag gene which codes for core and shell of virus and gag-pol genes which codes for polymerase, reverse transcriptase, protease, integrase and ii) non-structural genes which include (viral infectivity factor) gene that influences infectivity of viral particles. HIV testing is done with a standard ELISA technique and Western Blot technique.

1.2. Introduction to "oral controlled drug delivery"[6-11]

Oral drug delivery is used for wide range of pharmaceuticals. Some drugs possess physiological limitations like variable gastric emptying which leads to incomplete drug release and non-uniform absorption and shorter residence time of dosage form in stomach. Hence delivery system should possess the ability to control and prolong gastric emptying time. This system maintains constant level of drug in blood and tissues for extended period of time.

Advantages[12]

- Improved absorption, so enhanced bioavailability.
- Decreased local and systemic side effects, so reduced GI irritation.
- Dosing frequency can be reduced.

Disadvantages

- Stability difficulties.
- High cost.
- Dose dumping.

1.3. Scope of implementing "floating" drug delivery[13-16]

Main aim of extended drug delivery system is to prolong and control the emptying rate of dosage form. Biggest difficulty is to confine the dosage form in the desired area of GIT. Floating dosage forms have bulk density lower than the gastric fluids, hence remain buoyant on stomach fluids. This ability to float on gastric juices without affecting the gastric emptying rate is a biggest asset. Prolonged gastric retention improves bioavailability, reduces drug wastage, improve solubility of drugs that are less soluble in high pH environment.

Advantages

- This system is advantageous for drugs absorbed through stomach and treatment for peptic ulcer disease eg: antacid.
- Drug will be fully absorbed from floating dosage form.
- It is advantageous to keep the drug in floating condition in stomach to get better response.

Disadvantages

- It requires sufficient high levels of fluids in the stomach for the drug to float.
- Drugs that cause irritations and lesions to gastric mucosa are not suitable for this formulation.
- Floating system is not feasible for those drugs that have stability or solubility problem in gastric fluids.

2.0 MATERIALS AND METHODS

2.1 Materials[17-29]

- Atazanavir sulphate was supplied as a gift sample from Aurobindo Pharma Ltd, Hyderabad.

- DOW chemical company, USA gifted HPMC K100M.
- Ethylcellulose N20, N22, N45, N50, N100 are supplied as a gift samples from Aurobindo Pharma Ltd, Hyderabad.
- Magnesium Stearate was purchased from Himedia Pvt Ltd, Mumbai.
- Hydrochloric Acid was purchased from Merck specialties Pvt Ltd, Mumbai.

2.2 Instruments

- Electronic Weighing balance from AW 120, Shimadzu Corporation, Japan.
- Tablet Compression machine from Cadmach, Ahmedabad, India.
- Tablet dissolution apparatus from Electro lab TDT-08L, Mumbai.
- UV/Visible spectrophotometer from Elico, Ahmedabad, India.
- Digital Vernier Calipers from Mitutoyo corporation, Japan.

2.3 Pre-formulation studies[30,31]

Pre-formulation studies are the investigational studies of physical and chemical properties of a drug substance alone and when mixed with other ingredients.

The main aim of pre-formulation testing is to produce information useful to the formulation in generating stable and bioavailable dosage forms.

The scope of pre-formulation studies is that these parameters maximizes the chances in generating an acceptable, safe, efficacious and stable product.

The important pre-formulation parameters to be considered during formulation are particle size, solubility, compatibility, polymorphism, permeability, crystallinity etc.

Characterization of drug and excipient compatibility

✓ **Fourier transforms infrared spectroscopy (FTIR)**

The FT-IR spectrum of pure drug and formulation were determined. A FT-IR (Thermo nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm^{-1} and 4cm^{-1} resolutions. A quality equivalent to 2mg of pure drug was used for the study.

✓ **Differential scanning calorimetry (DSC)**

Thermal properties of pure drug and the formulation were evaluated by Differential scanning calorimetry (DSC) using a diamond (DSC) (Mettler star sw8.10). The analysis was performed at a rate 5^0c min^{-1} to 200^0C temperature range under nitrogen flow of 25 ml min^{-1}.

2.3 METHOD

Procedure for manufacturing of floating matrix tablets by Direct Compression method

- ✓ **Weighing & sifting:** Atazanavir bisulphate and the other ingredients are weighed accurately and sifted through sieve 44.
- ✓ **Mixing:** Atazanavir sulphate is thoroughly mixed with required quantity of polymers of different grades and then mixed in geometric proportions.
- ✓ **Lubrication:** The above mixture is lubricated with the previously weighed and sieved magnesium stearate in-order to get the blend suitable for compression.
- ✓ **Compression:** The lubricated blend is subjected to compression by using required 8mm or 9mm circular standard flat faced punch on a sixteen station rotary tablet punching machine.

3.0 FORMULATION

3.1. Prototype formulation development of Atazanavir Sulphate floating matrix tablets prepared with Ethyl cellulose and HPMC K100M

Floating matrix tablets of Atazanavir are manufactured by the combination of different grades of Ethyl Cellulose and HPMC K100M in different concentrations. The drug, Ethyl Cellulose and HPMC K100M of desired concentrations are mixed with each other thoroughly and sifted through sieve44, the above blend was lubricated with magnesium stearate and the blend is compressed with 8mm flat faced punch at a hardness of 5-6 kg/cm^2. The compressed tablets are now subjected to different evaluation tests for various physicochemical parameters.

In initial formulations when Ethyl cellulose of different grades viz; N20 N22 N45 N50 N100 are used and punched with 8mm punch at a hardness of 10 kg/cm^2 the desired floating property of Atazanavir sulphate was not obtained due to increased hardness of the tablet and the tablet remained at the bottom of the glass beaker.

Inorder to reduce the hardness of the tablet and to obtain the desired floating property of the Atazanavir sulphate tablet the further formulations were made by using a lubricant HPMC

K100M of different grades in different concentrations and the tablets are compressed with 8mm flat faced punch at a hardness of 5-6 kg/cm^2. Then tablets of desired physicochemical parameters were obtained with hardness of 5 kg/cm^2 and friability less than 1% with desired floating property.

Table 1: Formulation development of Atazanavir Sulphate floating matrix tablets using combination of different grades of Ethyl Cellulose and HPMC K100M.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Atazanavir sulphate	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Ethyl cellulose(N20)	100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ethyl cellulose(N22)	-	100	-	-	-	100	-	-	100	-	-	100	-	-	-	100
Ethyl cellulose(N45)	-	-	100	-	-	-	-	-	-	-	-	-	-	-	-	-
Ethyl cellulose(N50)	-	-	-	100	-	-	100	-	-	100	-	-	100	-	-	-
Ethyl cellulose(N100)	-	-	-	-	100	-	-	100	-	-	100	-	-	100	100	-
HPMC K 100 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	2	2	2	2	2
Total	202	202	202	202	202	227	227	227	252	252	252	277	277	277	242	272

4.0 RESULTS AND DISCUSSIONS

4.1 Pre compression parameters

Pre-compression studies is the main study to rule out any potential incompatibilities between the drug and excipients of the formulation. The interactions between drug and the excipients have been evaluated by comparison of FTIR and DSC spectra's of physical mixtures with the individual components.

- **FTIR studies on the selected formulations**[32-34]

The FTIR spectra of pure Atazanavir, physical mixture of excipients and physical mixture of Atazanavir and excipients are shown below. The appearance of new absorption bands or broadening of bands in the FTIR, appearance or disappearance of endothermic or exothermic peaks in DSC curves are the main characteristics to evidence interactions between drug and excipients. The FTIR spectra of pure Atazanavir and physical mixture confirmed that there was no major broadening, loss or appearance of functional peaks between the spectra of drug and physical mixture. Thus, no major drug-excipients interactions have been observed in FTIR spectra, confirming that Atazanavir is compatible with the components of the formulation.

- **Differential scanning calorimetric study (DSC)**[35-37]

DSC study was conducted on the selected formulations that indicating DSC thermogram of pure Atazanavir shows sharp endothermic peak at 210.1^0C. similar endothermic peaks were obtained at 211.1^0C for the formulation prepared with ethyl cellulose, at 208.3^0C for the physical mixture prepared with HPMC K 100 M, at 210.6^0C for the formulation prepared with combination of ethyl cellulose and HPMC K 100 M.

Table 2: DSC melting points of the selected formulations.

Formulations	DSC melting points in ^{0}c
Pure Atazanavir	210.1^0C
Atazanavir-Ethyl cellulose	211.1^0C
Atazanavir-HPMC K100 M	208.3^0C
Atazanavir-Ethylcellulose-HPMC K100 M	210.6^0C

1.2 Post compression parameters[38,39]

The evaluation tests are performed to assess the physicochemical properties and release characteristics of developed formulations. This include:-

- **Tablet thickness**

Thickness was measured individually for pre-weighed 10 tablets using Vernier calipers. Thickness is generally measured in millimeters. The average thickness and standard deviation of 10tablets were reported.

- **Tablet hardness**

It is the force required to break the tablet. The resistance of tablet to chipping, abrasion, during storage depends in tablet hardness. Hardness of 6 tablets was determined by using Monsanto hardness tester and average is calculated and presented along with standard deviation.[22]

- **Friability**

Friability is the tendency of solid substance to break into smaller pieces under stress or rubbing. Friability values of tablets was determined by using Roche friabilator. Accurately weighed 6 tablets were placed in friabilator and rotated at 25rpm for 4mins. The tablets were cleaned and re-weighed to determine weight loss from original tablets.

Percentage friability was calculated as

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where; W_O = weight of the tablet at time zero before revolution.

W = weight of the tablet after 100 revolutions

- **Weight variation test**

Twenty tablets were randomly selected from each batch and weighed individually using standard electronic weighing balance. The average weight and standard deviation of three batches were calculated. It is said to be passed the test for weight variation, if not more than two of the individual tablet weights deviate from the average weight and allowed percentage deviation.

Table 3: Weight Variation Tolerance.

Average weight (mg)	% Deviation allowed
130 or less	10
130-323	7.5
More than 324	5

- **Drug content estimation**

From each batch of prepared tablets, ten tablets were collected randomly and powdered. Quantity of powder equivalent to one tablet is weighed and transferred into 100ml volumetric flask, now add 10ml of 0.1N HCL and left for 20mins. Solution was made up to the mark with 0.1N HCL. Next, filter the solution and suitable dilutions were made with methanol. Likewise, same concentration of standard solution was also prepared. Record the absorbance at 250nm by using UV-Visible spectrophotometer.

It is calculated as,

$$\text{Drug content} = \frac{\text{sample absorbance}}{\text{standard absorbance}} \times \frac{\text{standard dilution}}{\text{sample dilution}} \times \frac{\%\text{purity of drug}}{100} \times \text{Avg.wt}$$

$$\%\ \text{Drug content} = \frac{\text{Drug content} \times 100}{\text{Label claim}}$$

- **Buoyancy / Floating test**[40-45]

In-vitro buoyancy was determined by using floating lag time. In this test, tables were placed in 100ml beaker containing 0.1N HCL. From this two assumptions were i.e.

a) Floating lag time: It is the time between the introduction of tablet into medium and its rise to upper one third of dissolution vessel.
b) Floating time: The time for which dosage form remains buoyant is called as Floatation/Floating time or Total Floating Time (TFT)

Based on the *in vitro* drug release, three formulations were subjected for further study (F10, F15 and F16). The tablets were dropped into 100ml of 0.1N HCl taken in a 250ml beaker. The tablets were examined for their floating time. Digital photographs were taken at initial time intervals of 4hrs, 8hrs, 12hrs, 16hrs & 24hrs. The matrix tablets prepared with combination of different grades of Ethyl cellulose and HPMC K100 M will remain to float for about 24hrs and more. Fig: 6.18-6.23 shows the photographs of floating property in the 0.1N HCl.

5. In vitro drug release studies of Atazanavir Sulphate floating matrix tablets prepared by combination of different grades of Ethyl Cellulose and decreased HPMC K100M concentration.[46-53]

In-vitro drug release study was carried out in USP-III, paddle type dissolution apparatus. In this test 900ml of duplicate gastric fluid of pH 1.2 was taken into dissolution vessel, where

medium temperature was maintained at 37˚±0.5˚c, speed is 50 rpm. 1ml of sample withdrawn at regular intervals of time and same volume is replaced with fresh sample. The samples were observed for drug content in UV-visible spectrophotometer using 0.1N HCL as a blank at λmax 250nm. In swellable matrix tablets drug release depends on diffusion through swelling gel layer, dissolution test is carried out by placing Atazanavir tablets inside the dissolution vessel. 5ml of samples were withdrawn at tine intervals of 1, 2, 3, 4, 5, 6, 8…….up to 2hrs, every time withdrawn sample is replaced with fresh medium. This is conducted for 3 tablets and mean values were plotted against time and each drug concentration is calculated using standard calibration curve.

6. Kinetics of drug release

The cumulative amount of drug released from tablets containing different drug and polymer at different time intervals was fitted to zero order kinetics using least squares. Statistical methods of analysis were utilized to find out whether the drug release from the formulations is providing a constant drug release. The correlation coefficient between the time and cumulative amounts were also calculated to find the fitness of the data to zero order kinetics. The data were also subjected to first order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug to be released from the formulations. The data were also subjected to Higuchi's model was assessed by determining correlation coefficient between the square root time and the amount of drug to be released from the formulations. Diffusion parameters were estimated using Kerseymere's equation.

$$M_t/M_\infty = K\, t^n$$

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

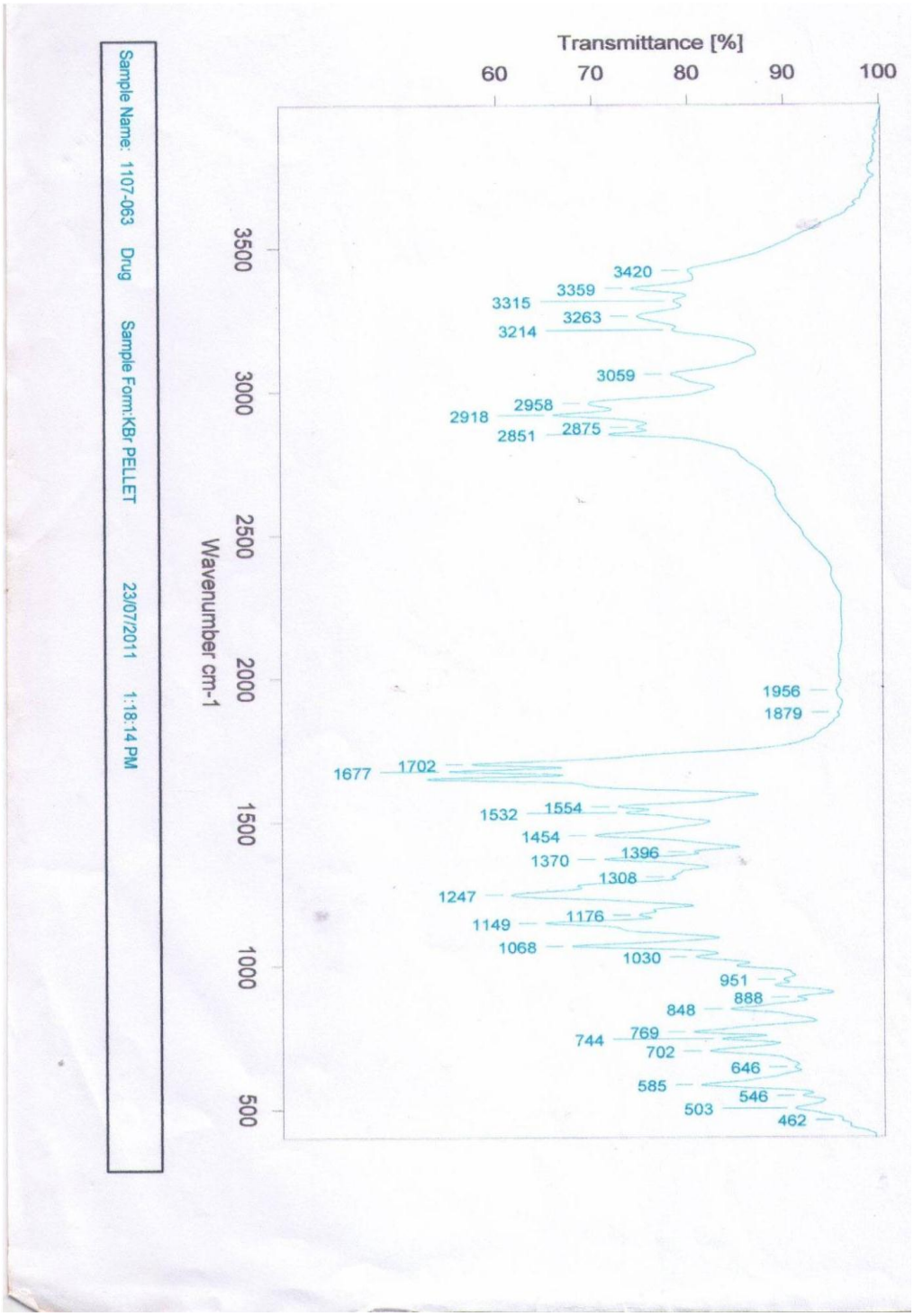

Fig 1: Ftir Spectra of Pure Atazanavir.

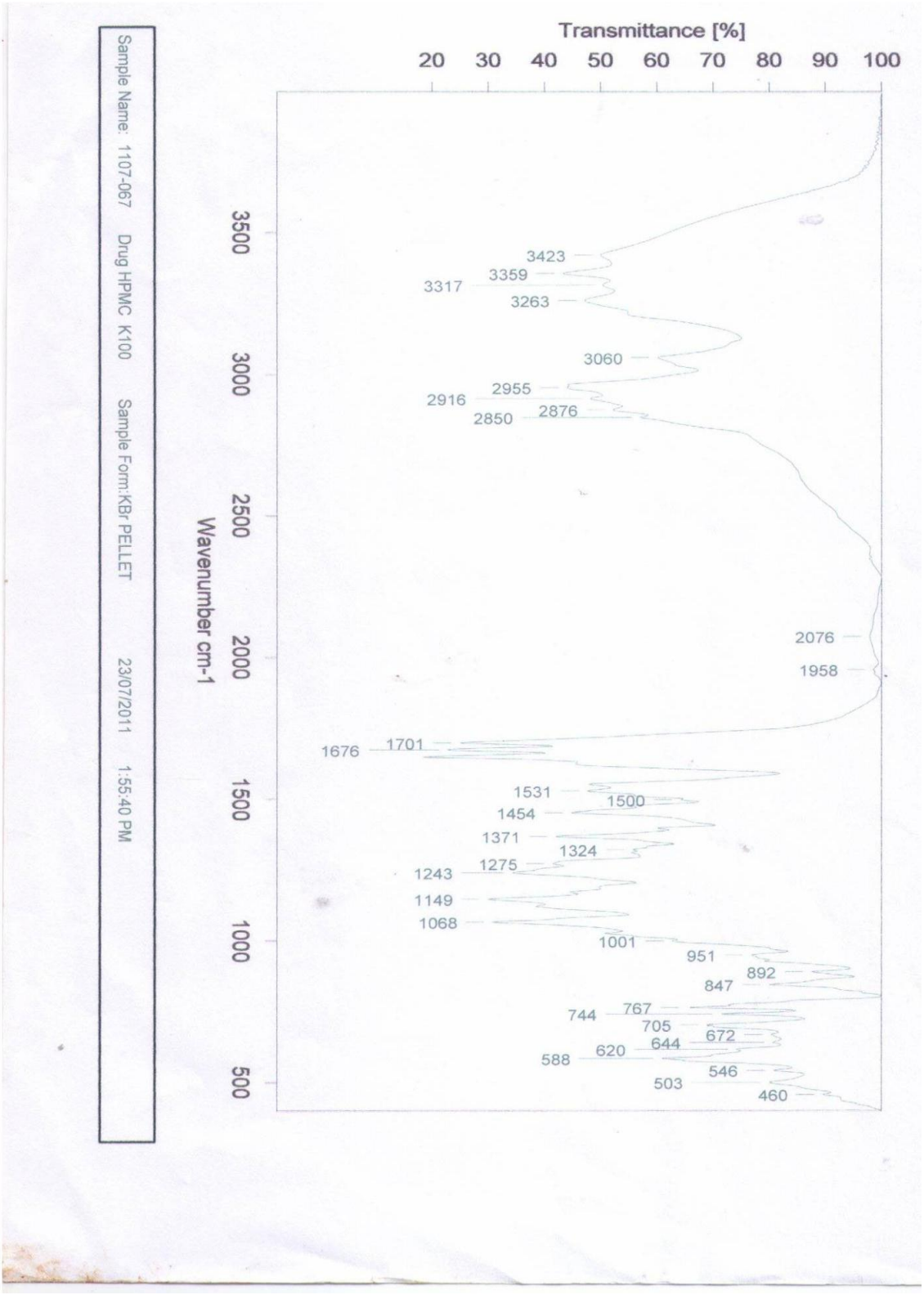

Fig 2: FTIR spectra of Atazanavir with HPMC K100M.

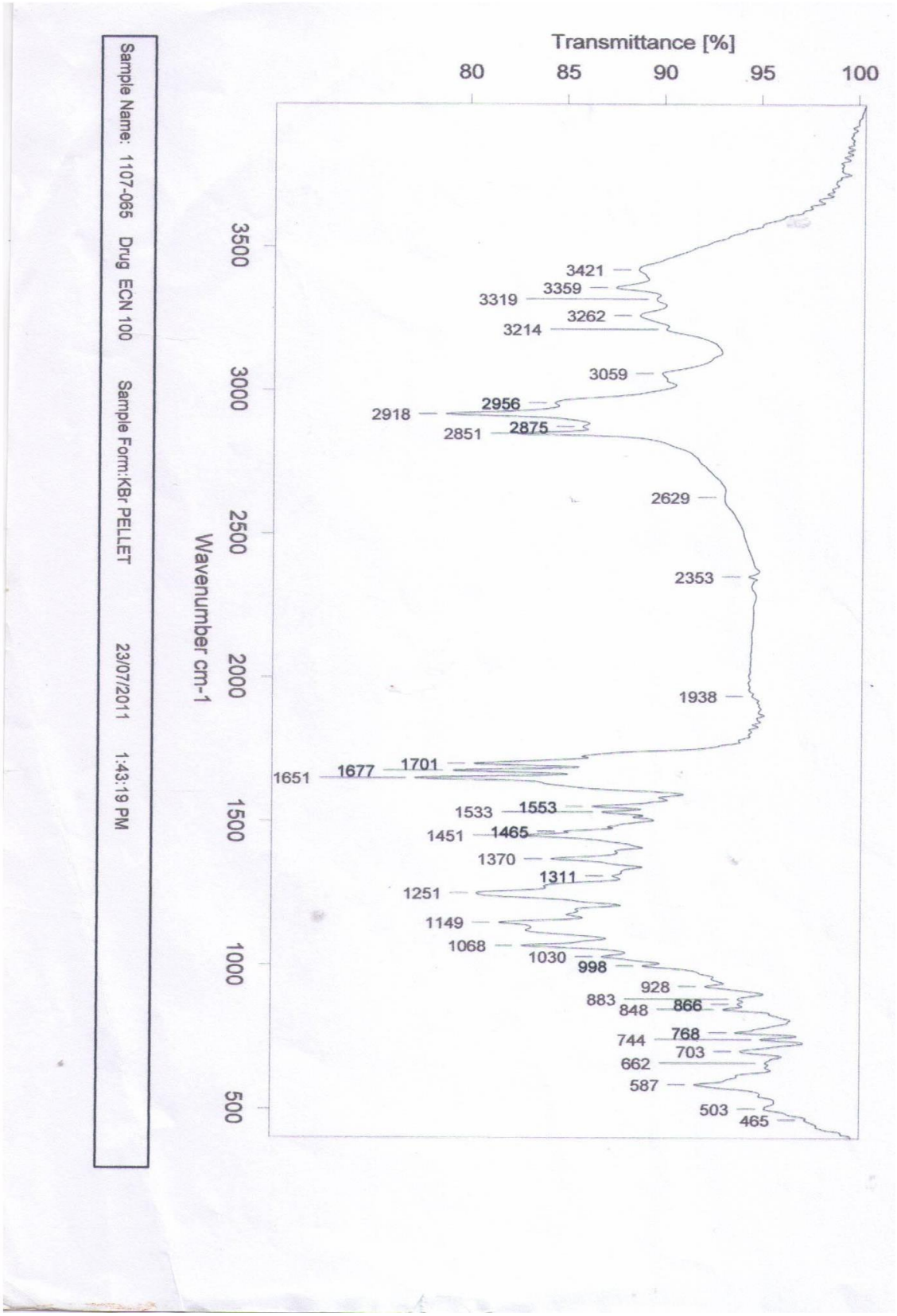

Fig 3: FTIR spectra of Atazanavir with Ethyl Cellulose N100.

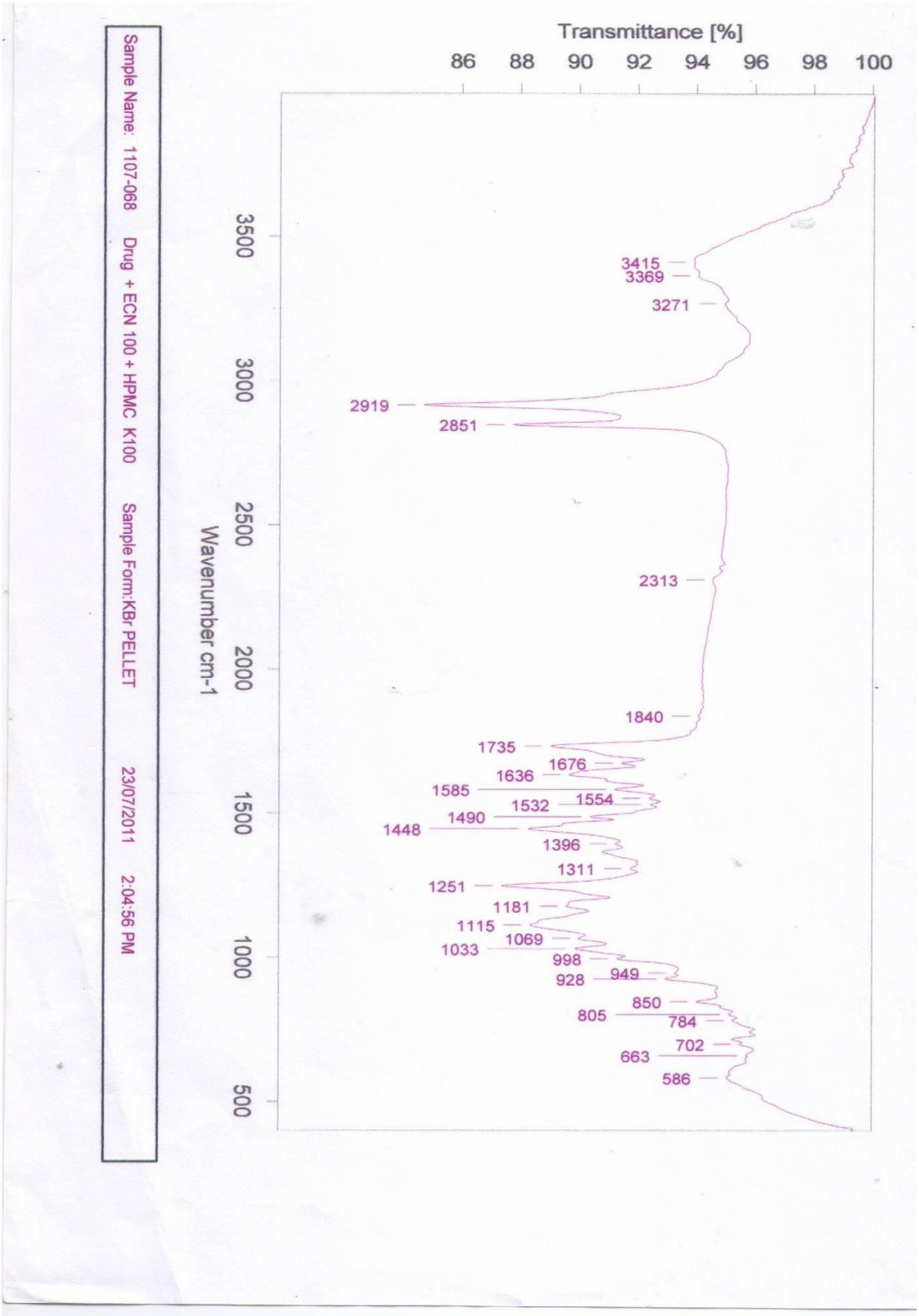

FIG 4: FTIR spectra of Atazanavir with combination of Ethyl Cellulose N100 and HPMC K100 M.

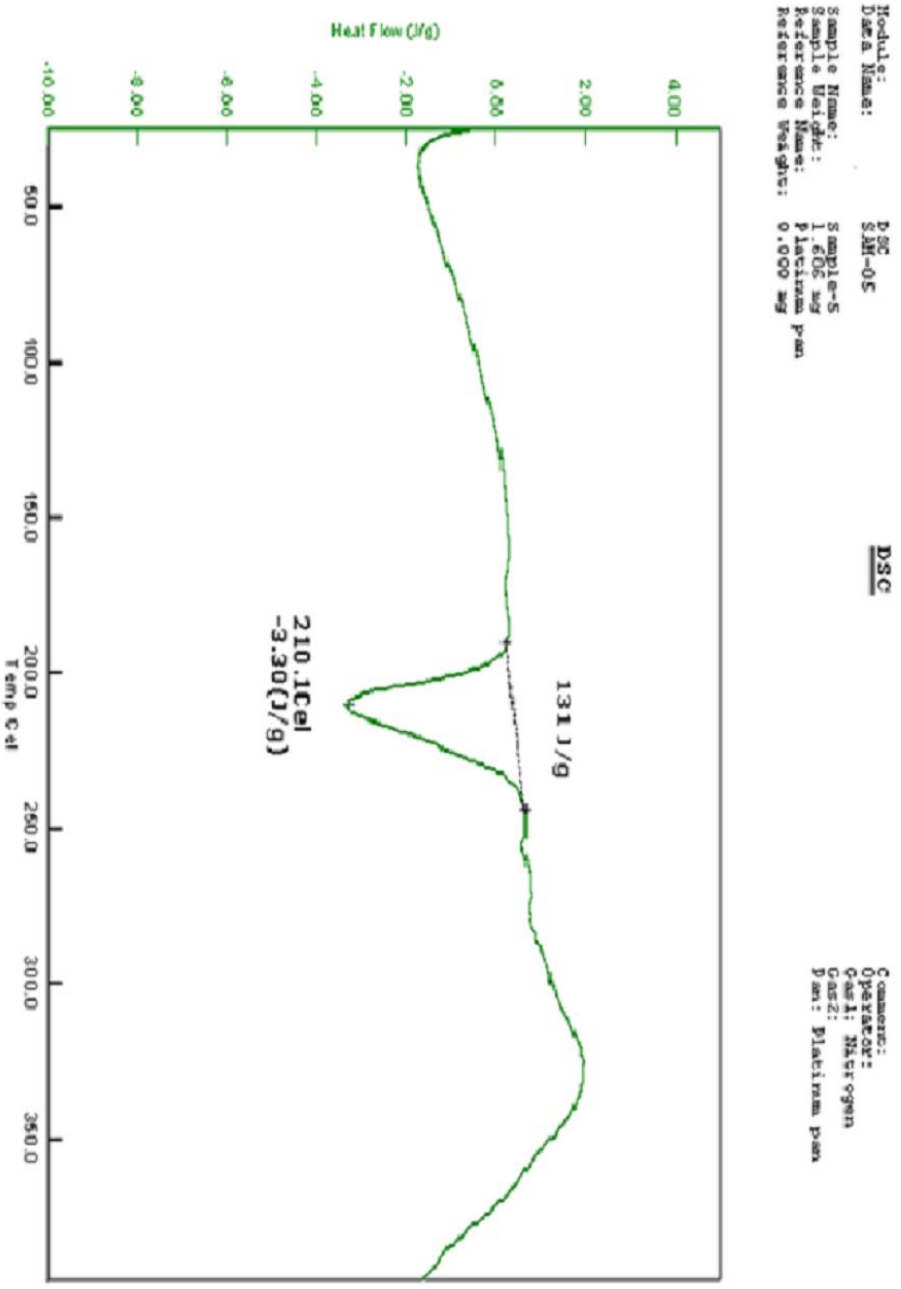

FIG 5: DSC thermograph of the pure Atazanavir.

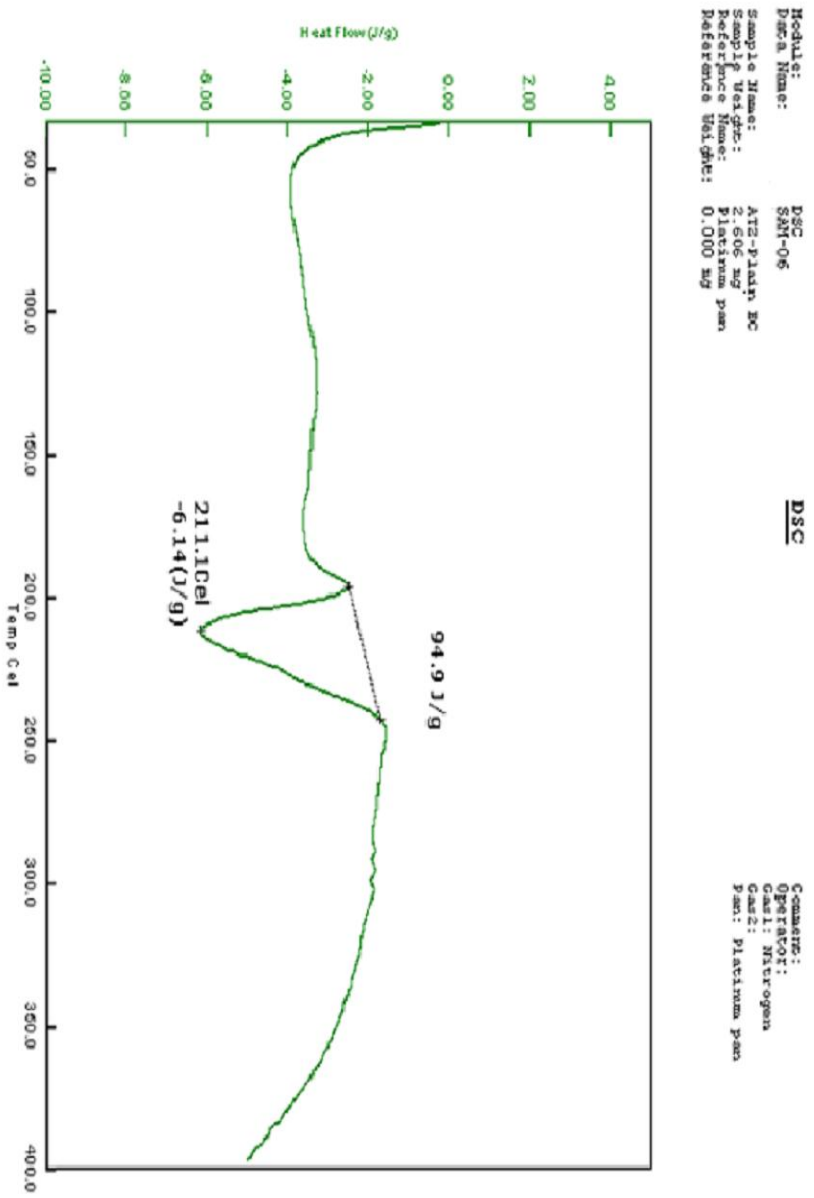

FIG 6: DSC thermograph of the Atazanavir-Ethyl Cellulose.

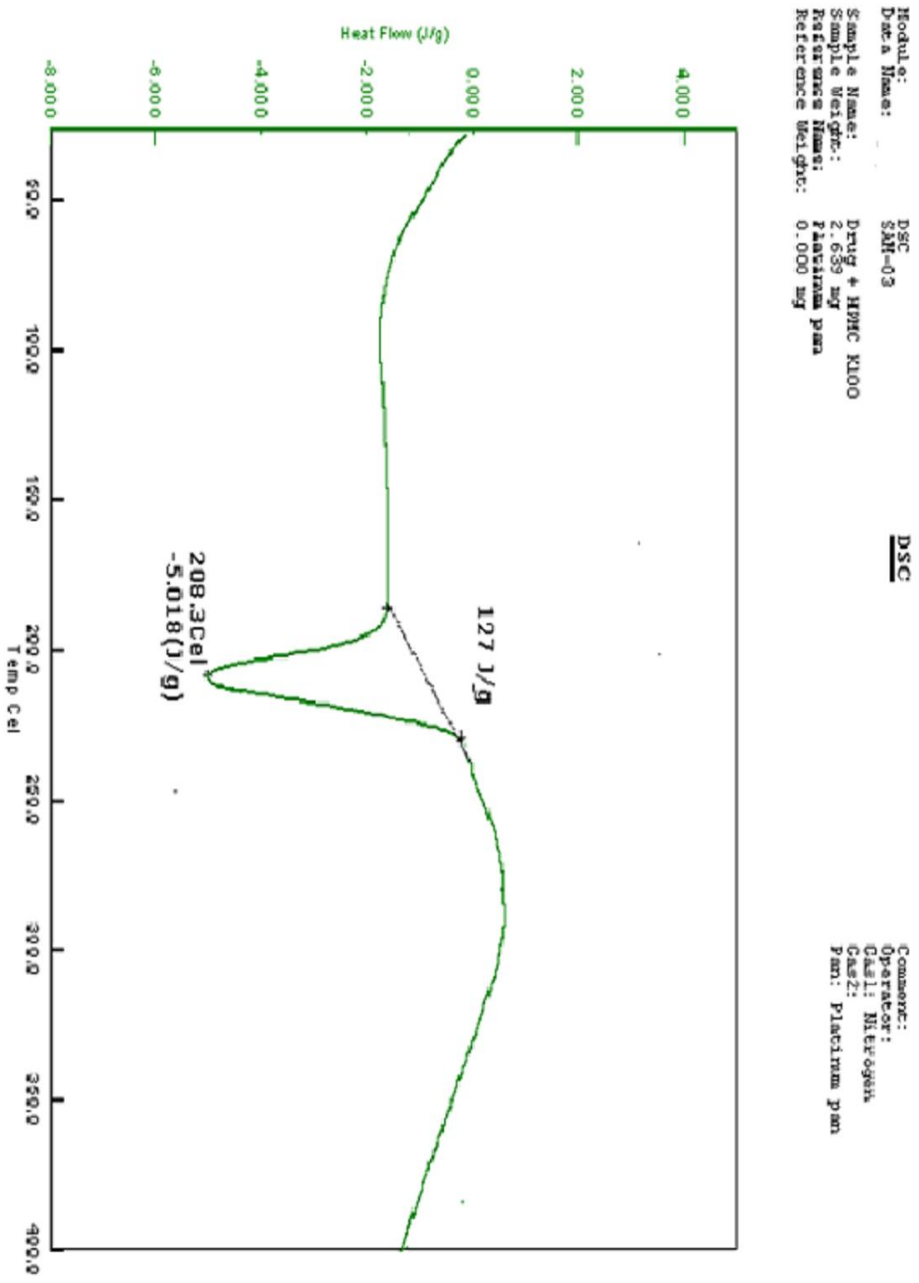

FIG 7: DSC thermograph of the Atazanavir-HPMC K100 M.

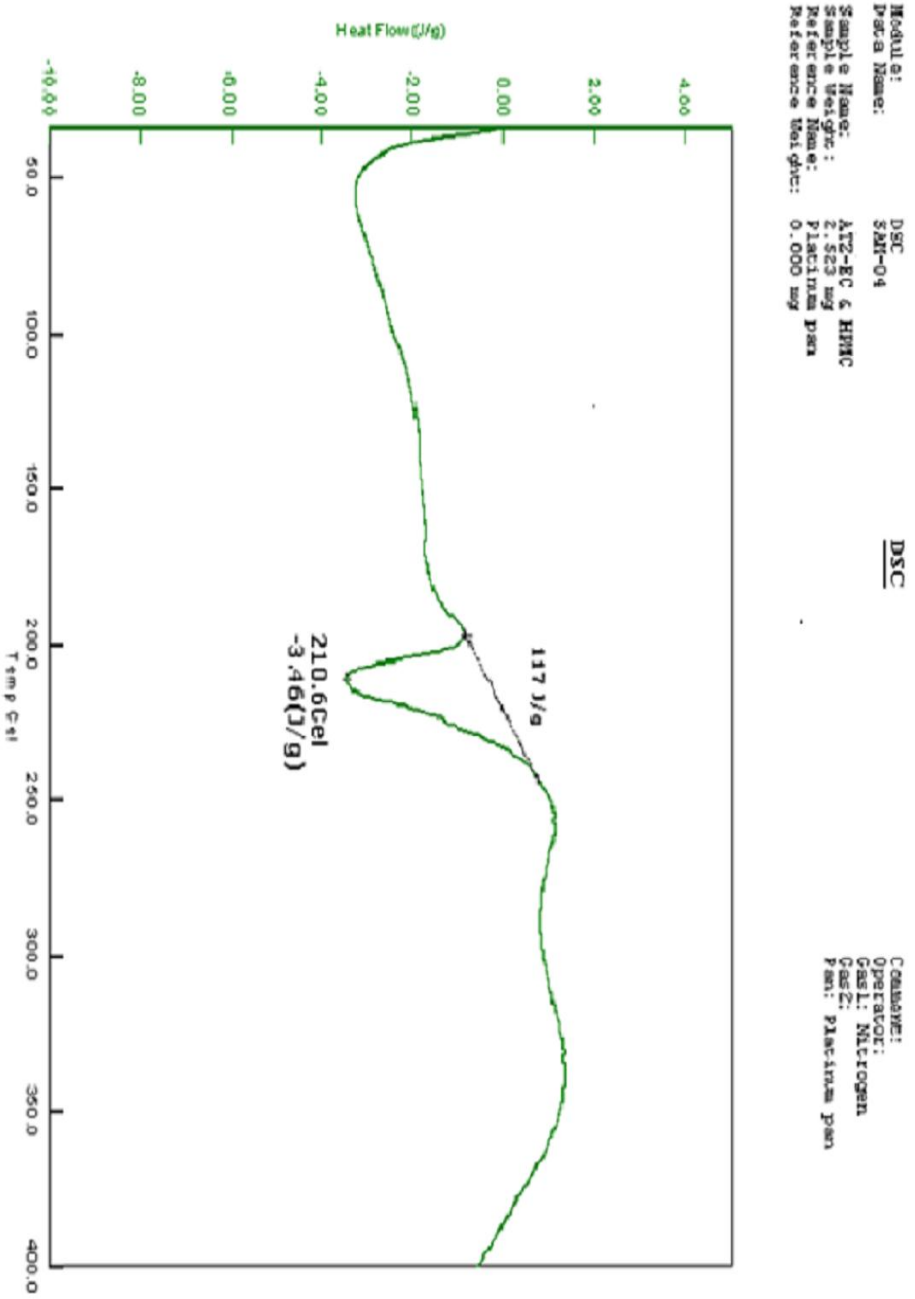

FIG 8: DSC thermograph of the Atazanavir-Ethyl Cellulose-HPMC K100M.

Table 4: Evaluation of Post Compression Parameters of Atazanavir Sulphate Free Floating Matrix Tablets.

Factors	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Weight variation (mg)	226±1.03	227±0.83	227±0.67	251±0.14	252±0.18	252±0.17	276±0.24	277±0.18	276±0.17	241±0.14	272±0.11
Tablet hardness (kg/cm²)	4.9±0.5	5.1±0.5	5.2±0.5	5.6±0.5	5.4±0.5	5.5±0.5	5.8±0.5	5.9±0.5	5.9±0.5	5.3±0.5	5.7±0.5
Tablet diameter (mm)	8	8	8	8	8	8	8	8	8	8	8
Tablet thickness (mm)	4.34	4.36	4.36	5.34	5.28	5.14	6.14	6.12	6.14	5.42	6.12
Friability (%)	0.73	0.75	0.74	0.94	0.97	0.95	0.95	0.96	0.94	0.95	0.96
Drug concentration (%)	97.75±2.3	96.25±1.8	97.48±2.8	98.75±2.3	97.25±1.8	97.48±1.8	96.15±2.3	97.35±1	96.48±1.8	98.15±1.3	97.35±1.9
Floating lag time	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec	>1 sec

- **In vitro buoyancy studies**

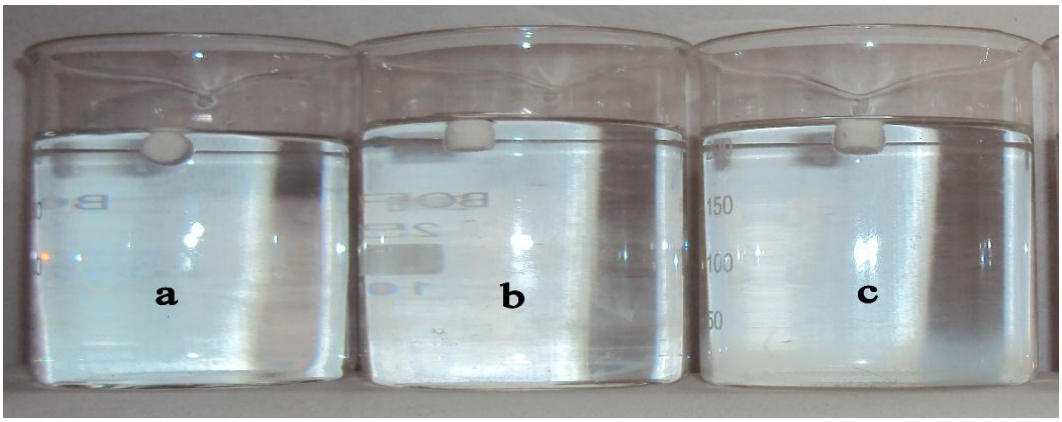

Fig 9: *In vitro* buoyancy studies: At initial time dosage form with a) F10, b) F15 and c) F16.

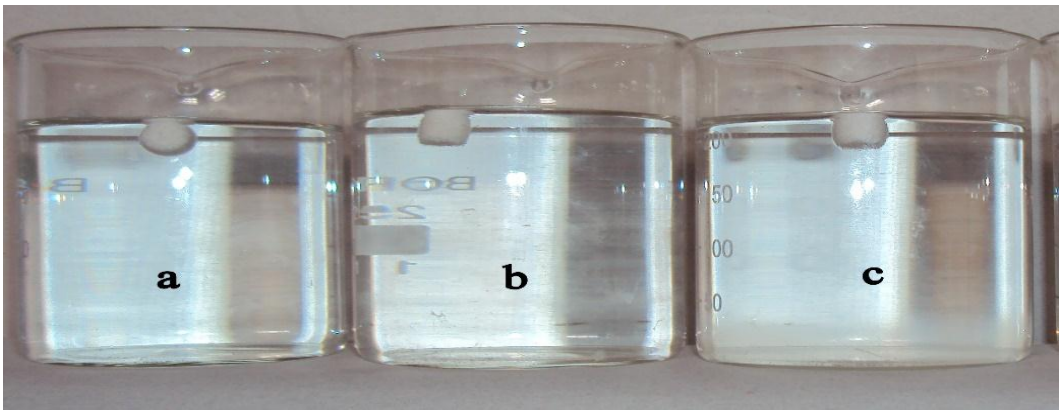

Fig 10: *In vitro* buoyancy studies: After 4hrs time dosage form with a) F10, b) F15 and c) F16.

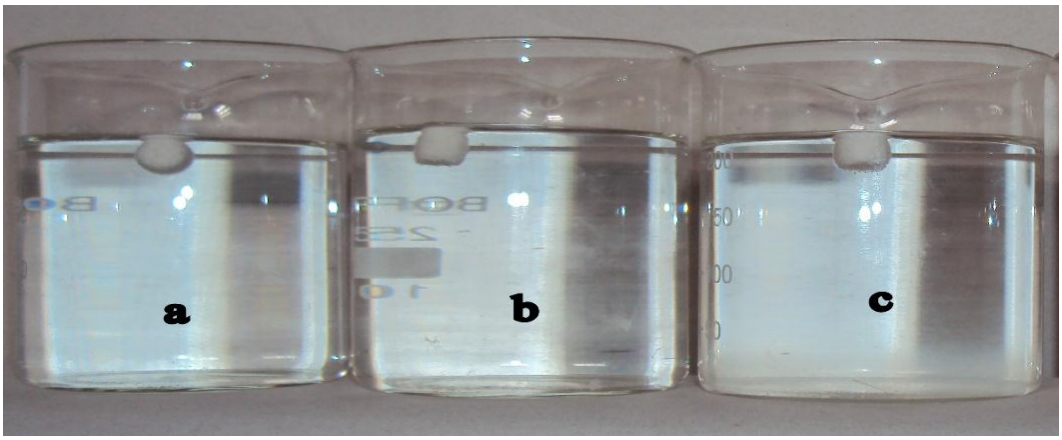

Fig 11: *In vitro* buoyancy studies: After 8hrs time dosage form with a) F10, b) F15 and c) F16.

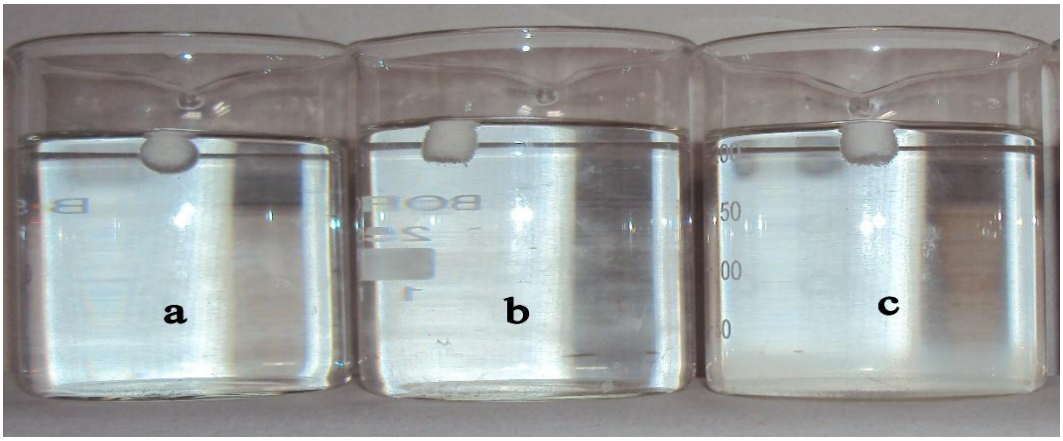

Fig 12: *In vitro* buoyancy studies: After 12hrs time dosage form with a) F10, b) F15 and c) F16.

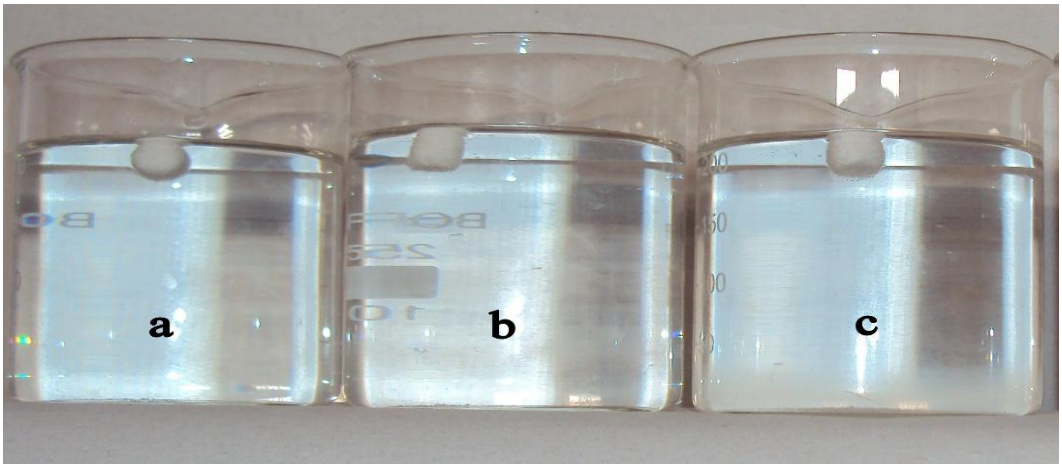

Fig 13: *In vitro* buoyancy studies: After 16hrs time dosage form with a) F10, b) F15 and c) F16.

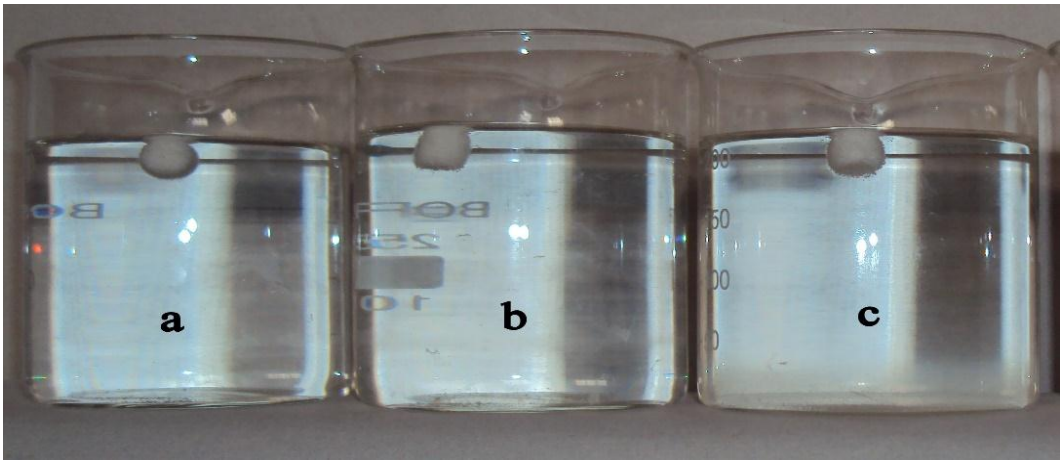

Fig 14: *In vitro* buoyancy studies: After 24hrs time dosage form with a) F10, b) F15 and c) F16.

Table 5: In vitro drug release studies of Atazanavir Sulphate floating matrix tablets prepared by combination of different grades of Ethyl Cellulose and decreased HPMC K100M concentration.

Time	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0	0	0	0
1	27±0.4	20±1.3	11±1.2	14±0.8	12±1.1	9±0.8	10±1.7	9±0.2	7±0.4	11±1.4	13±1.2
2	41±1.0	29±1.0	20±1.8	24±0.6	15±1.6	11±1.6	12±1.5	11±1.4	9±1.5	14±1.5	16±0.9
3	54±1.2	38±1.5	27±1.4	29±1.7	19±0.3	15±1.7	15±1.8	14±1.3	11±1.2	16±1.2	19±0.6
4	60±1.3	46±1.4	34±1.2	33±0.6	22±1.5	18±0.6	20±1.6	18±0.6	14±1.7	21±1.4	23±1.7
5	69±1.1	55±0.9	43±1.6	36±1.6	25±1.0	20±0.7	24±1.5	21±1.4	16±0.9	24±1.1	27±0.8
6	75±1.3	63±0.8	50±1.8	38±0.7	27±1.7	23±1.5	28±1.2	22±1.1	17±0.8	28±1.4	33±0.2
7	82±1.4	69±1.4	56±0.9	42±1.2	31±1.6	27±1.2	30±0.8	25±1.2	19±1.2	32±1.1	37±0.2
8	91±1.7	75±1.3	61±1.7	45±1.5	34±1.8	30±1.0	33±0.6	27±0.8	23±1.7	35±1.7	39±0.4
9	97±1.6	84±1.8	68±1.3	49±0.6	37±1.6	33±1.2	37±1.0	31±0.9	25±1.1	39±0.8	42±1.2
10	-	90±0.6	72±1.6	53±0.4	41±0.6	35±1.7	39±1.4	34±1.0	27±1.0	43±0.2	46±0.7
11	-	97±1.3	79±0.6	58±0.4	45±1.2	38±1.1	44±0.4	38±1.2	30±0.9	47±1.7	51±1.6
12	-	-	84±0.8	62±1.7	49±0.8	41±0.4	47±1.7	41±1.3	34±1.5	51±0.4	55±1.7
13	-	-	89±1.2	65±0.2	52±0.3	45±0.3	50±1.5	44±1.0	37±1.4	55±0.4	58±0.6
14	-	-	95±1.4	69±0.8	56±1.4	48±1.3	54±1.0	48±1.4	40±1.3	58±0.6	61±0.8
15	-	-	99±1.0	74±1.7	60±1.2	51±1.5	57±1.3	52±1.8	43±0.4	62±0.8	65±1.9
16	-	-	-	78±1.1	64±1.1	55±1.9	61±1.4	54±1.7	46±0.6	66±1.0	69±1.6
17	-	-	-	83±1.4	67±1.7	58±1.6	64±0.8	57±0.9	48±0.9	68±0.9	73±1.7
18	-	-	-	87±1.5	72±0.8	61±1.7	68±0.9	62±0.8	51±1.2	72±0.6	76±1.0
19	-	-	-	92±1.2	76±0.8	65±0.6	72±1.0	65±0.6	55±1.5	77±1.2	79±1.5
20	-	-	-	98±1.4	80±0.6	69±0.8	75±1.2	68±1.0	58±1.4	81±1.7	83±1.6
21	-	-	-	-	83±1.5	73±1.0	79±1.7	72±1.2	61±1.2	84±1.5	87±1.1
22	-	-	-	-	87±1.2	77±1.1	83±1.4	76±1.4	65±1.0	89±1.4	91±1.3
23	-	-	-	-	92±1.4	81±1.4	87±0.9	80±1.8	68±1.2	95±1.2	95±1.4
24	-	-	-	-	97±1.7	85±1.7	91±0.8	84±0.9	72±0.9	99±1.5	98±1.5

Table 6: Kinetic studies of Atazanavir Sulphate floating matrix tablets prepared by combination of different grades of Ethyl Cellulose and decreased HPMC K100M concentration.

Kinetics	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Zero order (r^2)	0.9432	0.9819	0.9894	0.9842	0.9957	0.9961	0.9975	0.9965	0.9952	0.9974	0.9955
First order (r^2)	0.8945	0.8637	0.796	0.7779	0.8114	0.9192	0.9045	0.929	0.9519	0.7224	0.8186
Higuchi (r^2)	0.9954	0.9761	0.9969	0.9612	0.936	0.932	0.9463	0.9299	0.919	0.942	0.9594
Peppas (n)	0.9954	0.6713	0.8118	0.6147	0.7098	0.7608	0.7572	0.7661	0.798	0.7547	0.6996

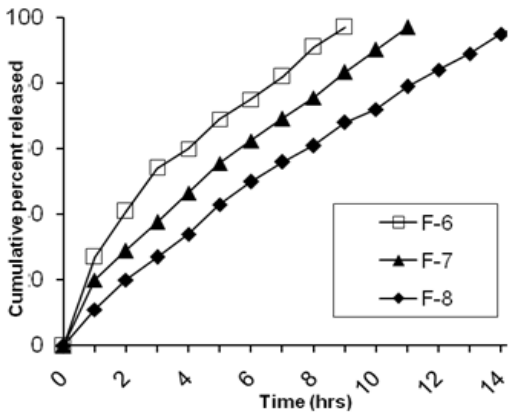

Fig 15: Cumulative percentage drug release vs time profiles of formulations (F6, F7, F8) prepared with combination of different grades of Ethyl cellulose and HPMC K100M.

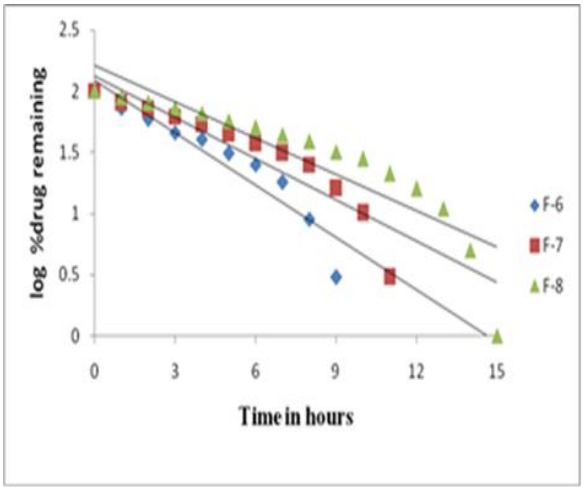

Fig 16: First order kinetics of Ethyl cellulose and HPMC K100M formulations (F6, F7, F8).

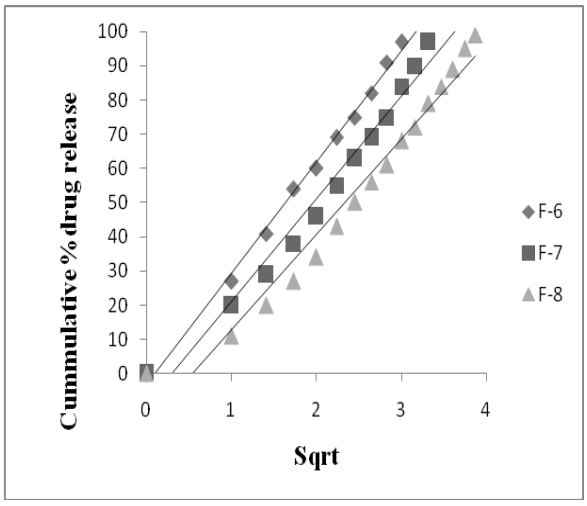

Fig 17: Higuchi release mechanism of Ethyl cellulose and HPMC K100M formulations (F6, F7, F8).

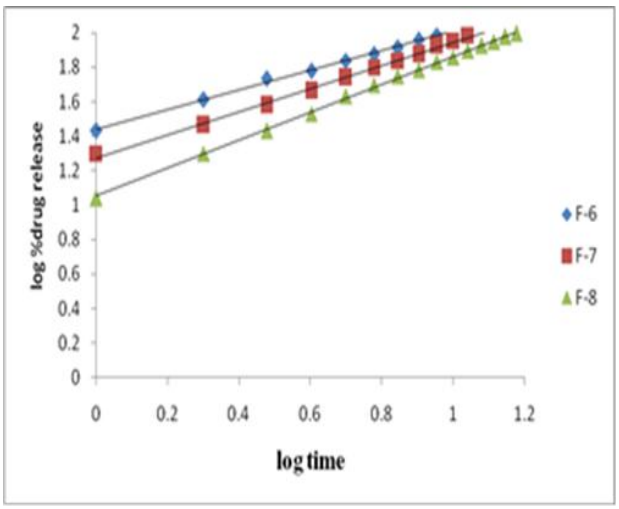

Fig 18: Korasmeyer & peppas release plots of Ethyl cellulose and HPMC K100M formulations (F6, F7, F8).

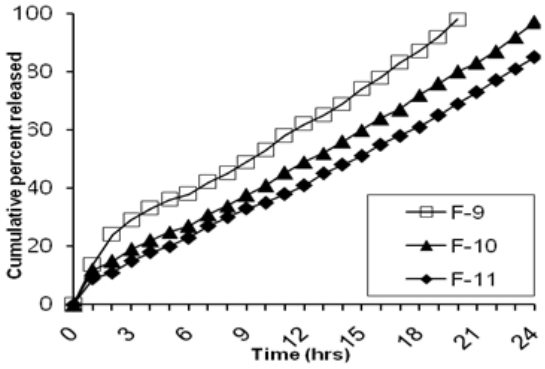

Fig 19: Cumulative Percentage drug release profiles of formulations (F9, F10,F11) prepared with combination of different grades of Ethyl Cellulose and HPMC K100M

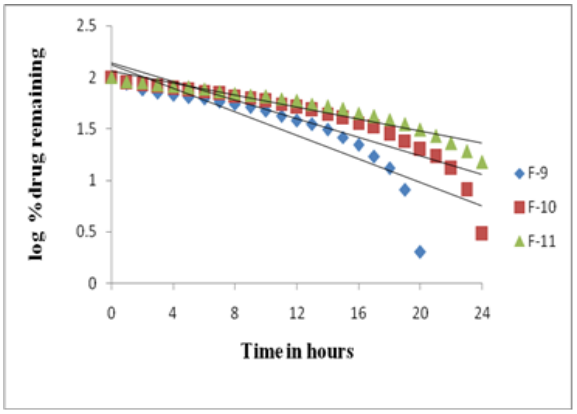

Fig 20: First order kinetics of Ethyl cellulose and HPMC K100M formulations (F9, F10, F11).

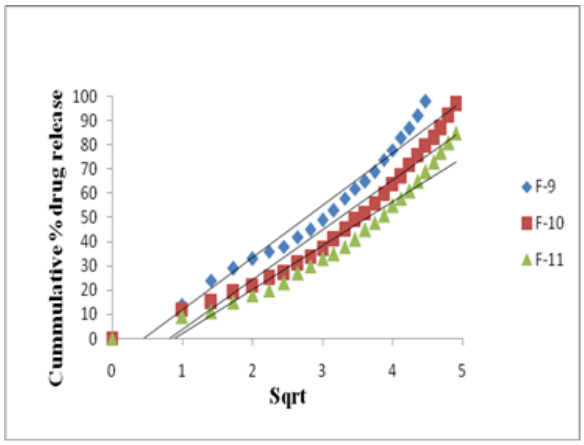

Fig 21: Higuchi release mechanism of Ethyl cellulose and HPMC K100M formulations (F9, F10, F11).

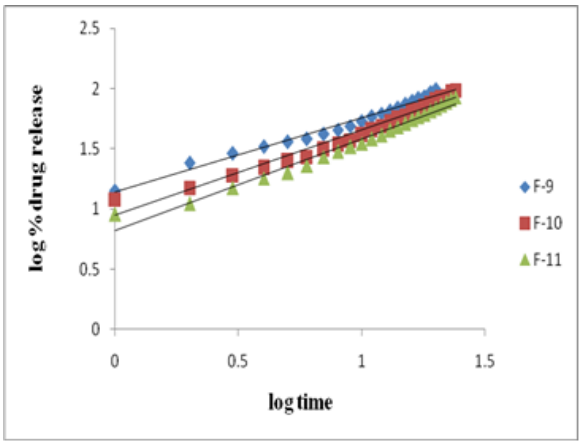

Fig 22: Korasmeyer & peppas release plots of Ethyl cellulose and HPMC K100M formulations (F9, F10, F11).

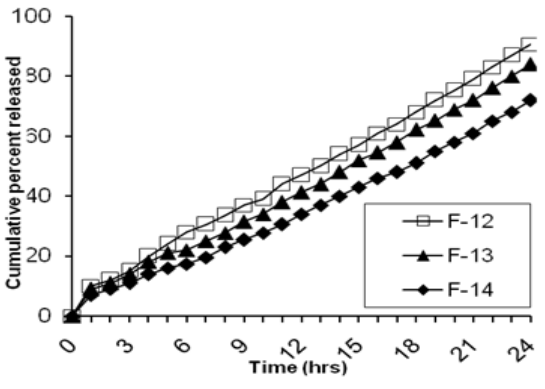

Fig 23: Cumulative percentage drug release profiles of formulations (F12, F13, F14) prepared with combination of different grades of Ethyl Cellulose and HPMC K100M.

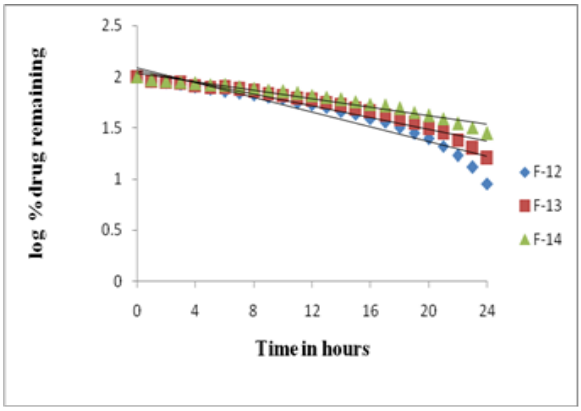

Fig 24: First order kinetics of Ethyl cellulose and HPMC K100M formulations (F12, F13, F14).

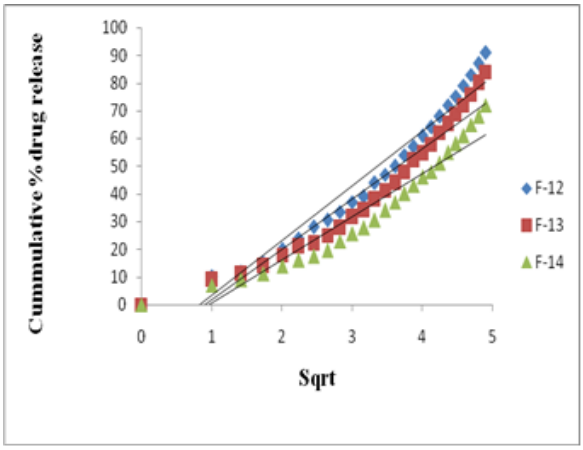

Fig 25: Higuchi release mechanism of Ethyl cellulose and HPMC K100M formulations (F12, F13, F14).

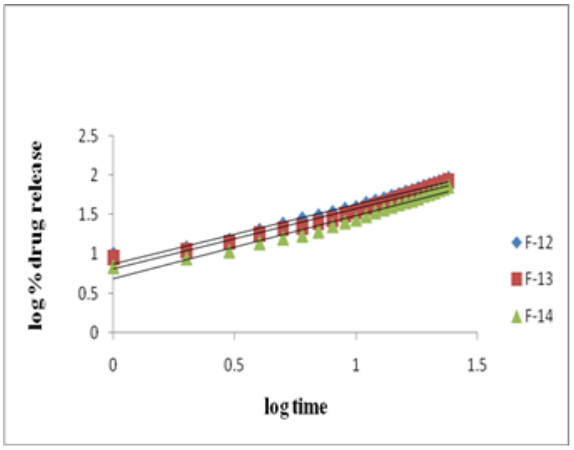

Fig 26: Korasmeyer & peppas release plots of Ethyl cellulose and HPMC K100M formulations (F12, F13, F14).

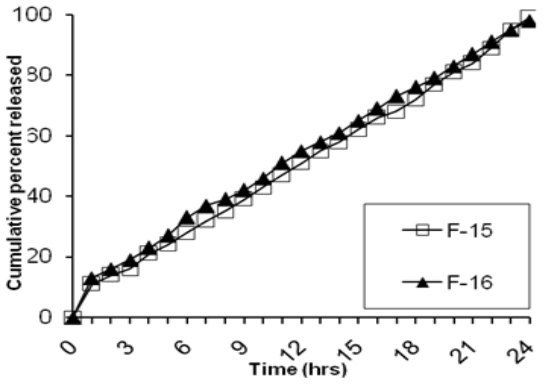

Fig 27: Cumulative percentage drug release profiles of formulations (F15, F16) prepared with combination of different grades of Ethyl Cellulose and HPMC K100M in different concentration.

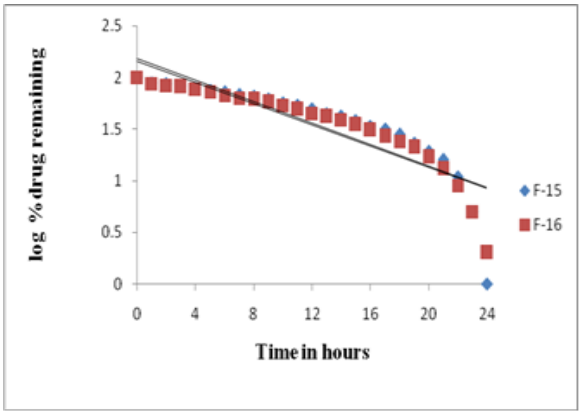

Fig 28: First order kinetics of Ethyl cellulose and HPMC K100M formulations (F15, F16).

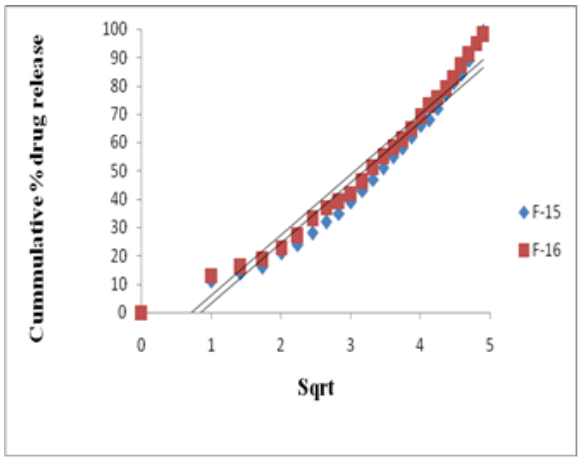

Fig 29: Higuchi release mechanism of Ethyl cellulose and HPMC K100M formulations (F15, F16).

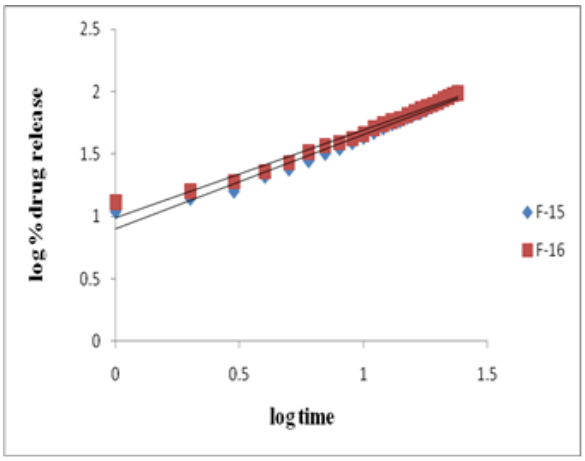

Fig 30: Korasmeyer & peppas release plots of Ethyl cellulose and HPMC K100M formulations (F15, F16).

SUMMARY AND DISCUSSION

The formulation of Atazanavir with Ethyl cellulose was developed with the use different grades of the Ethyl cellulose in the formulations such as EC N20(F-1), EC N22(F-2), EC N45(F-3), EC N50(F-4) and EC N100(F-5). The drug and polymer was mixed uniformly in the ratio of (1:1) and then the above blend was pre lubricated with magnesium stearate. The above lubricated blend was compressed into tablet using 8.0 mm punch, at a hardness of around 10kg/cm^2. To study the floating property, the prepared tablet was placed in 100ml of 0.1N HCL. The tablets were not floated and the tablet was remained at the bottom of the glass beaker. This is mainly may be due to high hardness of the tablets. The tablet became 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 the further formulation. The next formulation the tablets are compressed at hardness of 4-6 kg/cm^2 with different grades of Ethyl cellulose in the formulations such as EC N20(F-1), EC N22(F-2), EC N45(F-3), EC N50(F-4) and EC N100(F-5). Then the tablet found to be floating but disintegrated with in short period of time due to decrease in the hardness of the tablet.

Formulation of Atazanavir sulphate by using different grades of Ethyl Cellulose (EC N22, EC N50 and EC N100) and HPMC K100M and the blend is lubricated with Magnesium stearate and compressed with hardness of 5 kg/cm^2. Then the tablets with desired physicochemical properties and floating property were obtained.

Based on the results with all the polymers the order of drug release was mainly depends on the type of polymer and polymer proportion. Combination of polymer yields more retardation and floating time than individual polymer.

CONCLUSION

In this study, we have described the preparation and evaluation of Atazanavir sulphate floating matrix tablets composed of ethyl cellulose and HPMC K100M. In this present study, HPMC K100M is successfully employed in the formulation of controlled release floating tablets of Atazanavir. Good physicochemical properties were observed in the prepared formulations with a hardness of 5-6 kg/cm² and a friability of less than 1%. This clearly indicates that the prepared matrix tablets were having good strength. In vitro buoyancy study shows that the prepared matrix tablets were floated within 5 seconds. The formulation was made and succeeded without gas generating agent. Combination of two polymers can be employed for better results.

REFERENCES

1. Robinson BS, Riccardi KA, Gong YF, et al. BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. Antimicrob Agents Chemother, 2000; 44(8): 2093–2099.
2. Alatrakchi N, Di Martino V, Thibault V, Autran B. Strong CD4 Th1 responses to HIV and hepatitis C virus in HIV-infected long-term non-progressors co-infected with hepatitis C virus. AIDS, 2002; 16(5): 713–717.
3. Bristol-Mayers pharmaceuticals LTD, Reyataz® US prescribing information (09/08).
4. Clotilde Allevena, clinical medicine therapeutics, 2009; 243-252.
5. Laura Dickinson, journal of Antimicrobial chemotherapy, 2009; 63: 1233-1243.
6. Reddy, L., Murthy, R., Crit. Rev. Ther. Drug Carrier Syst., 2002; 19: 553-585.
7. Jantzen GM. and Robinson J.R., In:- Banker, G.S. and Rhodes, C.T., Eds., Modern Pharmaceutics, 2nd Ed., Marcel Dekker Inc., New York, 1995; 40: 577.
8. Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York, 1996; 678-721.
9. Li VHK, Robinson JR, Lee VHL, In, Robinson, J.R. and Lee, V.H.L., Eds., Controlled Drug Delivery; Fundamental and Applications, 2nd Edn., Marcel Dekker Inc., New York, 1987; 5.
10. Kydonius A. Treatise on Controlled Drug Delivery, fundamentals, Optimization, Applications. Marcel Dekker Inc., 1992; 256-304.
11. Lee HL and Robinson JR. Controlled Drug Delivery; Fundamental and Applications, 2nd Ed., Marcel Dekker Inc., New York, 1987; 253.
12. Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York, 1996: 678-721.
13. Singh BN and Kim KH. Floating drug delivery systems:- an approach to oral controlled drug delivery via gastric retention. *J Control Release*, 2000; 63: 235-259.
14. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res., 2008; 7(3): 1055-1066.
15. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharmacy, 1996; 22(6): 531-539.
16. Whishead B, Fell JT, Collett JH. Development of gastro retentive dosage from. Eur J Pharm Sci., 1996; 4: 182-186.

17. Hire NN and Derle D: A Review on Microsphere as drug carrier. International journal of advanced research, 2014; 2(3): 901-913.
18. Rishikesh G, Sunil Kumar P, Snigdha P and Peeyush B: Formulation and evaluation of novel stomach specific floating microspheres bearing famotidine for treatment of gastric ulcer and their radiographic study. Asian Pacific Journal of Tropical Biomedicine, 2014; 4(9): 729-735.
19. Jyothsna K and Vijaya Lakshmi G: Omeprazole Floating Delivery System. Research Journal of Pharmaceutical, biological and chemical sciences, 2013; 4(2): 374-380.
20. Raymond c Rowe, Paul J sheskey, Sian cowen, Hand book of Pharmaceutical excipients, May 200, 4th edition:-53-55, 138-140, 173-175, 253-256.
21. "Handbook of pharmaceutical excipients", 4th ed., American Pharmaceutical Association, edited by Raymond C Rowe, Paul J Sheskey and Paul J Weller.
22. Ozturk A. Mechanism of release from pellets coated with an ethyl cellulose-based film. J Controlled Release, 1990; 14(3): 203-213.
23. Narisawa S.Porosity-controlled Ethyl Cellulosefilm coating. IV. Evaluation of mechanical strength of porous Ethyl Cellulosefilm. Chem Pharm Bull, 1994; 42(7): 1491-1495.
24. Bodmeier R, Paeratakul O. The effect of curing on drug release and morphological properties of Ethyl Cellulose pseudo latex-coated beads. Drug Dev Ind Pharm., 1994; 20(9): 1517-1533.
25. Dressman J. Circumvention of pH-dependent release from ethyl cellulose-coated pellets. J Controlled Release, 1995; 36(3): 251-260.
26. Iyer U. Comparative evaluation of three organic solvent and dispersion-based Ethyl Cellulosecoating formulations. Pharmaceut Technol, 1990; 14(9): 68-86.
27. K. Chaturvedi, S.Umadevi and Subash vagini. Preparation and Evaluation of Propranolol HCl floating effervescent tablets with different polymers, Sci Pharm., 2010; 1-13.
28. Zadeh, T.Jamei, Fakher Rahim and Mohmad Reza; Preparation and evaluation of floating granules of diclofenac sodium, International Journal of Drug Delivery, 2010; 2: 344-35.
29. R.S. Radke, S.B. Deshmukh, P.S. Jagtap and P.S. angane; Development of captopril sustained release effervescent floating tablets using different polymers, International Journal of Pharma and Bio Sciences, 2010; 1(2): 1-10.
30. Mark Gibson, Pharmaceutical Preformulation, 2nd edition, 2008; 21.
31. Wells, James I. *Pharmaceutics Preformulation.* Ellis horwood ltd., 1998; 208-209.

32. Ami, D., Mereghetti P. & Doglia, S. M. In *Multivariate Analysis in management, engineering and the sciences* (Editors L. Valim de Freitas & A. P. Barbosa Rodrigues de Freitas) "Multivariate analysis for Fourier transform infrared spectra of complex systems and processes", 2013; 189–220. InTech, Croatia.
33. Chung, D. & Keles, S. Sparse Partial Least Squares Classification for High Dimensional Data. *Stat Appl Genet Mol Biol.*, 2010; **9:** 1–30.
34. Givens, G. H., Beveridge, J. R., Draper, B. A. & Bolme, D. In *Articulated Motion and Deformable Objects*. AMDO 2004. Lecture Notes in Computer Science. (Editors Perales F. J. & Draper B. A.). Using a Generalized Linear Mixed Model to Study the Configuration Space of a PCA+LDA Human Face Recognition Algorithm. Vol. 3179, (Springer, Berlin, Heidelberg, 2004.
35. Sturtevant J. Biochemical applications of differential scanning calorimetry. Ann Rev Phys Chem., 1987; 38: 463–88.
36. Biltonen RL, Lichtenberg D. The use of differential scanning calorimetry as a tool to characterize liposome preparations. Chem Phys Lipids, 1993; 64: 129–42.
37. Giron D. Applications of thermal analysis and coupled techniques in pharmaceutical. J Thermal Anal Calorim, 2002; 68: 335–57.
38. Aulton, M. E. *Pharmaceutics The Science of Dosage Form Design*. Churchill Livingstone, 2002; 2nd ed., 113-118.
39. Leon Lacheman, Herbert A. Liberman, Joseph L. Kanig. Theory and Practice of Industrial pharmacy 3rd edition, 296–313.
40. Li S, Lin S, Chien TW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium, AAPS Pharm Sci Tech, 2001; 2(1).
41. Janardhan D, Lingam M, Krishna C, Venkateswarlu V. Formulation and *In vitro* evaluation of gastroretentive drug delivery system for ranitidine hydrochloride, International journal of pharmaceutical sciences and nanotechnology, 2010; 1(3): 227-232.
42. Janez K, Jerneja O. A new amoxicillin/clavulanate therapeutic system: preparation, *In vitro* and pharmacokinetic evaluation, international journal of pharmaceutics, 2007; 335: 106-113.
43. Moursy NM, Afifi NH, Ghorab DM, El-Saharty Y. Pharmazie Applications of Gastro-retentive floating drug delivery system, 2003; 58: 38-43.

44. S. H. Shaha et al Gastro-retentive floating drug delivery system/Asian Journal of Pharmaceutical Sciences, 2009; 4(1): 65-80.
45. Ms. Julan. U. Desai; Floating Drug Delivery Systems:- An approach to Gastro retention pharmainfo.net, 2007; 5.
46. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using gastroretentive technologies. Current Opinion in Pharmacology, 2006; 6(5): 501-8.
47. Brahmankar.p and Jaiswal, Biopharmaceutics and Pharmacokinetics, Reprint, 2007: 290-292.
48. Extended Release Tablets. In United State Pharmacopoeia 28 National formulary 23, US Pharmacopoeial convention Inc: Rockville, MD., 2005; 1580.
49. Chen J, Park K. Synthesis and Characterization of Superporous Hydrogel Composites. J Control Release, 2006; 5(1-2): 73-82.
50. Degtiareva H, Bogdanov A, Kahtib Z. The use of Third Generation Antacid Preparations for the Treatment of Patients with Nonulcerous Dyspeosia and Peptic Ulcer Complicated by Reflux Esophagus [in Chinese]. Liakrs' ka sprava, 1994; 5-6: 119-122.
51. Singh N, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release, 2000; 63: 235-59.
52. Dinarvand R, Mirfattahi S, Atyabi F. Preparation, characterization and in vitro drug release of isosorbide dinitrate microspheres. Journal of Microencapsulation, 2002; 19: 73-81.
53. Abrol S, Trehan A, Katare OP. Formulation, characterization, and in vitro evaluation of silymarin-loaded lipid microspheres. Drug Deliv, 2004; 11: 185-91.