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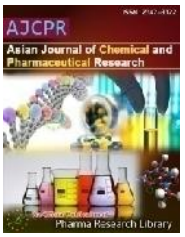

Research Article **Open Access**

Formulation Development and *In-Vitro* Evaluation of Delayed Release Drug Delivery System of Atazanavir Tablets

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A B S T R A C T

The aim of the present study was to develop delayed release formulation of Atazanavir to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of poly methacrylate polymers was employed as polymers. Atazanavir dose was fixed as 4 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 10, 20 and 30 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.33 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Atazanavir, Eudragit RL 100, Eudragit RS 100, Ethyl cellulose, Sustained release tablets.

A R T I C L E I N F O

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1. Introduction

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled release drug delivery system is capable of achieving the benefits like maintenance of optimum

therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half- life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances. The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

- The physiochemical characteristics of the drug
- Anatomy and physiology of GIT, Characteristics of Dosage forms

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery.

Gastro intestinal retention

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [5].

To successfully modulate the gastro intestinal transit time of a drug delivery system through floating drug delivery system(FDDS)For maximal gastro intestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. These are out lined and briefly discussed.

Stomach anatomy

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following phases

The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms. There are many difficulties faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa (**Hirtz, 1985**). Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. *In-vivo/in- vitro* evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

Advantaged of FDDS

1. The gastro retentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances, it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. FDDS improves patient compliance by decreasing dosing frequency.
7. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.

8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Enhanced absorption of drugs, which solubilize only in stomach.
11. Superior to single unit floating dosage forms as Such microspheres releases drug uniformly and there is no risk of dose dumping.
12. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

2. Materials and Methods

Materials: Atazanavir, Different Grades of HPMC polymers, Accural, Starch, Micro Crystalline Cellulose.

Methodology

Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve:

100 mg of Atazanavir pure drug was dissolved in 100 ml of 0.1N HCl (stock solution)10 ml of solution was taken and make up with 100 ml of 0.1N HCl (100 µg/ml).From this 10 ml was taken and make up with 100 ml of 0.1N HCl (10 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 1,2,3,4 and 5 µg/ml of Atazanavir per ml of solution.

The absorbance of the above dilutions was measured at 276 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Pre-formulation parameters: The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where,

Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations are given. The tablets were prepared as per the procedure given below and aim is to prolong the release of Atazanavir. Total weight of the tablet was considered as 500 mg.

Procedure:

1. Atazanavir and all other ingredients were individually passed through sieve no ≠ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc.
4. The tablets were prepared by using direct compression method.

All the quantities were in mg, Total weight is 300 mg.

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The

resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre-weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Atazanavir were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In-vitro* Buoyancy studies:**

The *in-vitro* buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In-vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl
RPM -- 75
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900 ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 266 nm using UV-spectrophotometer.

3. Results and discussion

The present study was aimed to developing gastro retentive floating tablets of Atazanavir using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method:

Graphs of Atazanavir was taken in Simulated Gastric fluid (pH 1.2) at 276 nm.

Table 2: Observations for graph of Atazanavir in 0.1N HCl (276 nm

concentration	absorbance
0	0
0.1	0.038
0.2	0.14
0.3	0.199
0.4	0.289
0.5	0.385
0.6	0.459

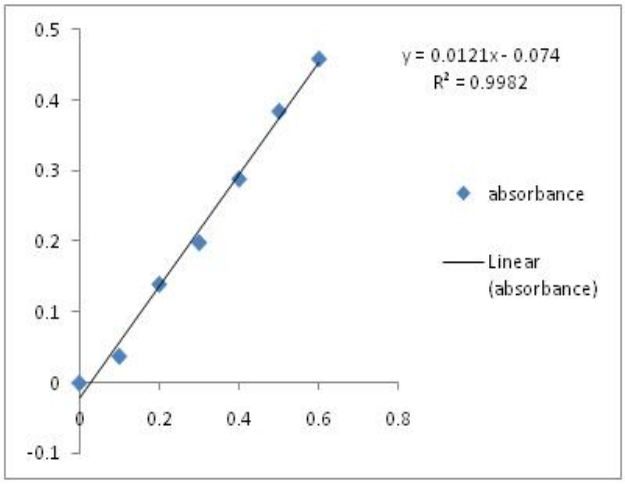

Figure 1: Standard graph of Atazanavir in 0.1N HCl

Pre-formulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18, which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

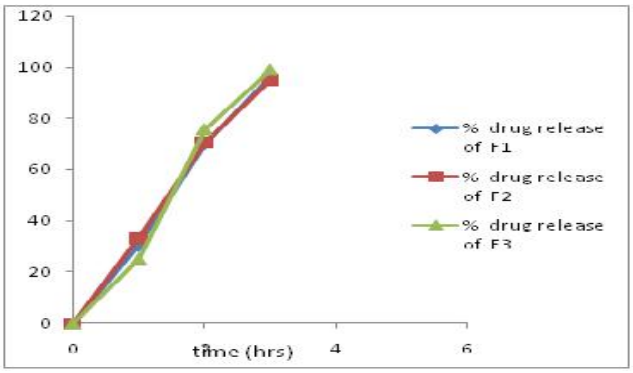

Figure 2: % drug release of Formulations from F1-F3

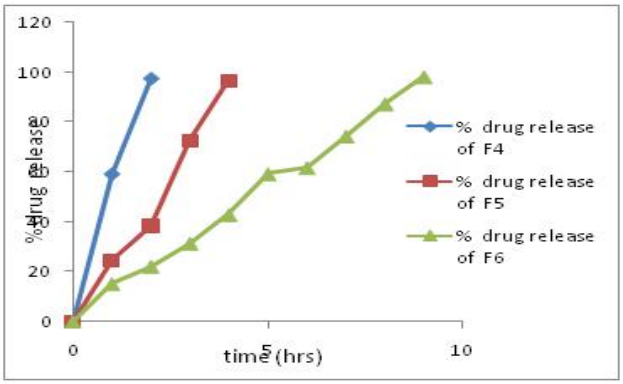

Figure 3: % drug release of Formulations from F4-F6

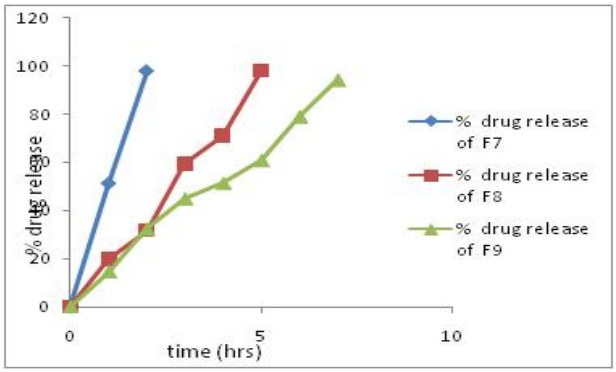

Figure 4: % drug release of Formulations from F7-F9

From the dissolution data it was evident that the formulations prepared with hpmc k15m as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with hpmck100m retarded the drug release in the concentration of 30 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.33 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

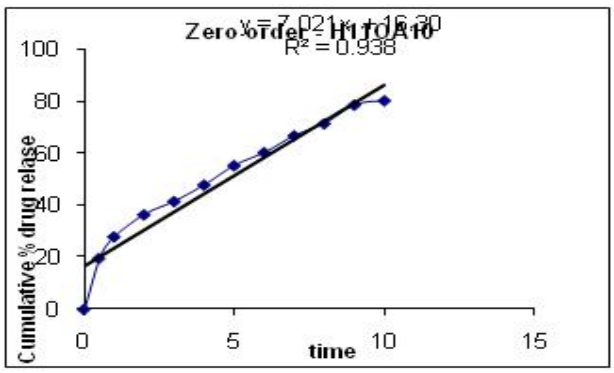

Figure 5: Zero order release kinetics graph

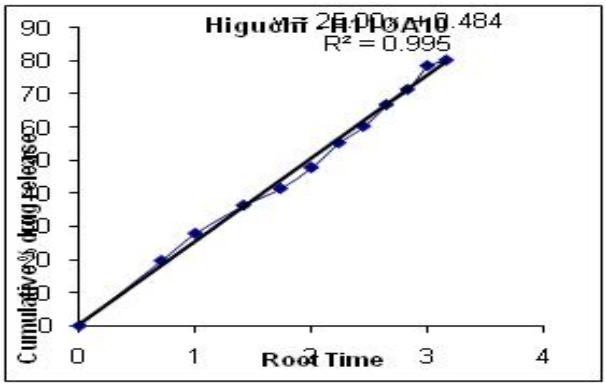

Figure 6: Higuchi release kinetics graph

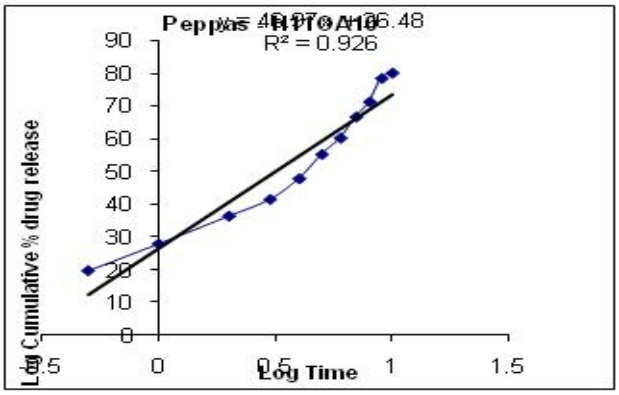

Figure 7: Kars mayer peppas graph

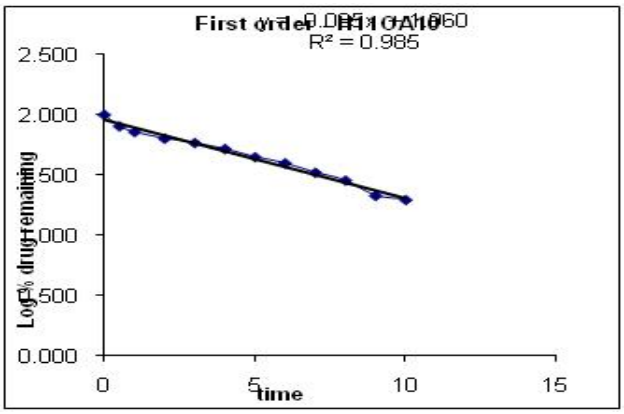

Figure 8: First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed Higuchi mechanism.

Table 1: Formulation composition for floating tablets

Formulation No.	Atazanavir	HPMC K4M	HPMC K15M	HPMC K100M	Accural	Mag. Stearate	Talc	MCC pH 102
F1	100	10	-----	-----	120	6	6	QS
F2	100	20	-----	-----	120	6	6	QS
F3	100	30	-----	-----	120	6	6	QS
F4	100	-----	10	-----	120	6	6	QS
F5	100	-----	20	-----	120	6	6	QS
F6	100	-----	30	-----	120	6	6	QS
F7	100	-----	-----	10	120	6	6	QS
F8	100	-----	-----	20	120	6	6	QS
F9	100	-----	-----	30	120	6	6	QS

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

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Table 4. Invitro quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
F1	302.5	4.5	0.52	4.8	99.76	4.0
F2	305.4	4.2	0.54	4.9	99.45	4.2
F3	298.6	4.4	0.51	4.9	99.34	4.5
F4	300.6	4.5	0.55	4.9	99.87	4.1
F5	299.4	4.4	0.56	4.7	99.14	4.0
F6	300.7	4.2	0.45	4.5	98.56	4.4
F7	302.3	4.1	0.51	4.4	98.42	4.5
F8	301.2	4.3	0.49	4.7	99.65	4.6
F9	308.3	4.5	0.55	4.6	99.12	4.7

***In-Vitro* Drug Release Studies**

Table 5: Dissolution Data of Atazanavir Tablets

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	30.22	33.26	25.02	59.21	24.66	15.12	51.10	19.80	14.54
2	69.88	70.65	75.55	97.52	38.44	22.05	97.73	31.58	32.23
3	96.25	94.82	98.69		72.85	31.29		59.28	44.85
4					96.66	42.83		71.01	51.31
5						59.21		98.06	60.86
6						61.70			78.98
7						74.33			94.26
8						87.26			
9						98.17			

4. Conclusion

In the present research work gastro retentive non effevescent floating matrix formulation of Atazanavir by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent accural concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various pre-formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations, the formulations prepared by using HPMC K100M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15M retarded the drug release up to 12 hours in the concentration of 30 mg (F6).The formulations prepared with HPMC K4M were also retarded the drug release for more than 12 hours. Hence, they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data, it was evident that the formulation followed Higuchi mechanism of drug release.

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