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Design and Evaluation of Atazanavir Sulphate Non-Effervescent Sustained Release Floating Matrix Tablets

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Abstract

Objectives: In this we made a sustained release floating matrix dosage form of the ATZ. This formulation extends retention time of G.I.T and delay in delivery after oral route intake.

Material and Methods: Pullulan gum, HPMC K100M and PEO WSR Coagulant were taken as polymers in developing the SR profile in order to get the desired sustained release profile over an extended period.

Results and Conclusions: All the formulation prolonged the drug release up to 10 hrs and more. The release and floating property were influenced by the polymer type and polymer proportion. The combination of PEO and HPMC yields more sustained release than the same individual polymers. The formulation prepared with PEO and HPMC have extra floating time, then the formulation made with the pullulan gum. The retardation of the polymer is in the following order combination of "PEO and HPMC > HPMC K 100M > PEO coagulant > Pullulan gum". The formulations prepared with pullulan gum were assessed for in vivo floating time, which shows the floating property up to 8 hrs. The DSC and FTIR findings show that there is no drug-polymer interaction. This finding gives the preliminary idea about the development of floating drug delivery systems of Atazanavir without the use of a gas generating agent. This study has potential commercial and industrial applications after establishing the real-time stability, safety and efficacy.

Keywords: Atazanavir Sulphate; Sustained Release Floating Matrix Tablets; Pullulan Gum; HPMC K100M; PEO WSR Coagulant; *In Vivo* Floating Time

Introduction

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus. This condition gradually reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a biological fluid containing HIV, such as blood, semen, vaginal fluid, pre seminal fluid, and breast milk.

This transmission can include anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, an exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above biological fluid. Even though treatments for AIDS and HIV can slow the course of the disease, at present no vaccine to cure. Antiretroviral treatment reduces both the mortality and the illness of HIV infection, but these drugs are costly and routine access to antiretroviral medication is not accessible in all countries. Due to the exertion in treating HIV infection, preventing infection is a key aim in directing the AIDS pandemic, with health organizations promoting safe sex and needle-exchange programmes in attempts to slow the spread of the virus.

Atazanavir sulphate (ATZ) is a human immunodeficiency virus (HIV) protease inhibitor. It is an azapeptide that blocks the processing of viral gag-pol proteins in HIV-1 infected cells, thus inhibiting the formation of mature virions. Atazanavir is rapidly absorbed with a Tmax approximately 2.5 hours. Atazanavir reveals nonlinear pharmacokinetics with greater than dose-proportional increases in AUC and Cmax values over the dose range of 200–800 mg once daily. Plasma half-life is 6.5hrs [1].

Atazanavir sulphate (ATZ) easily soluble in organic solvents and slightly soluble in water (4-5mg/ml). The solubility of the substance is pH dependent (maximum solubility at pH 1.9) i.e. Stomach pH range [2]. Atazanavir sulphate dissolution and absorption relies heavily on an acidic environment [3].

By oral conventional capsule dosage form of ATZ shows more side effects like Cardiac conduction abnormalities, rashes, hyperbilirubinemia, nephrolithiasis, nausea, jaundice and abdominal pain, jaundice etc. [1]. To minimize or reduce the above side effects which require developing sustained release floating matrix tablets. Characterization of Atazanavir sulphate (ATZ) drug absorption, solubility and plasma half-life are very suitable for formulation into a sustained release floating matrix tablet. Sodium bicarbonate as a gastric antacid, it has several drawbacks: its duration of action is short; its reaction with hydrochloric acid produces carbon dioxide, which may cause stomach pains or exacerbate an ulcer, and it will produce systemic alkalosis [4].

Due to these drawbacks not employing sodium bicarbonate as an ingredient in the development of floating sustained release matrix tablets of Atazanavir sulphate. ATZ with a view of prolonging gastric residence time with a controlled release mechanism achieve improved patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system.us (HIV).This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid, and breast milk.

This transmission can involve anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above body fluids. Although treatments for AIDS and HIV can slow the course of the disease, there is currently no vaccine or cure. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but these drugs are expensive and routine access to antiretroviral medication is not available in all countries. Due to the difficulty in treating HIV infection, preventing infection is a key aim in controlling the AIDS pandemic, with health organizations promoting safe sex and needle-exchange programmes in attempts to slow the spread of the virus.

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By oral conventional capsule dosage form of ATZ shows more side effects like Cardiac conduction abnormalities, rashes, hyperbilirubinea, nephrolithiasis, nausea, jaundice and abdominal pain, jaundice etc. [1]. So, to minimize or reduce the above side effects which require developing sustained release floating matrix tablets. Characterization of Atazanavir sulphate (ATZ) drug absorption, solubility and plasma half-life are very suitable for formulation into sustained release floating matrix tablets. Sodium bicarbonate as a gastric antacid, it has several drawbacks: its duration of action is short; its reaction with hydrochloric acid produces carbon dioxide, which may cause stomach pains or exacerbate an ulcer, and it will generate systemic alkalosis [4]. Due to these drawbacks not employing sodium bicarbonate as an ingredient in the development of floating sustained release matrix tablets of Atazanavir sulphate. ATZ with a view of extending the gastrointestinal residence time with a controlled release mechanism to achieve enhanced patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system.

Materials and Methods

Gift sample from Aurobindo Pharma Ltd, Hyderabad, HPMC K100M -DOWchemicalcompany, USA. Pullulan gum Gift sample from Aurobindo Pharma Ltd, Hyderabad. PEO WSR Coagulant from-DOW chemical company, USA. Microcrystalline cellulose Signet chemicals Magnesium Stearate Himedia Pvt Ltd, Mumbai. TalcS.D. Fine Chemicals Pvt Ltd, Mumbai. Hydrochloric Acid Merck from Specialties Pvt Ltd, Mumbai.

Methods

Construction of Standard Calibration Curve

The standard calibration curve of Atazanavir was prepared by using 0.1N HCl. The standard graph was plotted between the concentration range of 10-100 (µg/ml) at 250nm using a UV spectrophotometer.

Procedure for Floating ATZ Tablet Preparation

Floating matrix tablets containing Atazanavir sulphate were prepared by direct compression technique using varying concentrations of different grades of polymers.

Method (Direct Compression)

a) Atazanavir bisulphate and other ingredients are specifically weighed and sifted through sieve # 40.

b) Atazanavir sulphate is correctly mixed with an amount of needed chemical compound (pullulan gum, HPMC K100M, and Polyethylene oxide WSR coagulant) then mixed with the remaining ingredients in geometric proportions.

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c) Then lubricated with the antecedently weighed and sieved magnesium stearate and talc to get the mix for compression. Then the lubricated mix is subjected to compression by needed 8mm or 9mm circular standard flat faced punch on a sixteen-station rotary tablet punching machine.

Results and Discussion

Standard Calibration Curve for Atazanavir Sulphate

Table 1: Standard values of Atazanavir sulphate.

Concentration (µg/ml)	Absorbance
0	0
10	0.11
20	0.215
30	0.381
40	0.539
50	0.66
60	0.78

Initially, the pure atazanavir was scanned in between UV-range like 200-400nm. The utmost absorbance for atazanavir was found at 250nm. A standard concentration of atazanavir within the vary of 10-100µg/ml was prepared in 0.1N HCl and the absorbances were measured at 250nm. Atazanavir is showing decent linearity between 10-60µg/ml (Table 1) with a correlation coefficient of 0.993 (Figure 1).

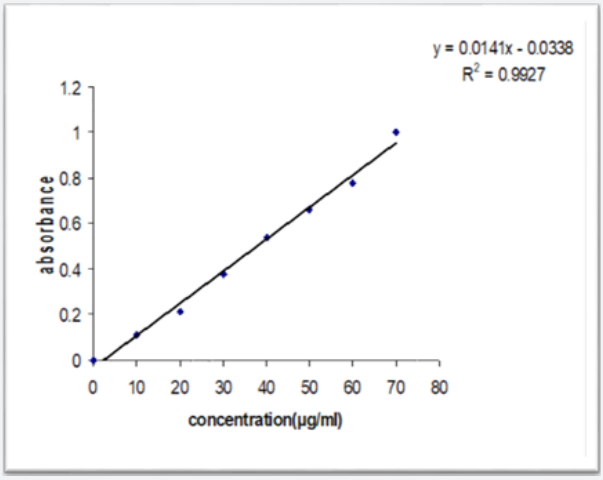

Figure 1: The standard curve of Atazanavir sulphate in 0.1N HCl.

Prototype Formulation Development of Atazanavir Floating Matrix Tablets Prepared with Pullulan Gum

Table 2: Formulation composition and physicochemical parameters of the prepared Atazanavir sulphate matrix tablets with Pullulan gum.

Ingredients	F1	F2	F3	F4
	mg/tab			
Atazanavir sulphate	100	100	100	100
Pullulan gum	100	125	150	175
Microcrystalline cellulose- PH 200	20	20	20	20
Talc	3.5	3.5	3.5	3.5
Magnesium stearate	1.5	1.5	1.5	1.5
Total weight	225	250	275	300
Evaluation Parameters				
Weight variation (mg)	225.8±1.48	250.4±0.4	275.6±0.41	300.8±1.64
Tablet Hardness kg/cm^2	4.6±0.5	5.1±0.5	6.3±0.5	6.7±00.5
Tablet diameter (mm)	8	8	9	9
Thickness (mm)	5.58	5.6	6.21	6.32
Friability (%)	0.26	0.23	0.48	0.51
Drug Content (%)	97.32±2.3	95.9± 1.5	98.21±1.8	98.56±2.0
In vitro buoyancy	>10sec	>15sec	>13sec	>10sec

The formulation with pullulan gum was developed with the use of drug and polymer percentage of (44.4%). The drug and polymer were mixed uniformly and compress into a tablet using 8.0mm 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. There is no floating property was observed and the tablet has 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 to entrap the air and water. Based on the above observation, it was decided to reduce the tablet hardness in the further formulation. The next formulation was compressed at 4-5kg/cm^2 of hardness and the floating property was observed at the above hardness, the tablet floats immediately. Based on the above observation, it was decided to keep the hardness at the lower range.

Formulation Development of Atazanavir Floating Matrix Tablets with Pullulan Gum

The matrix tablets of atazanavir were ready by using diverse concentrations of the pullulan gum. The drug, Pullulan gum and MCC-PH 200 were directly mixed uniformly, and then the above

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blend was pre-lubricated with talc and lastly lubricated with magnesium state. The concentration of the pullulan gum used in the above formulation is 44.4 % (F-1), 50 % (F-2), 54.5 % (F-3) and 58.3 % (F-4). The lubricated mixture was compacted by using 8mm flat faced punch for F-1and F-2 formulation and 9mm flat faced punch for F-3and F-4. Numerous physicochemical properties were studied. The results were given in (Table 2).

All the Atazanavir floating matrix tablets with Pullulangum (F-1 to F-4) were evaluated for various physicochemical parameters like weight variation, hardness, thickness, friability, and drug content. The Hardness of the tablets was found within the range of 4.6-5.1kg/cm2 for tablets prepared with 8mm (F-1 & F-2). The Hardness of the tablets prepared with 9 mm (F-3 & F-4) was found in the range of 6.3-6.7kg/cm^2. Friability of below 1% clearly indicates a stronger mechanical strength of the prepared tablets. Assay of the prepared matrix tablets was found in the range of 97- 99% clearly representing the good content uniformity. In vitro buoyancy study in 100ml of the 0.1 N HCl shows that the prepared matrix tablets were rapidly floated to the surface of the medium within 15sec. This clearly specifies the good floating property. The floating time was studied and discussed later in this chapter.

In vitro Drug Release Studies of Atazanavir Floating Matrix Tablets Prepared with Pullulan Gum

Table 3: Cumulative percentage drug release and release kinetics of formulations prepared with Pullulan gum. Each value represents mean ± S.D (n=3).

Time (HR)	Formulation Code			
	F-1	F-2	F-3	F-4
0	0	0	0	0
1	30.13±1.7	22±2.3	14±0.4	10.3±0.8
2	56.41±1.5	43±1.8	27±1.0	19.6±1.2
3	100.2±2.2	64±1.6	39±1.3	26.1±1.1
4		87±0.6	52±1.2	32.6±1.4
5		99±1.0	85±1.0	51.3±0.6
6			97.8±0.9	66.4±1.3
8				87.1±1.4
10				98.3±0.2
Kinetics				
Zero order (r^2)	0.9872	0.9945	0.9727	0.984
First order (r^2)	0.9938	0.8033	0.7504	0.8297
Higuchi (r^2)	0.9171	0.929	0.9177	0.9287
Peppas (n)	1.0734	0.9714	1.0904	1.0251

In vitro dissolution studies were conducted in 900ml of 0.1 N HCl using USP-Type-II apparatus. The results showed that as the polymer concentration of pullulan gum will increases the drug release rate was retarded. All the formulation shows smart floating properties. An F-1 formulation holding 44.4% retards the drug only for 3 hours. An F-2 formulation containing 50% of the pullulan gum retarded the drug release for around 5 hours, F-3 and an F-4 formulation containing 54%and 58% of pullulan gum retards the drug for 6hrs & 10hrs severally. The dissolution data of all formulations were fitted to several kinetic models such as zero-order, first-order, and Higuchi, and Peppas models.

The method of Bamba and Puisieux [5] was implemented for predicting the most appropriate model (Table 3). Describes the in vitro drug release kinetics of Atazanavir floating matrix tablets. The release kinetics of all the formulations follows zero order except F-1 formulation as it releases the drug in 3 hours. The Higuchi kinetic study shows that the drug release mechanism was diffusion controlled, but the release exponent of Peppas having n values in the range of "1" shows case-II transport [6]. This clearly suggests that diffusion is not the only mechanism, may be due to the polymer relaxation and or erosion. The outcomes of in vitro dissolution and release kinetics of the prepared Atazanavir floating matrix tablets were summarized in (Table 3) and (Figure 2) shows the plots of the cumulative percentage release Vs time profile of the prepared matrix tablets [7].

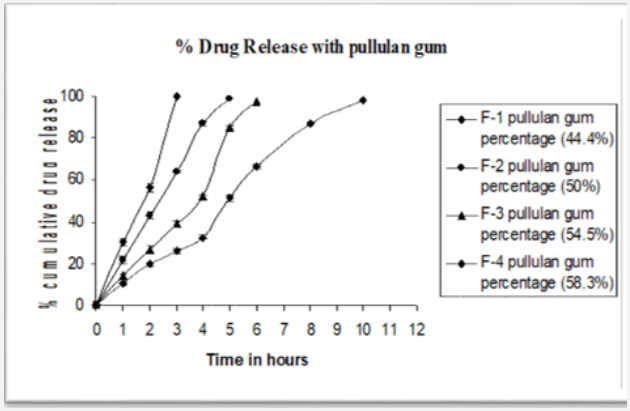

Figure 2: Cumulative percentage drug releases of formulations prepared with pullulan gum.

Formulation Development of Atazanavir Floating Matrix Tablets Prepared with PEO WSR Coagulant

Floating matrix tablets of the Atazanavir were prepared using PEO WSR Coagulant. The drug, PEO and MCC were mixed and sifted through # 30 sieve, the above mixture was pre-lubricated with talc and lubricated with magnesium stearate. The blend was compacted with an 8mmflat-faced punch at a hardness of 4.5 - 6.1kg/cm^2. The tablets were assessed for various physicochemical parameters.

Good physicochemical properties were ascertained in the prepared formulations with a hardness of 4.5 -6.1kg/cm2 and a friability of less than 1%. This clearly indicates that the prepared matrix tablets were having worthy strength. In vitro buoyancy study shows that the prepared matrix tablets were floated within 15seconds. The formulation composition and physicochemical properties were précised in the table was shown in (Table 4).

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Table 4: Formulation composition and physicochemical parameters of the prepared Atazanavir sulphate matrix tablets with PEO WSR Coagulant.

Ingredients	F5	F6	F7	F8
	mg/tab			
Atazanavir sulphate	100	100	100	100
PEO WSR Coagulant	25	50	75	100
Microcrystalline Cellulose-PH 200	20	20	20	20
Talc	3.5	3.5	3.5	3.5
Magnesium sterate	1.5	1.5	1.5	1.5
Total weight	150	175	200	225
Evaluation Parameters				
Weight variation (mg)	150±1.14	175±0.83	200.9±0.67	225±0.043
Tablet hardness kg/cm2	4.6±0.5	5.1±0.5	5.9±0.5	6.1±00.5
Tablet diameter (mm)	8	8	8	8
Thickness (mm)	3.35	3.67	4.18	4.21
Friability (%)	0.76	0.89	0.77	0.91
Drug Content (%)	97.75±2.3	96.25±1.8	97.48±2.8	97.69±2.4
Invitro buoyancy	>10sec	>15sec	>13sec	>12sec

In vitro Drug Release Studies of Atazanavir Floating Matrix Tablets Prepared with PEO WSR Coagulant

Table 5: Cumulative percentage drug release and release kinetics of formulations prepared with PEO WSR Coagulant. Each value represents mean ± S.D (n=3).

Time (h)	Formulation Code			
	F-5	F-6	F-7	F-8
0	0	0	0	0
1	39±0.4	24±1.6	18.6±1.6	10.6±1.3
2	57±1.0	32±1.3	19.4±1.3	14.7±0.8
3	66±1.2	40±2.8	22.3±1.6	18.3±1.4
4	81±1.3	47±1.2	26.1±0.1	21.3±0.9
5	93±1.1	53±1.3	30.3±1.6	23.3±1.4
6	99±1.3	61±0.9	35.9±1.3	29.7±1.5
8		75±1.7	48±0.6	36±1.0
10		89±1.4	59±1.8	42±1.3
Kinetics				
Zero order (r2)	0.9872	0.9633	0.9561	0.9885
First order(r2)	0.9938	0.9434	0.9541	0.9655
Higuchi(r2)	0.9171	0.9803	0.9252	0.9705
Peppas(n)	0.9171	0.5702	0.5154	0.5813

In vitro dissolution study of the prepared matrix, tablets were performed in 900ml of 0.1N HCl USP type II apparatus maintained at 37.5±0.50c for about 10hours. The in vitro dissolution study show that the prepared matrix tablet prolongs the drug release more than 10 hours. The formulations with 16% of polymer release the drug in 6 hours. As the polymer concentration increased the drug release was retarded. Only 42% of the drug was released in 10 hours for the formulation F-8 which contains the 44% of polymer. In vitro drug release follows the zero-order release kinetics with a correlation coefficient ranging from 0.9251-0.9885. Good correlation in Higuchi kinetics (0.9252-0.9968) clearly indicates that the drug release mechanism was principally diffusion controlled. This was further confirmed by Peppas release exponent in the range of 0.5111 to 0.5813, which was non-fickian diffusion mechanism. The outcomes of in vitro dissolution and release kinetics of the prepared Atazanavir floating matrix tablets were summarized in (Table 5) and (Figure 3) shows the plots of the cumulative % release vs time profile of the prepared matrix tablets [8,9].

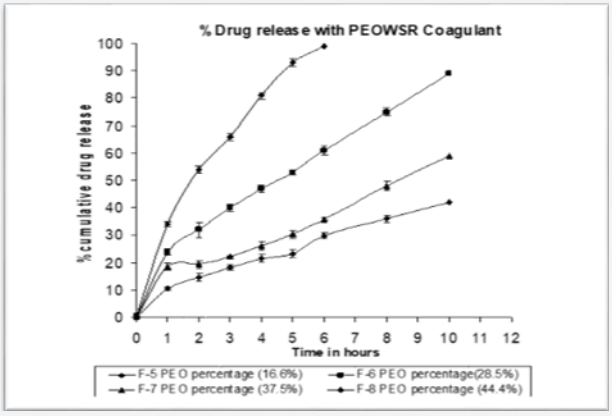

Figure 3: Cumulative percentage drug release profiles of formulations prepared with PEO WSR Coagulant.

Formulation development of Atazanavir floating matrix tablets prepared with HPMC K100M

With 8mmflat-faced punch at a hardness of 5-6kg/cm^2. The tablets were evaluated for several physicochemical of parameters. Acceptable physicochemical properties were observed in the prepared formulations with a hardness of 5-6.5kg/cm^2 and a friability of less than 1 %. This clearly specifies that the prepared matrix tablets were having good strength. The drug content of the tablet was found in the 94.48%-97.35% clearly indicates

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the good content uniformity of the drug in the prepared matrix tablets. In vitro buoyancy study shows that the prepared matrix tablets were floated in lee than 20 seconds. The formulation composition and physicochemical properties were shortened in the table was shown in (Table 6).

Table 6: Formulation composition and physicochemical parameters of the prepared Atazanavir sulphate matrix tablets with HPMC K 100 M.

Ingredients	F-9	F-10	F-11	F-12
	mg/tab			
Atazanavir sulphate	100	100	100	100
HPMC K 100 M	25	50	75	100
Microcrystalline Cellulose- PH 200	20	20	20	20
Talc	3.5	3.5	3.5	3.5
Magnesium sterate	1.5	1.5	1.5	1.5
Total weight	150	175	200	225
Evaluation Parameters				
Weight variation (mg)	150±0.80	175±0.83	200.9±0.93	225±0.097
Tablet hardness kg/cm^2	4.9±0.5	5.3±0.5	6.3±0.5	6.4±0.5
Tablet diameter (mm)	8.00	8.00	8.00	8.00
Thickness (mm)	3.35	3.67	4.18	4.21
Friability (%)	0.41	0.29	0.38	0.41
Drug Content (%)	97.35±1.7	96.55±2.4	94.48±1.8	95.42±. 09
Invitro buoyancy	>20sec	>19sec	>15sec	>17sec

In vitro Drug release Studies of Atazanavir Floating Matrix Tablets Prepared with HPMC K 100M

Table 7: Cumulative percentage drug release and release kinetics of formulations prepared with HPMC K 100M. Each value represents mean ± S.D (n=3).

Time (h)	Formulation Code			
	F-9	F-10	F-11	F-12
0	0	0	0	0
1	37.6±1.4	23.6±1.6	19.7±0.8	11.4±0.6
2	50.3±1.5	33±0.3	22.5±0.6	15.6±0.4
3	62.1±1.2	39.6±1.5	23.9±1.7	16.9±0.4
4	79.6±1.4	45.9±1.0	26.4±0.6	19.2±1.7
5	87±1.3	51.2±1.7	27.4±1.6	23.7±0.2
6	99±1.1	60±1.6	30.5±0.7	27.1±0.8
8		71±1.9	38.18±1.2	33.6±1.7
10		79±1.6	45.8±1.5	37.9±1.1
Kinetics				
Zero order (r^2)	0.9447	0.9904	0.9093	0.973
First order(r^2)	0.8025	0.9863	0.8617	0.9497
Higuchi(r^2)	0.9913	0.994	0.951	0.9766
Peppas(n)	0.5485	0.5301	0.479	0.5268

In vitro dissolution studies exhibited that the drug release was extended from 6-10 hours and more. Only 37% of the drug was released in 10hours in the formulation F-12 which encloses 44%of the polymer approximately. The drug release mainly depended on the polymer ratio, as the polymer ratio was increased the drug release was delayed. The drug release kinetics study discloses that the formulations follow zero order release. This clearly designates that the release was not depending on the concentration. The correlation coefficient of the Higuchi model was observed between 0.9510-0.9913 is clearly indicates the diffusion mechanism [10,11]. Peppas release exponent openly indicates the drug release follows non-fickion diffusion mechanism. The results of in vitro dissolution and release kinetics of the prepared Atazanavir floating matrix tablets were summarized in (Table 7) and (Figure 4) shows the plots of the cumulative % release vs time profile of the prepared matrix tablets.

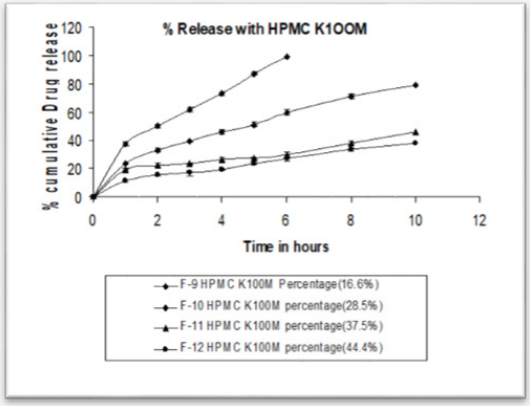

Figure 4: Cumulative percentage drug release profiles of formulations prepared with HPMC K 100 M.

Formulation Development of Atazanavir Floating Matrix Tablets Prepared with a Combination of PEO and HPMC K100M

The formulation of Atazanavir matrix tablets was prepared with a combination of polymers. The separable formulations containing 28.5% of polymer proportion were selected and the same proportion of individual polymers were merged in

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the tablets formulation as mentioned in (Table 8). The matrix tablets were prepared by the same method adopted previously for individual polymers. The tablets were compressed with 8mm round, flat-faced punch. Then the prepared tablets were evaluated for various physicochemical parameters such as weight variation, hardness, thickness, friability, and drug content. Good physicochemical properties were perceived with a drug content of 99.99 %. The formulation composition and physicochemical properties were summarized in the table was shown in (Table 8).

Table 8: Cumulative percentage drug release and release kinetics of formulations prepared with a combination of PEO and HPMC K 100M. Each value represents mean ± S.D (n=3).

Ingredients	F13 (mg/tab)
Atazanavir sulphate	100
PEO WSR Coagulant	25
HPMCK100M	25
Microcrystalline cellulose	20
Talc	3.5
Magnesium sterate	1.5
Total weight	175
Evaluation parameters	
Weight variation (mg)	175±0.83
Tablet hardness kg/cm^2	4.9
Tablet diameter (mm)	8
Thickness (mm)	4.03
Friability (%)	0.52
Drug Content (%)	99.99±1.3
Invitro buoyancy	>20sec

In Vitro drug release studies of atazanavir floating matrix tablets prepared with a combination of PEO & HPMC K 100 M

Table 9: Formulation composition and physicochemical parameters of the prepared Atazanavir sulphate matrix tablets with the combination of PEO and HPMC K100M.

Time (hr)	F-13
0	0
1	20±1.0
2	27±0.9
3	33±1.0
4	39±1.0
5	41±1.0
6	52±3.18
8	67±1.34
10	74±2.05
Kinetics	
Zero order (r^2)	0.9714
First order(r^2)	0.9657
Higuchi(r^2)	0.9671
Peppas(n)	0.5784

In vitro dissolution study shows that the drug release was retarded more in the combination of polymer used when compared with the individual formulation i.e. F-6 and F-10. The drug release kinetics were followed zero order with a correlation coefficient 0.9714. Higuchi correlation indicates that the drug release mechanism was diffusion controlled. Peppas release exponent n values were 0.5784 clearly indicating the release was non-fickian diffusion mechanism [12]. The results of in vitro dissolution and release kinetics of the prepared Atazanavir floating matrix tablets were summarized in (Table 9) (Figure 5).

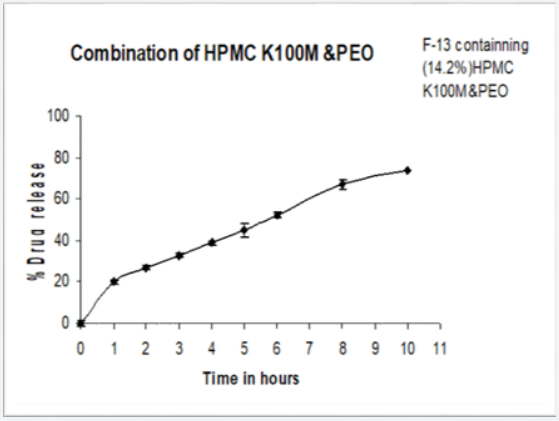

Figure 5: Cumulative percentage drug release profiles of formulations prepared with a combination of HPMC and PEO WSR Coagulant.

Selection of formulations for further study

Table 10: Release kinetics of selected formulations of Atazanavir.

Polymer Used	F4	F6	F10	F13
	Pullulangum	PEO	HPMC	HPMC&PEO
Polymer %	58.30%	28.50%	28.50%	28.50%
% Drug release in 10hrs	98%	89%	79%	74%
Zero-order (r)	0.9841	0.9633	0.9904	0.9714
First order®	0.8297	0.9434	0.9863	0.9657
Higuchi	0.9287	0.9803	0.994	0.9671
Peppas	1.0251	0.5702	0.5301	0.5784

Some formulations were selected from the floating matrix tablets prepared with pullulan gum, HPMC K 100M, and polyethylene oxide. The formulation releases above 74% in 10hours were selected for the comparative study. The formulation F-4 prepared with 58.3%of pullulan gum release 98% of the drug in 10hours. The drug release was slow up to 4 hours when compared with the formulations prepared with other polymers and mixture of polymers. The release was drastically increased from the 5th hour and the release was faster at the later stage. The formulations prepared with PEO alone at 28.5% of the polymer, release 89% of the drug in 10 hours. The formulations prepared with HPMC K 100 M releases only 79% of the drug in 10 hours. In all the formulation the drug release follows zero order kinetics with diffusion mechanism. The Peppas release exponent showing the case II transport for the tablets prepared

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with pullulan gum. For matrix tablets prepared with HPMC, PEO and combination of HPMC and PEO follow non-fickian diffusion. (Table 10) and (Figure 6) shows the comparative release kinetics of the selected formulations [13,14].

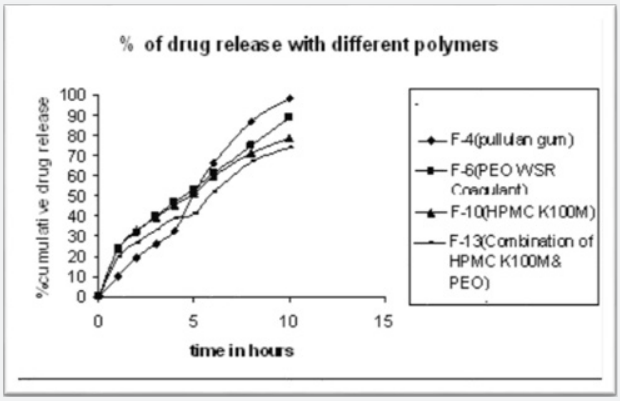

Figure 6: Cumulative Percentage drug releases of optimized formulations with different polymers such as Pullulan gum, PEO WSR coagulant, HPMC K100M.

In vitro buoyancy studies

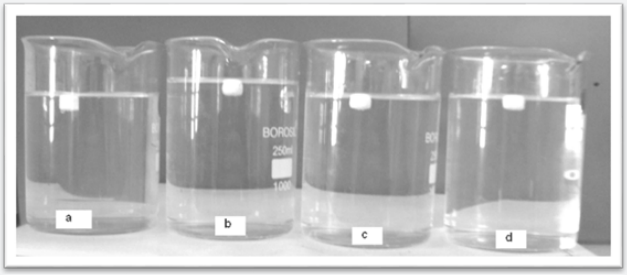

Figure 7: *In-vitro* buoyancy studies: At an initial time,

a) dosage form with pullulan gum
b) with PEO
c) With HPMC K100M
d) dosage form with a combination of PEO& HPMC K100M.

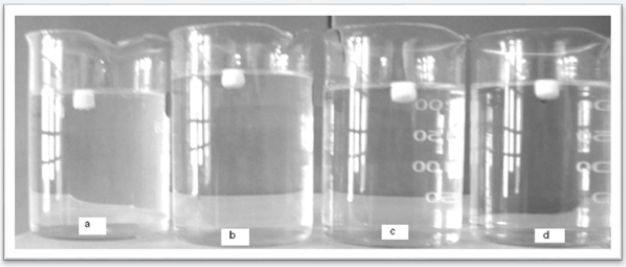

Figure 8: *In-vitro* buoyancy studies: After 3hr

a) Dosage form with Pullulan gum
b) with PEO
c) with HPMC K100M
d) Dosage form with a combination of PEO& HPMC K100M.

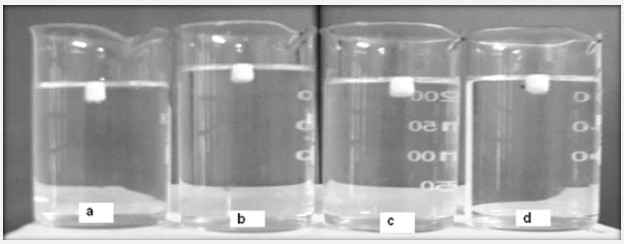

Figure 9: *In-vitro* buoyancy studies: After 6hr

a) dosage form with pullulan gum
b) with PEO
c) With HPMC K100M
d) dosage form with a combination of PEO&HPMCK100.

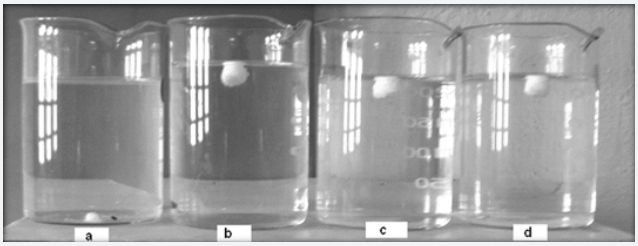

Figure 10: *In-vitro* buoyancy studies: After 12hr

a) Dosage form with pullulan gum
b) with PEO
c) With HPMC K100M
d) Dosage form with a combination of PEO&HPMC K100M.

In vivo buoyancy study was evaluated for the formulations (F-4, F-6, F-10, and F-13). The tablets were fallen into 100 ml of 0.1 N HCl taken with 250 ml of the beaker. The tablets were observed for the floating time. Digital snapshots were taken at initial, 3 hours, 6 hours and 12 hours. The matrix tablets prepared with pullulan gum floats up to 8 hours in the media. The tablets prepared with HPMC, PEO, and combination of HPMC and PEO remain floating for about 12 hours and more. (Figure 7-10) shows the pictures of floating property in the 0.1 N HCl [15].

Differential scanning calorimetric study (DSC)

Table 11: DSC melting points of the selected formulations.

Formulations	DSC Melting Point in °C
Pure ATZ	208.2
ATZ-Pullulangum	207.2
ATZ-PEO	204.7
ATZ-HPMC K 100 M	203.7
ATZ-PEO&HPMC K 100 M	211.4

DSC study was accompanied on the selected formulations. DSC thermogram of pure Atazanavir illustrations a sharp endothermic peak at 208.2°C. Similar endothermic peaks were obtained at 207.2°C for the formulations prepared with Pullulan gum, at 204.7°C for the formulation prepared with PEO, at 203.7°C for the formulations prepared with HPMC K 100 M and

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at 211.4 °C for the formulations prepared with PEO and HPMC K 100 M. The DSC thermograms were given in the following (Table 11). DSC images were shown (Figure 11-15).

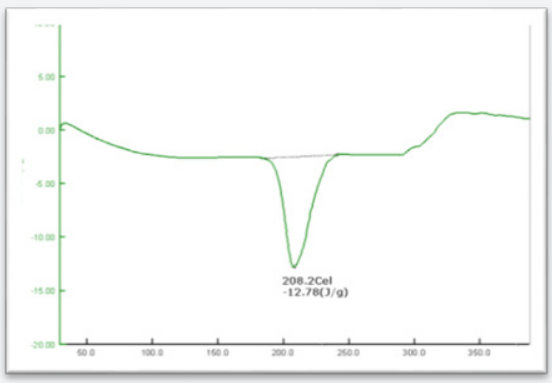

Figure 11: Pure ATZ.

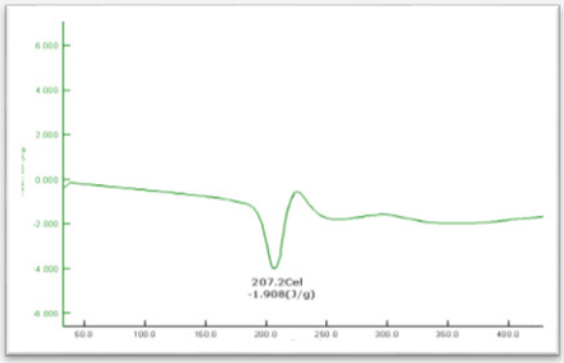

Figure 12: ATZ-Pullulangum.

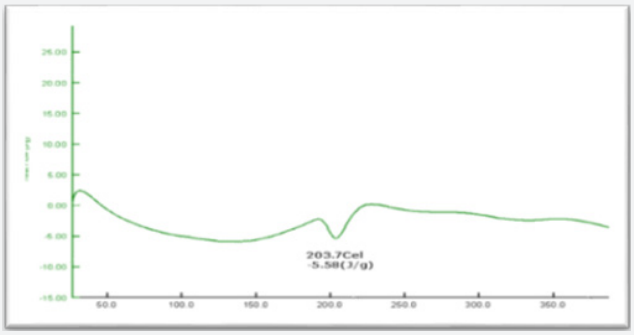

Figure 13: ATZ-PEO.

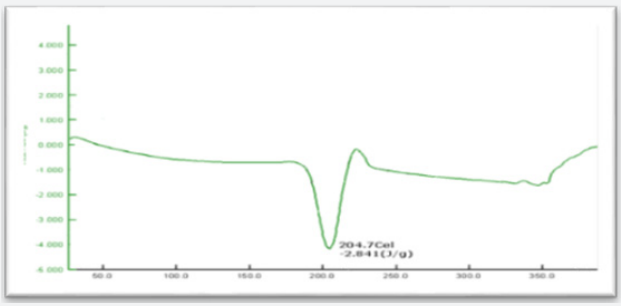

Figure 14: ATZ-HPMC K 100 M.

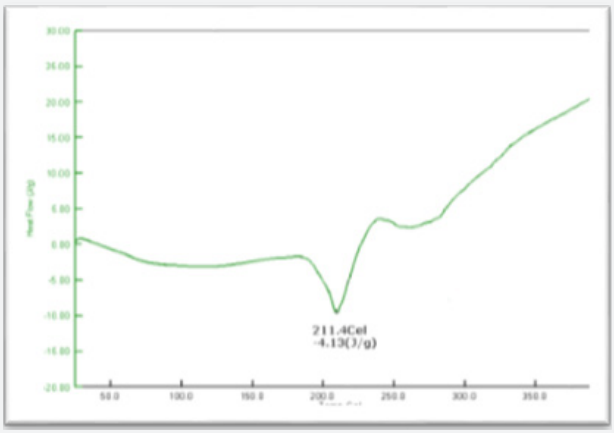

Figure 15: ATZ-PEO&HPMC K 100 M.

FTIR studies on the selected formulations

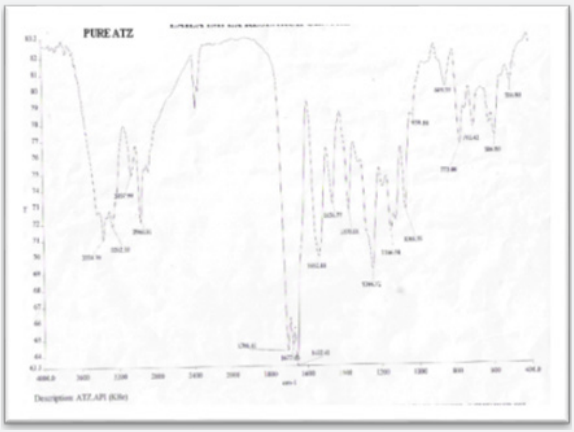

Figure 16: Pure atazanavir.

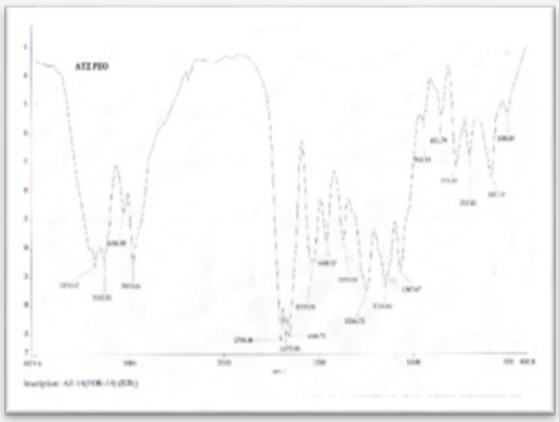

Figure 17: Atazanavir-PEO.

FTIR studies on the selected formulation prepared with different polymers such as Pullulan gum, PEO, HPMC K 100 M and the combination of PEO and HPMC K 100 M. The spectrum peak points of the formulation were analogous to that of the pure Atazanavir, clearly indicating that there is no drug-polymer

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interaction. The FTIR spectra of pure Atazanavir and formulation were given in the following section. (Table 12) describes the FTIR spectrum peak points of pure Atazanavir and the prepared formulations. FTIR images were shown in (Figure 16-19).

Table 12: FTIR spectrum peak points of pure Atazanavir and the prepared formulations.

Pure ATZ	ATZ-Pullulangum	ATZ-PEO	ATZ-HPMC K 100 M	ATZ-PEO& HPMC K 100 M
Wave Number cm^{-1}				
506.88	505.89	500.00	507.40	506.91
586.80	589.61	587.19	588.00	588.27
702.42	706.97	702.43	702.69	702.89
773.00	771.05	773.33	773.88	774.70
849.39	851.69	851.79	851.93	848.51
939.63	935.21	944.44	944.44	952.99
1068.35	1066.25	1067.67	1067.95	1068.19
1146.94	1149.68	1146.64	1147.18	1145.93
1244.72	1244.39	1246.72	1246.17	1246.07
1370.01	1368.89	1370.19	1369.88	1368.57
1456.72	1457.96	1458.57	1458.37	1459.26
1532.44	1537.92	1532.03	1531.27	1528.43
1652.41	1652.87	1656.72	1653.27	1651.11
1677.08	1677.00	1672.05	1676.17	1678.12
1701.41	1700.83	1700.46	1701.27	1701.02
2960.51	2960.94	2959.46	2959.66	2959.55
3057.99	3062.18	3056.05	3055.61	3055.02
3262.50	3264.02	3262.82	3263.83	3361.97
3358.70	3364.20	3359.62	3359.71	3359.28

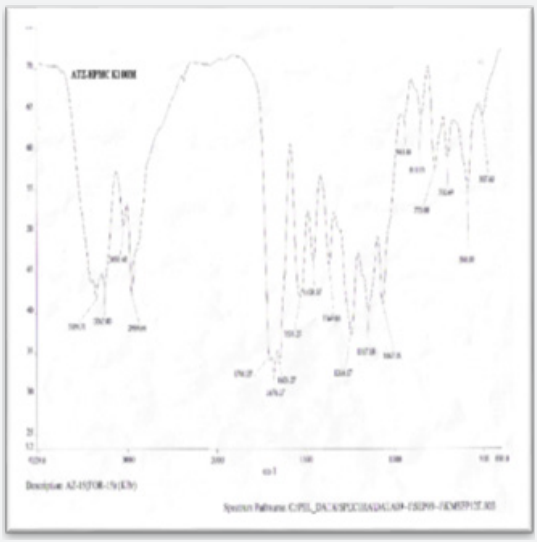

Figure 18: Atazanavir-HPMCK100.

In Vivo radiographic studies

In vivo studies were accompanied on 3 healthy male human volunteers to find the gastric residence time of the tablet. The studies were based on X-ray radiography. The tablets prepared with Pullulan gum were tested for the in-vivo gastric residence time. The tablets were replaced with 50 mg of BaSO4 which was used in the various diagnostic tests. The tablets were compressed by same compression force. All the physicochemical properties were found within the range [16]. The tablets were given to the volunteers with a glass of water and standard diet was provided. X rays were taken at diverse time intervals such as initial, 4 hours and 8 hours. The X-ray images show the tablet residence in the stomach for about 8 hours clearly indicating the good floating property. The institute's human ethical committee approved the protocol for the study and the protocol no was KLRPC/IHEC/2008-2009/001. (Figure 20). describes the x-ray images showing the tablet of Atazanavir in the stomach [17,18].

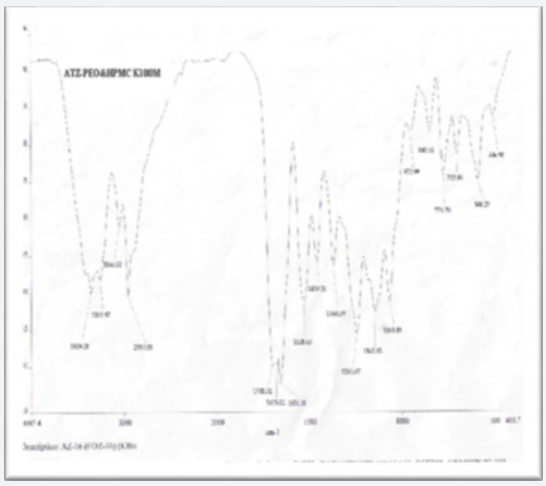

Figure 19: Atazanavir- PEO& HPMCK100.

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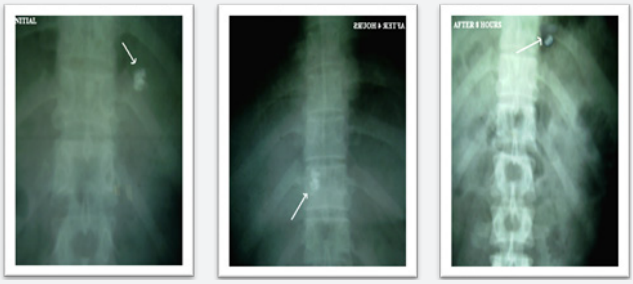

Figure 20: X-ray image showing the Atazanavir tablet prepared with Pullulan gum at the initial time, after 4 Hours, after 8 Hours.

Summary

Atazanavir floating matrix tablets prepared with an aim to provide the drug for a prolonged period in the stomach. Atazanavir was targeted to stomach because it has the solubility in the acidic pH at the same time it has provided for a prolonged period for better therapeutic activity and to reduce the side effects associated with this drug. A standard concentration of atazanavir was prepared in 0.1N HCl and the absorbances were measured at 250nm. Atazanavir is showing good linearity between 10-60µg/ml with a correlation coefficient of 0.993. The formulation with pullulan gum was developed with the use of drug and polymer percentage of (44.4%). The drug and polymer were mixed uniformly and compress into a tablet using 8.0 mm punch, at a hardness of around 10kg/cm^2.

The hardness has a greater impact on the floating property. A decrease in hardness gives good floating property. Further, the matrix tablets were prepared at different drug-polymer ratios. All the formulations show good physicochemical properties. It was clearly observed that the polymer concentration has a greater impact on the floating property and release rate. The drug release was extended up to the 10 hours and more. The release kinetics shows that the prepared matrix tablets with pullulan gum follow zero order kinetics with diffusion mechanism. The release exponent of the Peppas equation suggests the drug release mechanism was case II transport. Floating matrix tablets of the Atazanavir were prepared using PEO WSR Coagulant. Good physicochemical properties were observed in the prepared formulations. In vitro drug release follows the zero-order release kinetics [19].

Good correlation in Higuchi kinetics clearly indicates that the drug release mechanism was predominantly diffusion controlled. Peppas release exponent shows non-fickian diffusion mechanism. Floating matrix tablets of the Atazanavir were formulated using HPMC K 100 M. Good physicochemical properties were observed in the prepared formulations. In vitro buoyancy study shows that the prepared matrix tablets were floated in less than 20 seconds. The drug release kinetics study discloses that the formulations follow zero order release. This clearly indicates that the release was not depending on the concentration. The correlation coefficient of the Higuchi model indicates the diffusion mechanism. Peppas release exponent clearly shows the drug release follows non-fickion diffusion mechanism. The formulation of Atazanavir matrix tablets was prepared with a combination of polymers such as PEO and HPMC shows better physicochemical properties. were observed. Drug release kinetics were followed zero order. Higuchi correlation indicates that the drug release mechanism was diffusion controlled. Peppas release exponent clearly indicating the release was non-fickian diffusion mechanism. Based on the results with all the polymers the order of the drug release mainly depended on the type of polymer and polymer ratio. HPMC K 100 M shows more retardation than PEO than Pullulan gum. Combination of polymer yields more retardation than the individual polymers [20].

In Vivo buoyancy study was evaluated on selected formulations

The results suggested that the prepared matrix tablets show the floating property of more than 8 hours. DSC and FTIR study of pure Atazanavir and formulations showed that there is no drug-polymer interaction.

In vivo studies were conducted on 3 healthy male human volunteers to discover the gastric residence time of the tablet. The matrix tablets prepared with Pullulan gum were used for the study. The X-ray images show the tablet residence in the stomach for about 8 hours, undoubtedly indicating the good floating property in the gastric juice [21,22].

Conclusion

In conclusion, different swelling polymers such as Pullulan gum, PEO WSR Coagulant, and HPMC K 100 M can be successfully employed in the preparation of controlled release floating tablets of Atazanavir. The formulation was prepared and succeeded without a gas generating agent. Combination of a polymer can be successfully employed for better results. The research study provided helpful information for the formulation scientists on the formulation, characterization during the development of controlled drug delivery systems of Atazanavir using these hydrophilic polymers. The prepared formulations can be effectively commercialized afterwards establishing the safety and efficacy in healthy human volunteers.

Acknowledgements

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