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Formulation and *in vitro* Evaluation of Gastro-Retentive Drug Delivery System for Atazanavir

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Abstract

The main purpose of the study was to develop Atazanavir floating tablets via a non-effervescent technique using various polymers by direct compression. Before compression, the particulate powdered mixture was evaluated for pre-compression parameters. Compatibility among the formulation components was assessed by FTIR studies. FTIR studies revealed no interaction between the drug and the polymers used. The prepared Atazanavir floating tablets were evaluated for post-compression parameters, swelling index, floating lag time, *in vitro* buoyancy studies, and *in vitro* drug release studies. Optimized formulation (F2) revealed that the tablet was constantly floating in the stomach region, thereby indicating improved gastric retention time for more than 8 hr. Consequently, all the findings and outcomes have showed that developed Atazanavir floating tablets could be effectively used for a floating drug delivery system.

Keywords

Atazanavir, Natural Polymers, FTIR studies, Direct compression technique, *In vitro* drug release studies.

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1. INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in formulation. [1] Floating system or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. [2] Floating drug delivery systems have a bulk density

less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After drug release, the remaining system is emptied from the stomach. This result is an increased gastric retention time and control of the fluctuation in plasma drug concentration.[3]Various approaches have been pursued over the last three decades, to increase the retention of oral dosage forms in the stomach.[4] The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include Co-administration of the DDS with pharmacological agents that slow gastric motility. Bio adhesive systems.Size increasing systems, which are either due to expansion and shape modification or swelling .[5] Density controlled systems which are either, high density systems or floating systems.[6]The main purpose of the study was to develop Atazanavir floating tablets via non-effervescent technique using various polymers by direct compression. The prepared Atazanavir floating tablets were evaluated for post-compression parameters, swelling index, floating lag time, *in vitro* buoyancy studies, and *in vitro* drug release studies.

2.MATERIALS AND METHODS

Atazanavir was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

METHODOLOGY

Drug excipient compatibility studies[7]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in high density polyethylene bags and low density poly ethylene bags. Glass vials were exposed to 60^0C and 40^0C/75 % relative humidity for 4 weeks and low-density polyethylene bags were exposed to 40^0C±75 % relative humidity for 4 weeks. Samples were observed periodically for any physical change.

Preparation and evaluation of Atazanavir floating tablets

Table-1: Composition of Atazanavir floating tablets

Ingredients (mg)	F1	F2	F3	F4
Atazanavir	200	200	200	200
Sodium alginate	100	200	-	-
Guar gum	-	-	100	200
MCC	180	80	180	80
Citric acid	5	5	5	5
Sodium bi Carbonate	10	10	10	10
Magnesium Stearate	3	3	3	3
Talc	2	2	2	2
Total Wt	500	500	500	500

Preparation of Formulation:

Different tablet formulations were prepared by direct compression method. The formulations are composed of natural polymers. All powders were passed through 40-mesh sieve. The other excipients and the polymer were mixed uniformly. Drug was added to the polymers and other excipients for 20 min. The resulting mixture were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 8 mm punch (single punch tablet machine) in to tablets. Compression pressure was adjusted during tablet ting of each formula to get the tablet hardness in the range of 2.5 to 5 Kg/cm$^{2.}$ The total weight of tablet was kept at 500 mg.

Evaluation of tablets[8,9,10]

Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by another device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight.

Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity:
Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labelled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labelled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:
A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.
The percentage friability was determined by the formula:
% friability = (W_1-W_2) / W_1 X 100
W_1 = Weight of tablets before test
W_2 = Weight of tablets after test

Floating lag time:
The time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1NHCl maintained at 37 ^{0}C, by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium.

Drug release studies:
The drug release from the Atazanavir tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 0.1N HCl (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analysed with UV spectrophotometry.

Stability studies:
The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Atazanavir floating tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

3.RESULTS & DISCUSSION

FT-IR Spectrum of Atazanavir
FT-IR Spectra of Atazanavir and F2 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Atazanavir and polymer. It also confirmed that the stability of drug during microencapsulation process.

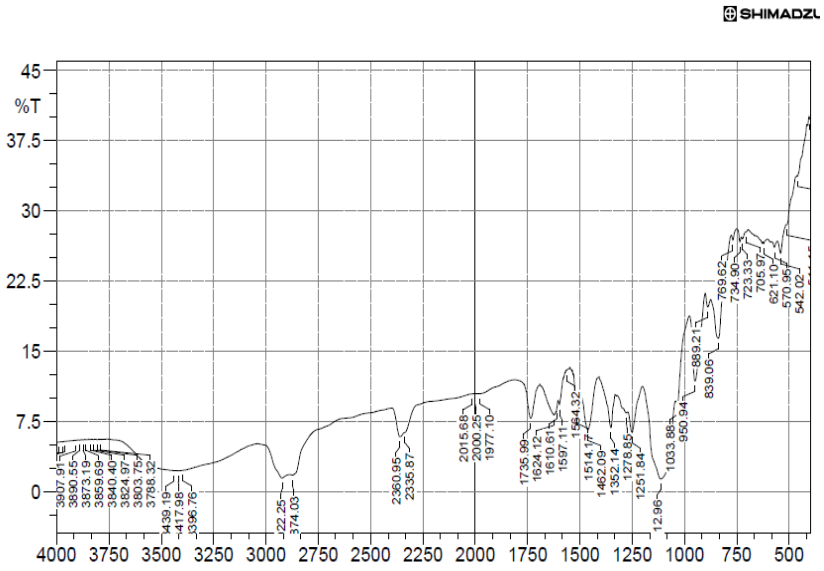

Fig-1: FT-IR Sample for Atazanavir

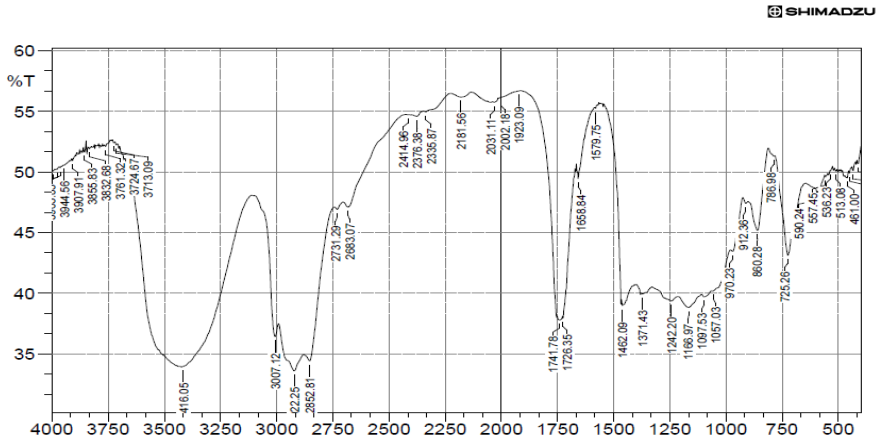

Fig-2: FT-IR Sample for physical mixture of drug and excipients

The IR spectrum of drug and Drug Excipients mixture was shown in respectively. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used. From the figures it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation of Preformulation parameters

Pre-compression Parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.479-0.493.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.580-0.589.

Angle of repose: The angle of repose for the formulated blend was carried out and the results were shown in Table No 6. It concludes that all the formulations blend was found to be in the range of 27^0 to 30^0

Compressibility index: Compressibility index was carried out, it found between 10% to 17.47 % indicating the powder blend have the required flow property for compression.

Hauser ratio: Hauser ratio was carried out, it found between 1.20 to 1.21 indicating the powder blend have the required flow property for compression.

Table-2: Evaluation parameters of Atazanavir

S. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose (0)
F1	0.493	0.589	15.62	1.20	30^0
F2	0.479	0.580	17.47	1.21	27^0
F3	0.484	0.582	16.83	1.20	30^0
F4	0.490	0.585	16.15	1.21	29^0

Evaluation of the Prepared Tablets for Physical Parameters

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeia limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table-3: Evaluation parameters of Atazanavir floating tablets

Parameter	F1	F2	F3	F4
Weight variation	499	500	500	500
Thickness (mm)	3.6	3.2	3.4	3.7
Hardness (kg/cm^2)	3.6	3.8	3.4	4.1
Friability	0.39	0.42	0.46	0.40
Content uniformity	78.42	80.12	76.98	78.12

Floating lag time (Sec)	49	45	53	50

Floating lag time

The prepared formulations were evaluated for floating lag time and buoyancy time. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N HCl). It was observed that the gas generated is trapped and protected within the matrix, formed by polymers, thus density of the tablet decreased and it becomes buoyant. The floating lag time of the optimized formulation F3 was 45 sec.

***In vitro* Dissolution studies**

The dissolution conditions used for studying the drug release from the tablet of Atazanavir. The samples were withdrawn at predetermined time points and were analyzed spectrophotometrically at 245 nm.

Table-4: *In vitro* drug release of Atazanavir floating tablets

Time	F1	F2	F3	F4
0	0	0	0	0
1	16.12	17.58	15.69	14.59
2	34.58	35.42	36.86	35.42
3	46.92	48.16	49.81	45.81
4	58.73	59.50	53.31	55.50
5	66.82	68.22	66.82	67.28
6	78.20	79.68	74.30	75.69
7	85.69	86.39	84.86	85.40
8	93.75	95.67	93.69	94.56

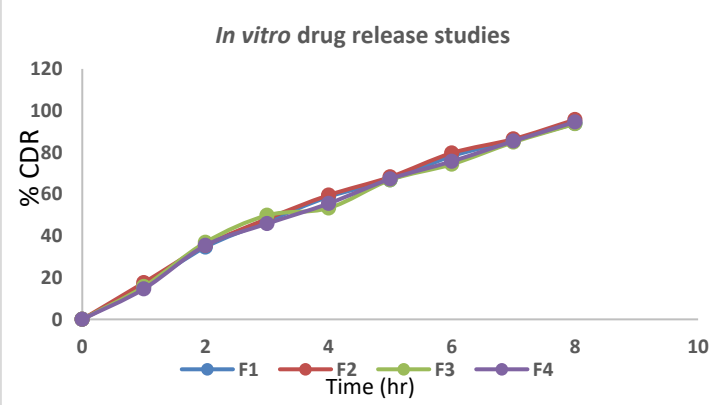

Fig-3: *In vitro* drug release for all the formulations

Stability Study

There was no significant change in the physical and chemical properties of the tablets of formulation F-2 after 90 days. Parameters quantified at various time intervals were shown. Optimized formulation F2 was selected for accelerated stability studies as per ICH guidelines. The floating tablets were observed for % cumulative drug release of the formulation was found to be decreasing.

Table-5: Stability study for optimized formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-2	**25^{0}C/60%RH % Release**	95.67	94.62	93.54	92.51	**Not less than 85 %**
F-2	**30^{0}C/75% RH % Release**	95.67	94.63	93.45	92.47	**Not less than 85 %**
F-2	**40^{0}C/75% RH % Release**	95.67	94.29	93.56	92.34	**Not less than 85 %**

3.CONCLUSION

The objective of the present study is to formulate a Floating tablet of Atazanavir. In this present study an

attempt was made to increase the GI residence time of Atazanavir, as the drug is having less gastric residence time, by formulating in to Floating tablets. Systematic studies were conducted using different concentration of rate releasing different polymers for extending the drug release in upper GIT. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, Preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and solubility studies and all the formulations gave good results for above Preformulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, buoyancy, content uniformity, all the formulations were found within the permissible range.

Finally, it was concluded that:

Among all the formulations (F1-F4), it was observed that formulation-2 has shown better buoyancy and dissolution profile. So, Formulation-2 was found to be the best formulation among others.

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