Research Article

Formulation and Evaluation of Immediate Release Tablets of Atazanavir

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ABSTRACT

The objective of this research work is to formulate an immediate release tablet of "Atazanavir" for rapid action, by using suitable super-disintegrants like Crospovidone, Croscarmellose sodium, Sodium starch glycolate and Carmellose calcium at different concentrations ranging from 2-10 percent by direct compression method. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and *In-vitro* dissolution profile. The spectral analysis revealed that there was no interaction between the drug & excipients. The drug release from immediate release tablets increased with increasing concentration of super-disintegrants and was found to be highest with formulation (F_{18}) containing Crospovidone with 10% concentration.

Keywords: Atazanavir, Crospovidone, Super-disintegrants.

INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the most preferred, convenient route for drug administration. Any drug delivery system is based on the nature of disease and its causing agent as well as the anatomy and physiology of affected organ.[1] 'Atazanavir' marketed under the trade name 'Reyataz' by Bristol Myers (formerly known as BMS-232632) is an anti-retroviral drug of the protease inhibitor (PI) class. Atazanavir is distinguished from other PIs in that it can be given once-daily (rather than requiring multiple doses per day) and has lesser effects on the patient's lipid profile (the amounts of cholesterol and other fatty substances in the blood).

Immediate Release Tablets

Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.[2] Immediate release (IR) tablets are a better choice for drugs which need to elicit their action immediately. IR tablets are intended to disintegrate in the stomach, where the pH is acidic. Immediate release tablet should disperse; disintegrate in less than three minutes and must release 85% or more of drug within 30 min.[3]

For the manufacture of Immediate Release Tablets there are four conventional techniques namely Tablet Molding, Direct Compression, Granulation and Mass Extrusion technique.[4] In Tablet Molding technique the powder blend is moistened with a hydro alcoholic solvent and is molded into tablet using compression pressure lower than used in conventional tablets compression and the solvent is then removed by air-drying. In Direct Compression tablets are compressed directly from powder mixture of API and suitable excipients. Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. It is classified as Dry and Wet granulations. Mass Extrusion technique involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

MATERIALS AND METHODS

Materials

Atazanavir, Crospovidone, Sodium Starch Glycollate, Croscarmellose Sodium, Carmellose Calcium, Mannitol and Magnesium Stearate.

Method of Preparation

Immediate release tablets of 'Aatazanavir' were prepared by Direct Compression technique. All the ingredients were weighed. Required quantity of drug and excipients mixed thoroughly (table 1) in a polybag. The blend was compressed using Rotary Tablet Machine-6 station with 8mm flat punch, B tooling.

Evaluation Tests[5-9]

Pre compression parameters

The following are pre compression parameters (table 2):

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This

initial volume is called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M / V_b$$

Where,

M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Where,

M is the mass of powder

V_t is the tapped volume of the powder.

Angle of Repose (Θ)

The friction forces in a loose powder can be measured by the angle of repose (Θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\text{Tan}(\Theta) = h / r$$

$$\Theta = \tan^{-1}(h / r)$$

Where,

Θ is the angle of repose.

h is the height in cm

r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. This explains relationship between angle of repose and powder flow property.

Carr's index (or) % compressibility index

It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where,

D_t is the tapped density,

D_b is the bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression parameters

The following are post compression parameters (table 3):

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Hardness

Hardness or tablet crushing strength (f_c), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Friability (F)

Friability of the tablet was determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet from a height of 6 inches in each revolution. Pre weighed sample of tablets were placed in the friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Disintegration

Place one tablet in each of the six tubes of the basket and operate the apparatus using 0.025 N HCl maintained at 37±0.5ºC as the immersion fluid. Note down the time for complete the disintegration of tablets.

Drug Content

10 tablets were taken and diluted appropriately with 0.025N HCl and the drug content of samples was estimated by UV-Visible spectrophotometer at 245nm.

In-vitro drug release (Dissolution) studies

The *In-vitro* drug release study was performed for all the formulations using USP type II dissolution apparatus under the following conditions (table 4):

Dissolution test parameters

Dissolution medium : 900mL of 0.025N HCl

Rotation speed : 50 rpm

Temperature : 37 ± 0.5°C

Sampling time : 5, 10, 15, 20, 25, 30, 40, 50 & 60 min

At predetermined time intervals aliquot samples (5mL) were collected and replenished with same volume of fresh medium. The aliquot samples (5mL) were diluted appropriately and the drug content was estimated by using UV-Visible spectrophotometer at λ_{max} 245nm.

FTIR spectroscopic studies were also performed for pure drug and optimized formulation as shown in figures 1 & 2.

RESULTS AND DISCUSSION

The weight and drug content of all the tablets were found to be uniform with low SD values. All the 20 formulations comply with the Indian Pharmacopoeial specifications. Results with respective to disintegration and dissolution, **F_{18}** formulation was found to be better which contains Crospovidone as super disintegrant when compared to other formulations. **F_{18}** formulation showed relatively more cumulative drug release i.e., 100.17% in 15 min when compared to other formulations (Table 4).

The drug content of the diluted samples of 20 formulations was found to be in the range of 97.06 to 99.98 %. **F_{18}** formulation showed 99.98 % of drug content (Table 3).

Table 1: Formulation using direct compression technique

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Atazanavir	300	300	300	300	300	300	300	300	300	300
Sodium starch glycolate	10	-	-	-	20	-	-	-	30	-
Crospovidone	-	10	-	-	-	20	-	-	-	30
Croscarmellose sodium	-	-	10	-	-	-	20	-	-	-
Carmellose Calcium	-	-	-	10	-	-	-	20	-	-
Mannitol	180	180	180	180	170	170	170	170	160	160
Mg. Stearate	10	10	10	10	10	10	10	10	10	10
TOTAL	500	500	500	500	500	500	500	500	500	500

(All ingredients are expressed in mg only)

Table 1: Formulation using direct compression technique (Continued.....)

Ingredients	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}
Atazanavir	300	300	300	300	300	300	300	**300**	300	300
Sodium starch glycolate	-	-	40	-	-	-	50	**-**	-	-
Crospovidone	-	-	-	40	-	-	-	**50**	-	-
Croscarmellose sodium	30	-	-	-	40	-	-	**-**	50	-
Carmellose Calcium	-	30	-	-	-	40	-	**-**	-	50
Mannitol	160	160	150	150	150	150	140	**140**	140	140
Mg. Stearate	10	10	10	10	10	10	10	**10**	10	10
TOTAL	500	500	500	500	500	500	500	**500**	500	500

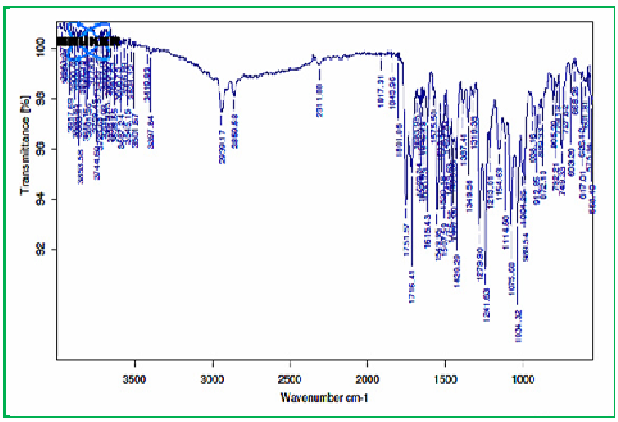

Figure 1: FT-IR spectra of pure optimized formula

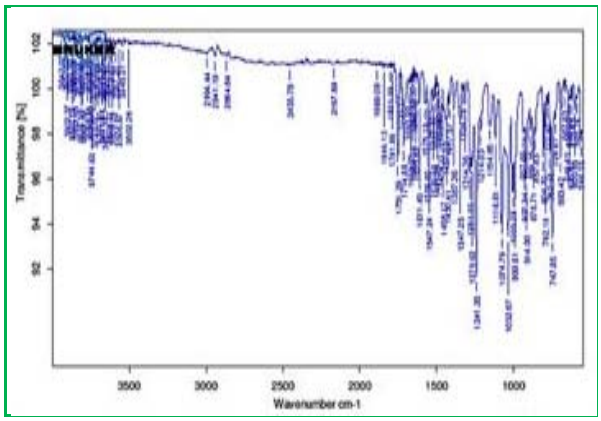

Figure 2: FT-IR spectra of pure Drug Atazanavir

Table 2: Pre-compression parameters

Formulation codes	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose(^{0})
F_1	0.452±0.01	0.482±0.001	6.637±0.08	1.066±0.14	29.52±0.16
F_2	0.395±0.02	0.395±0.002	8.516±0.01	1.085±0.11	28.63±0.18
F_3	0.425±0.01	0.483±0.01	9.647±0.05	1.136±0.01	28.13±0.21
F_4	0.417±0.02	0.452±0.004	8.393±0.01	1.084±0.09	27.63±0.26
F_5	0.387±0.01	0.421±0.02	8.786±0.02	1.088±0.13	26.78±0.11
F_6	0.336±0.04	0.368±0.01	9.524±0.06	1.095±0.4	28.63±0.04
F_7	0.434±0.03	0.466±0.004	7.558±0.09	1.076±0.01	29.75±0.01
F_8	0.421±0.02	0.478±0.006	6.539±0.00	1.135±0.05	30.1±0.13
F_9	0.465±0.01	0.498±0.08	7.097±0.07	1.071±0.11	28.71±0.4
F_{10}	0.395±0.02	0.368±0.01	6.637±0.08	1.095±0.4	28.71±0.4
F_{11}	0.387±0.01	0.482±0.001	8.516±0.01	1.066±0.14	28.63±0.18
F_{12}	0.452±0.01	0.421±0.02	6.539±0.00	1.084±0.09	29.52±0.16
F_{13}	0.336±0.04	0.483±0.01	9.524±0.06	1.088±0.13	27.63±0.26
F_{14}	0.421±0.02	0.466±0.004	7.558±0.09	1.135±0.05	30.1±0.13
F_{15}	0.387±0.01	0.452±0.004	7.097±0.07	1.071±0.11	28.63±0.04
F_{16}	0.336±0.04	0.368±0.01	6.637±0.08	1.095±0.4	26.78±0.11
F_{17}	0.465±0.01	0.478±0.006	9.524±0.06	1.084±0.09	27.63±0.26
F_{18}	**0.452±0.01**	**0.483±0.01**	**8.393±0.01**	**1.136±0.01**	**29.52±0.16**
F_{19}	0.395±0.02	0.395±0.002	8.516±0.01	1.071±0.11	27.63±0.26
F_{20}	0.387±0.01	0.466±0.004	7.097±0.07	1.135±0.05	30.1±0.13

Table 3: Post-compression parameters

Formulation codes	Weight variation (mg)	Hardness (kg/±cm^2)	Friability (%)	ASSAY (%)	DT
F_1	510±0.99	5.3±0.02	0.42±0.01	98.2±0.56	4.282±0.08
F_2	511±0.99	5.2±0.05	0.24±0.01	97.6±046	3.27±0.05
F_3	506±0.38	5.6±0.05	0.25±0.00	99.1±0.88	3.524±0.01
F_4	503±0.99	5.8±0.06	0.23±0.03	97.4±0.34	4.351±0.04
F_5	500±0.33	5±0.00	0.31±00.1	98.4±0.38	4.300±0.018
F_6	498±0.99	5.6±0.02	0.18±0.01	99.5±0.88	3.454±0.01
F_7	496±0.40	5.3±0.01	0.14±0.06	98.7±0.83	3.120±0.04
F_8	511±0.11	5.5±0.07	0.18±0.04	98.3±0.45	3.231±0.34
F_9	495±0.17	5.7±0.03	0.19±0.01	98.56±0.64	3.364±0.005
F_{10}	503±0.99	5.1±0.05	0.23±0.04	99.1±0.88	4.282±0.08
F_{11}	511±0.99	5.8±0.06	0.19±0.01	98.2±0.56	3.231±0.34
F_{12}	506±0.38	5.3±0.03	0.42±0.01	99.5±0.88	4.351±0.04
F_{13}	498±0.99	5.6±0.02	0.18±0.01	97.4±0.34	3.124±0.01
F_{14}	495±0.17	5.2±0.05	0.25±0.00	98.3±0.45	4.300±0.018
F_{15}	496±0.40	5.5±0.02	0.31±00.1	98.56±0.64	3.524±0.01
F_{16}	511±0.99	5.7±0.03	0.24±0.01	98.2±0.56	4.423±0.02
F_{17}	503±0.99	5±0.00	0.19±0.01	97.6±046	3.231±0.34
F_{18}	**510±0.99**	**5.6±0.02**	**0.18±0.04**	**99.1±0.88**	**4.282±0.08**
F_{19}	495±0.17	5.8±0.05	0.24±0.01	98.3±0.45	3.231±0.34
F_{20}	496±0.40	5.2±0.05	0.25±0.00	97.4±0.34	4.300±0.018

Table 4: Dissolution profile and percentage of drug release of all formulations

Formulations	Cumulative % Drug Release							
	5min	10min	15min	20min	30min	40min	50min	60min
F_1	12.56	21.36	36.45	41.47	61.59	72.52	80.44	88.11
F_2	16.34	25.13	41.47	49.02	68.62	82.95	90.50	99.42
F_3	14.07	22.62	31.42	47.00	67.87	75.41	86.72	98.04
F_4	16.21	27.65	37.70	46.25	67.12	75.66	81.70	88.23
F_5	21.36	35.19	40.22	57.31	75.31	86.85	92.88	99.17
F_6	24.51	38.96	49.77	58.07	79.18	90.37	98.92	-
F_7	22.62	30.79	39.71	48.76	72.27	85.47	95.40	100.55
F_8	31.92	42.86	51.40	68.25	74.15	84.21	91.88	99.55
F_9	29.78	39.09	47.88	59.45	74.91	80.44	98.92	-
F_{10}	32.68	44.49	53.29	66.11	88.36	99.92	-	-
F_{11}	30.16	39.09	44.24	59.07	81.70	92.00	100.17	-
F_{12}	42.98	51.91	62.97	71.89	78.05	89.87	98.29	-
F_{13}	31.29	41.10	50.27	61.08	76.92	89.99	99.55	-
F_{14}	33.30	47.38	56.93	69.13	85.47	98.04	-	-
F_{15}	32.80	45.37	54.04	68.62	88.23	94.39	98.92	-
F_{16}	53.29	62.84	71.77	77.93	82.95	90.87	99.04	-
F_{17}	48.51	75.29	89.87	99.04	-	-	-	-
F_{18}	**61.21**	**84.46**	**100.17**	**-**	**-**	**-**	**-**	**-**
F_{19}	57.69	80.69	91.88	100.05	-	-	-	-
F_{20}	59.32	72.02	80.94	89.62	99.92	-	-	-

CONCLUSION

In the present work, an attempt has been made to develop immediate release tablets of Atazanavir. The IR spectra revealed that, there was no interaction between Super disintegrants (Crospovidone, Sodium starch glycollate, Croscarmellose sodium & Carmellose calcium) and API (Atazanavir). The results of preliminary trials of pre-compression parameters showed good flow property. Amongst the various disintegrants used in the study, tablets that were formulated by direct compression using. Crospovidone exhibited quicker disintegration and dissolution of tablets when compared to other disintegrants in different concentrations. Formulation **F_{18}** was the optimized formulation having least disintegration time as well as all other parameters was as per IP. Based on the optimization studies it is concluded that the objective of formulation of Immediate Release Tablets containing Atazanavir has been achieved with success.

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