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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM OF ATAZANAVIR

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Abstract:

The aim of the preset study was to develop oral fast dissolving films of Atazanavir by solvent casting method. Low viscosity grades of HPMC such as E3, E6, and E15 were used in the ratio of 1:3, 1:6 and 1:9 as the film forming polymers. taste masking was done by incorporating suitable sweeteners and flavours. The prepared films were evaluated for properties like weight variation, folding endurance, thickness, % drug content, invitro disintegrating time and invitro drug release study. Drug and excipient compatibility was established through FTIR and DSC study. Form the obtained results, it was concluded that formulations prepared with HPMC E3, showed good film forming capacity with complete drug release in 10 mins. FTRI and DSC study proved that there is no drug and polymer interaction.

Keywords: *Atazanavir, oral fast dissolving films, HPMC, taste masking, urticaria.*

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INTRODUCTION:

Oral route is considered as the most preferred route of administration of many pharmaceutical dosage forms [1-3]. But now they are experiencing several limitations like chocking and swallowing difficulties in the geriatric and paediatric patients [4-5]. Due to the tremendous advancements in the oral drug delivery system, the plethora of avenues explored oral strips gained much attention as an emerging new platform for paediatric and geriatric patients [6-8]. The concept of development of oral films came from confectionary industry [9]. Oral films are the thin novel formulation with size of normal postage stamp and contain active pharmaceutical ingredients along with excipients [10]. The oral films when comes in contact with saliva, disintegrate rapidly within seconds without the need of water [11-12]. Efficacy of API can be improved as it gets dissolved in the oral cavity. Not only for geriatric and paediatric patients, oral fast dissolving films are useful for patients suffering from allergic attacks, bedridden patients, cough, diarrhoea, emesis, mental disorder etc [13]. Oral films can also be used for local effects like local anaesthetics for cold scars, oral ulcers, toothaches and teething. The shelf life of film is 2-3 years and depends on the API added to the film [14].

Bioavailability of drug can be improved; due to pregastric absorption of the drug in buccal cavity and a well supplied vascular and lymphatic drainage. The films are intended to place in the buccal cavity and fewer doses are required which improves the patient compliance. Stability of the dosage form can also be enhanced when formulated as film. In addition, ODF solid unit dosage form provides accurate dosing and great precision [15-17].

Polymers play an important role in the formation of film. Hydrophilic polymers are most widely used in the preparation of film that dissolves rapidly in the oral cavity and drug is delivered to the systemic circulation [18]. Different viscosity grades of HPMC such as E3, E6, and E15 polymers are used in the present study. The polymers can be used either alone or in combination to get the desired film properties. Robustness of film mainly depends on the type and amount of polymer incorporated in the formulation. Both natural and synthetic polymers can be used in development of ODFs. Natural polymers are effective, safe and devoid of side effect and are more preferred than synthetic polymers [19 – 22].

Atazanavir acts by selectively inhibiting the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the active site of HIV-1 protease. This prevents the formation of mature virions. Monooxygenation and dioxygenation are the major biotransformation pathways of atazanavir in humans. In humans, Atazanavir is extensively metabolized in liver. Atazanavir is rapidly absorbed and has T_{max} of approximately 2.5 hours and has Oral bioavailability of 60-68% [23- 26].

MATERIALS AND METHOD:

Materials:

Atazanavir was received as a gift sample from Strides acrolabs Banglore, India. HPMC grades were received as a gift sample from Colorcon asia PVT Ltd, Goa, India., polyethylene glycol 400 (PEG 400) were purchased from S.D. Fine Chem Ltd., Mumbai, India. Aspartame was purchased from Himedia Lab Pvt Ltd., Mumbai, India. Orange flavour was received as gift samples from Pentagon trading company, Ahmedabad, India. All other chemicals used were of analytical grade and were used without further purification.

Method:

The FDF of Atazanavir was prepared using HPMC E3, HPMC E6 and HPMC E15 with different ratios of 1:3, 1:6 and 1:9. The polymeric solution of

HPMC was prepared by using dichloromethane and methanol in the ratio of 1:1 and kept aside for about 5 to 6 hrs for swelling of polymer. Atazanavir was dissolved in 4 ml of dichloromethane and this drug solution was added to the above polymeric solution. This is followed by the addition of plasticizers such as PEG 400, sweetener, flavour. Uniformity of drug content is achieved by mixing in cyclo mixer for 10 minutes. The solution was cast on a petri dish and dried at 45^0C in hot air oven for 45 minutes. The film was carefully removed from the petri dish, then checked for imperfections and cut to the required size to deliver the equivalent dose (2.5 × 2.5 cm^2) per strip. Film samples with air bubbles, cuts or imperfections were excluded from the study shown in table-1.

Evaluation parameters of Films [27 -28]:

The prepared film was evaluated for following specifications.

Visual Inspection: Oral fast dissolving films were inspected manually for their transparency and presence of any air bubbles.

Weight: the weights of the prepared Oral fast dissolving films were determined by using analytical balance.

Thickness: Film thickness was measured by using a micrometer screw gauge. A strip of 2.5 x 2.5cm^2 was placed between the thickness was measured in five different positions.

Folding Endurance: Folding endurance was measured by manually for the prepared films. A strip of film (2.5 X 2.5 cm^2) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

Invitro disintegrating time:

The strip of prepared film was placed in a petri dish containing 25 ml of 0.1 N HCl. The solution was swirled for every 10 sec and the time taken by the strip to disintegrate was noted. A mean of 3 values was recorded.

% Drug content:

One strip was placed in a 100 ml volumetric flask. The strip was dissolved by adding few ml of 0.1 N HCl acidic buffer and final volume was made upto 100 ml with the buffer. The solution was sonicated for 20 mins. It was diluted suitably and absorbance was measured at λ max 246 nm against blank solution.

Dissolution Studies [30]:

The release rate of Atazanavir from fast dissolving film was determined using USP Dissolution Test Apparatus (Type II). The dissolution test was performed using 900 ml of 0.1 n HCl acidic buffer, at 37 ± 0.5°C with the basket speed of 50 rpm. Aliquot of 5 ml of the solution was collected at time interval of 5mins and were replaced with same amount of fresh prewarmed dissolution medium. The aliquots were filtered through Whattman filter paper. Aliquots were diluted suitably and absorbance of was measured at λ max 246 nm against blank solution. Cumulative percentage drug release was calculated. All the release studies were performed in triplicate. (IP 2007, b).

Fourier transform infrared spectroscopy (FT-IR) [31]

The compatibility of drug Atazanavir and the formulation was confirmed by IR spectra of pure drug and formulations were determined using Simadzu FTIR- 8400S Spectrophotometer by KBr Disc method results were shown in figure 4,5.

Differential scanning calorimetric studies (DSC) [31]

The pure drug Atazanavir and formulation was evaluated for DSC study. The DSC measurements were performed using a mettler equipped with an intracooler 2P cooling accessory. Samples of 4 mg were placed in standard aluminum pans and sealed with a lid. Heating scans by 10oC/min were applied

with a nitrogen purge of 20 ml/min, over a temperature range of 35oC to 380oC. An empty aluminum pan was used as reference.

RESULTS AND DISCUSSION:

Atazanavir oral fast dissolving films were prepared by solvent casting method using different viscosity grades of HPMC such as E3, E6, E15 in the ration of 1:3, 1:6, 1:9. The prepared films were clear and found to have smooth surface and texture. The film forming capacity of HPMC polymer was good. The folding endurance was above 300 and thickness ranged from 0.11 ± 0.05 to 0.17 ± 0.03 mm. the weight variation of the films was within in the limits. The in vitro disintegrating time of the films was in the range of 26 sec to 68 sec.

In vitro drug release of Atazanavir from oral fast dissolving films:

The drug release study was conducted by using USP type II (basket method). The release of Atazanavir from the films prepared with HPMC E 3, F1, and F2 showed complete release with in 5 mins whereas F3 released 89 % of drug in 10 mins. The formulation prepared with HPMC E6, F5 and F6 showed 88.5% and 70 % of drug release in 10 mins and extended the drug release upto 15 mins. In the formulation prepared with HPMC E15, 65.4 to 50.3 % of the drug released within 5 mins, however the drug release was extended upto 25 mins shown in figure-1.

Drug – excipient interaction study:

Fourier Transform infrared spectroscopy study:

Selected formulation of were evaluated for FTIR study. The FTIR spectrum of pure Atazanavir showed 1703cm−1 (C=O of ester), 1560 and 1474cm−1 (stretching vibrations of benzene ring), and 1227cm−1 (C–O stretching), similar spectrum points in the prepared formulation were shown in the FTIR spectrum further conformed that there is no drug polymer interaction.

Differential scanning Colorimetry:

The selected formulations were evaluated for DSC study. Results of the DSC study of pure drug showed sharp endothermic peak at 208.2.8^{O}C. Similar endothermic peaks were obtained in the formulations at 207.1^{O}C clearly indicated that there was no drug polymer interaction shown in figure-2,3.

CONCLUSION

We have developed Atazanavir oral fast dissolving films using different low viscosity grades of HPMC such as E3 E6 E9 by solvent casting method. The quality control test results were within acceptable limits. It was found that the Hpmc grades used in the study has good film forming capacity. The prepared films were clear with smooth surface and texture. The prepared formulations were shown good mechanical properties. The best formulation was selected based on the film forming capacity and invitro dissolution profiles. Taste masking was achieved with the use of aspartame and orange flavour. The films were having good commercial success.

Table 1: Formulation Development of Atazanavir Fast Dissolving Films.

Ingredients	Formulation codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atazanavir	100	100	100	100	100	100	100	100	100
HPMC E3	300	600	900	-	-	-	-	-	-
HPMC E6	-	-	-	300	600	900	-	-	-
HPMC E15	-	-	-				300	600	900
Dichloromethane*	12ml	12ml	12ml	12ml	12ml	12ml	12ml	12ml	12ml
Methanol*	8ml	8ml	8ml	8ml	8ml	8ml	8ml	8ml	8ml
PEG 400	50	50	50	50	50	50	50	50	50
Aspartame	40	40	40	40	40	40	40	40	40
Orange flavour	10	10	10	10	10	10	10	10	10

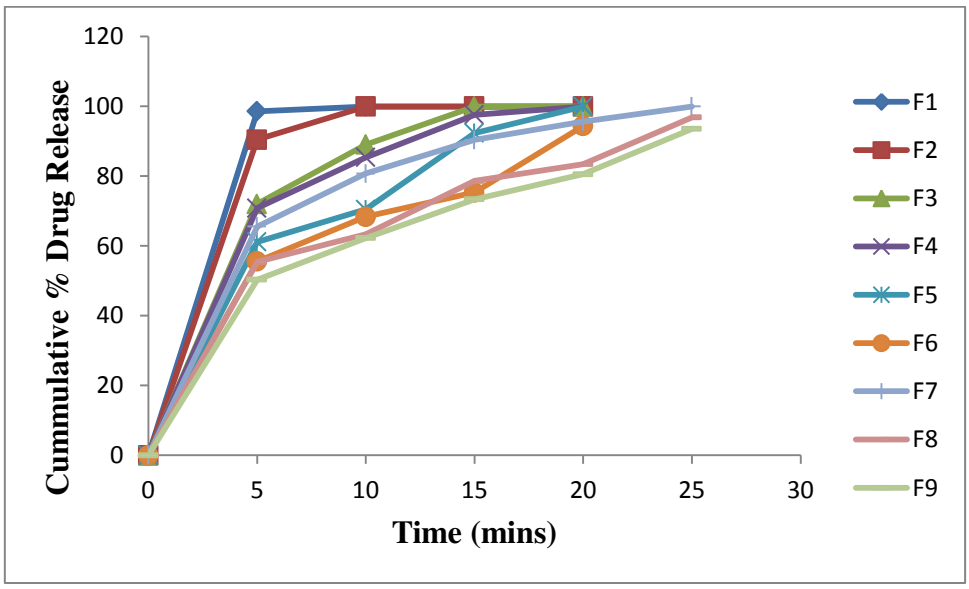

Figure 1: Cumulative % Drug release profile of Atazanavir from fast dissolving films.

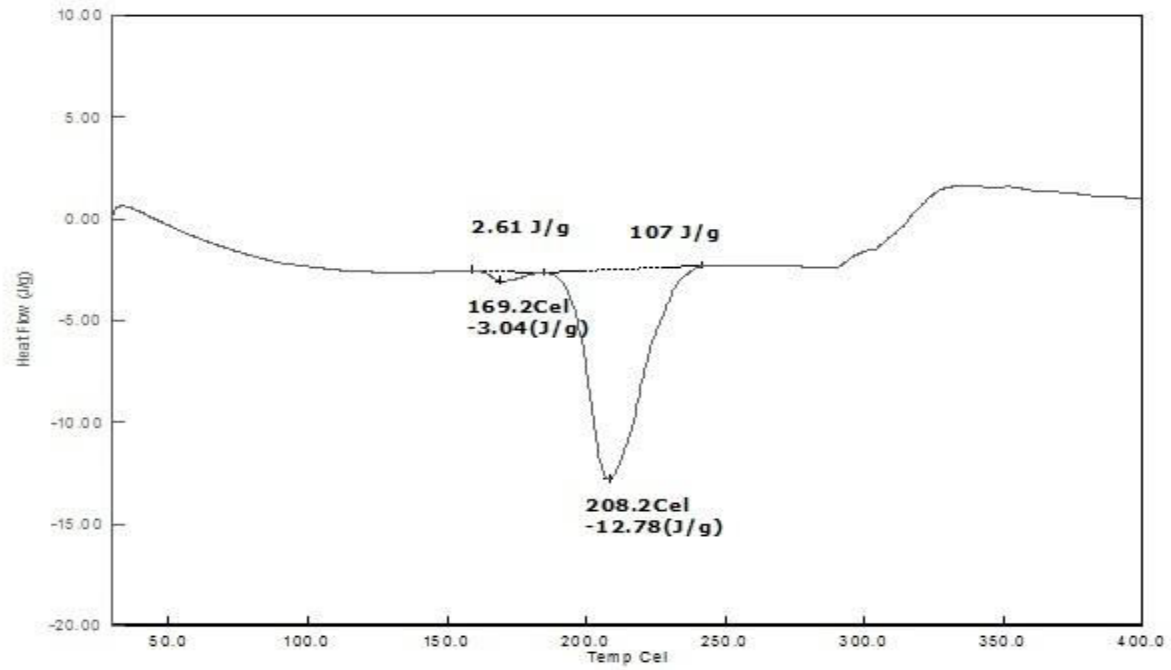

Figure 2: DSC thermogram of pure Atazanavir

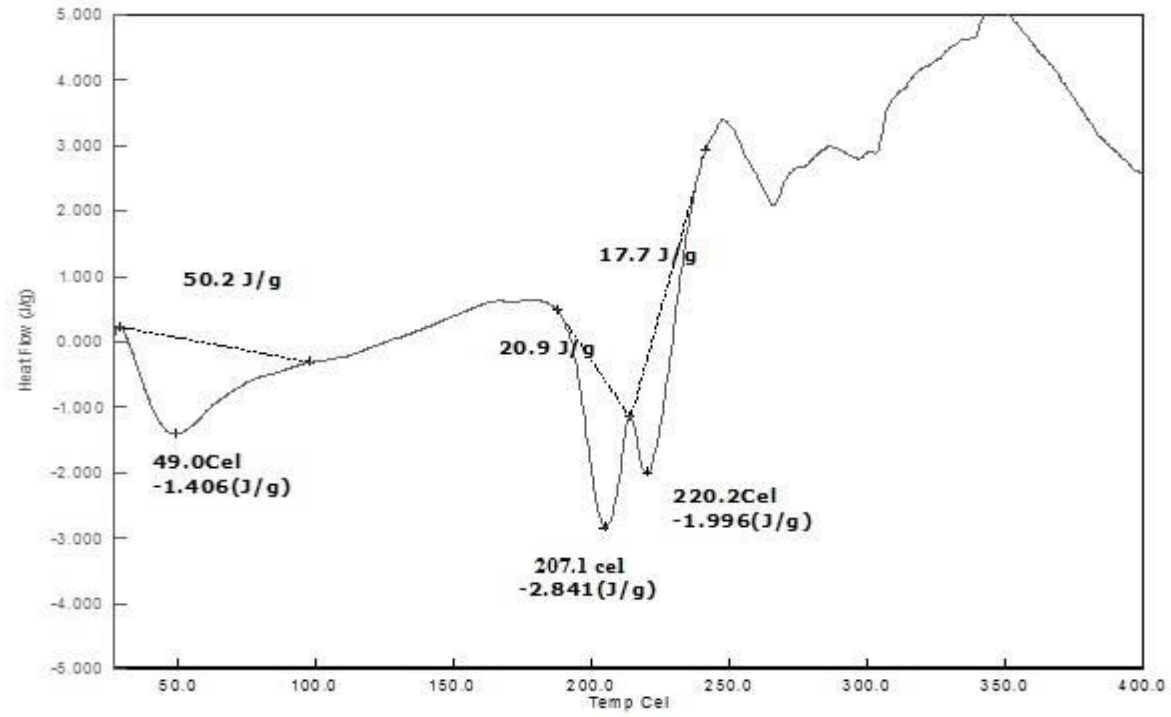

Figure 3: DSC thermogram of Atazanavir Fast disintegrating films.

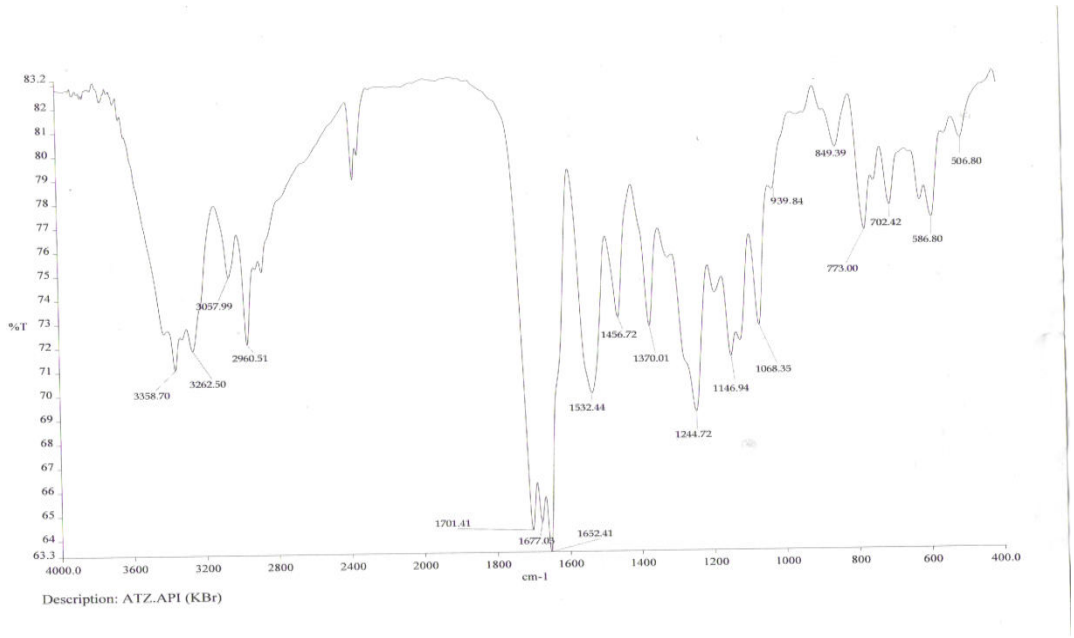

Figure 4: FTIR spectrum of Pure Atazanavir

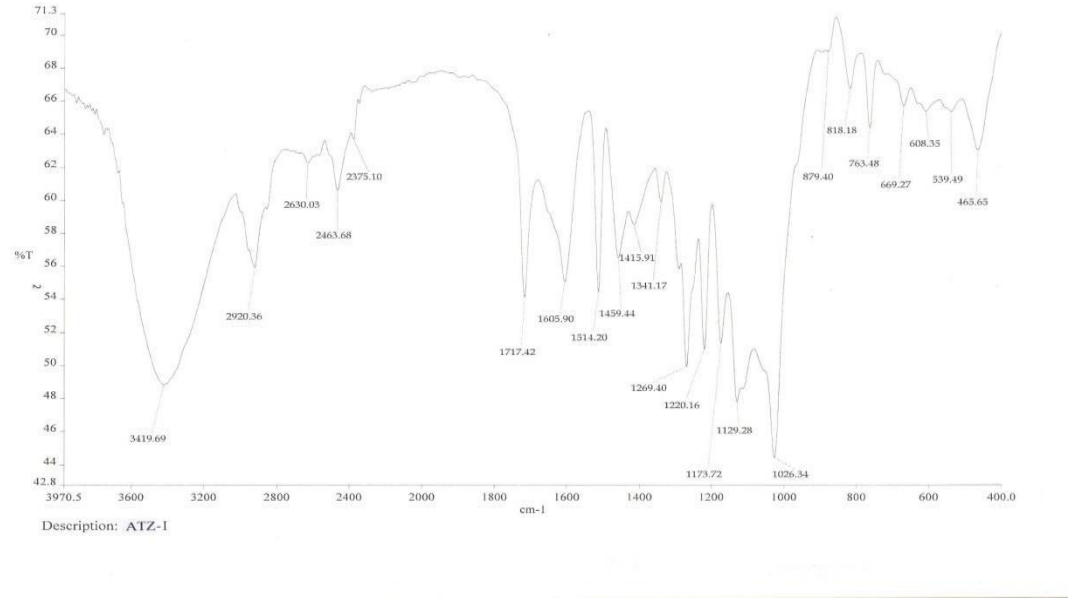

Figure 5: FTIR spectrum of Atazanavir Fast disintegrating films.

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