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Use of Sintering Technique to Sustain the Release of Atazanavir Sulphate from Gastro Retentive Floating Matrix Tablets

Chandan Mohanty[1]*, K V Subrahmanyam[2], Tapan Kumar Jena[3], Devarashetti Sreekanth[4]
1. St. Mary's Pharmacy college, Deshmukhi (V), Pohamplly (M), Behind Mount Opera, Nalgonda (Dist)-508284, Telengana, India
2. Samskruti college of Pharmacy, Kondapur (V) Ghatkesar (M), RR Dist, Telengana, India
3. DR. Reddy's Laboratories ltd, Bachupally, RR Dist, Telengana, India.
4. Deevena College of Pharmacy, Chivemla, Suryapet, Nalgonda (Dist), Telengana, India.

ABSTRACT

The concept of the sintering technique in the pharmaceutical sciences is relatively new.The objective of the present study was to prepare and evaluate thermally sintered gastro retentive floating matrix tablets of Atazanavir sulphate. The formulations were prepared by direct compression method using EC N100 and HPMC K100 as polymer. The prepared tablets were exposed at two different temperatures like 50^0C and 60^0C for two different periods like 1.5 hr and 3 hr in a hot air oven. Effects of sintering conditions were studied on *in vitro* dissolution studies, hardness, friability, floating lag time and total floating time. The sintering temperature and the sintering time markedly affected the drug release properties. The release rate of the drug was inversely related to the sintering temperature and the sintering time. The hardness was increased with increase in sintering temperature and duration of sintering; but friability of tablets was found to be decreased with increasing sintering time. Floating lag time was inversely proportional to the sintering temperature and sintering time, whereas total floating time was directly proportional to the sintering temperature and sintering time. The formulation F2 sintered at 60^0 for 3 h was selected as an optimized formulation based on the drug retarding properties and the optimized formulation followed Fickian diffusion mechanism with Korsmeyer-Peppas release kinetics. FTIR and DSC studies were used to characterize the optimized formulation and those studies showed no evidence on interaction between the drug and polymer used.

Keywords: Sintering, Gastro retentive, Floating, Atazanavir sulphate (ATZ).

*Corresponding Author Email: chandan_mohanty31@rediffmail.com
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INTRODUCTION

The oral controlled drug delivery system have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, flip flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages of controlled /sustained release dosage form over conventional dosage form such as improved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost, etc[1]. In powder metallurgy, sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in compact, by the application of heat. Conventional sintering technique involves the heating of compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. In the pharmaceutical science, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powders at elevated temperatures, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film coatings. The sintering process has been used for the fabrication of sustained – release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices[2, 3]. The concept of the sintering technique in the pharmaceutical sciences is relatively new, but research interests regarding this technique have been continuously growing. There are only few reports on the applicability of thermal sintering technique for controlled release of drugs. Venkata Srikanth Meka *et al* (2012)[4] prepared thermally sintered floating tablets of propranolol HCL by direct compression method with polyethylene oxide (PEO) as a sintered polymer to retard the drug release. Uhumwangho *et al*., (2011)[5] developed an oral sustained release dosage formulation of Diltiazem HCL wax matrix granules by sintering the polymer matrix using melt granulation technique. Bhanja Satyabrata *et al*., (2010)[3] formulated mucoadhesive buccal tablet of Perindopril by sintering technique with direct compression method containing polymer Polyethylene oxide and carnauba wax which are sintered at various temperatures like 60^0 C and 70^0C for 1.5 hr and 3 hr. Monica Rao *et al*; (2009)[6] studied the effect of sintering technique in the development of a controlled release formulation for ketorolac tromethamine with wax powder (Compritol® 888 ATO) by direct compression at room temperature followed by sintering at 80°C for 1, 2, and 3 h. In this present study Atazanavir sulphate (ATZ) was selected as model drug which is an Anti-Retro Viral Drug and is an Azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions[7-9]. Atazanavir on Oral

absorption it is rapidly absorbed with a Tmax of approximately 2.5 hours and its plasma half life is 5-6.5 hours, hence Atazanavir need to administer frequently for better therapeutic activity. The frequent administration leads to plasma fluctuations and side effects like cardiac conduction abnormalties, rashes, hyperbilurubinea, nephrolithiasis, nausea, jaundice. To overcome these problems it is required to deliver the single dose for a prolonged period of time. Moreover Atazanavir shows maximum solubility at acidic pH and as the pH increases the solubility of Atazanavir sulphate decreases, leading to poor absorption in the intestine. Hence it is beneficial to deliver the drug in the stomach and can be formulated into the floating drug delivery system. Since there are very few reports on gastro retentive floating drug delivery system with sintering technique, the objective of the present work was to develop sustained release floating matrix tablets of ATZ with thermal sintering technique, which were designed to extend the gastric residence time and prolong the drug release after oral administration.

MATERIALS AND METHOD

Atazanavir sulphate was obtained as Gift sample from Aurobindo Pharma Ltd, Hyderabad. Sodium bicarbonate and Magnesium sterate were procured from Lobachem Pvt Ltd Mumbai. HPMC K100M and Ethyl cellulose N100 was provided by Aurobindo Pharma Ltd, Hyderabad. All other reagents and chemicals used for the study were of analytical grade.

Preparation of gastro retentive floating tablets (GRFT) of Atazanavir sulphate

The tablets were prepared with different compositions and are shown in Table 1.The measured quantity of drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture was then compressed into tablets using an 8 mm, biconcave punch, 16-station rotary tablet machine **(**Cadmach, Ahmedabad, India).

Table 1: Composition of gastro retentive floating tablets (GRFT) of Atazanavir sulphate

Ingredients*	**F 1**	**F 2**	**F 3**
Atazanavir sulphate	100	100	100
EC N100	100	100	100
HPMC K100M	30	50	70
Sodium biocarbonate	20	24	28
Magnesium stearate	2	2	2
Total weight (mg)	**252**	**276**	**300**

*All the ingredients are in milligram per tablet

Preparation of thermally sintered gastro retentive floating tablets (TSGRFT) of Atazanavir sulphate

The prepared tablets were exposed at two different temperatures like 50^0C and 60^0C for two different periods like 1.5 hr and 3 hr in a hot air oven. The temperature of the oven was maintained constantly. After exposing to the respective temperature and time tablets are removed, cooled to room temperature and stored in closed desiccator for further use.

Evaluation of Unsintered and Sintered floating tablets of Atazanavir sulphate

The Unsintered and Sintered floating tablets of Atazanavir sulphate are evaluated for various physiochemical parameters like hardness, friability, drug content uniformity, floating lag time, total floating time and *in vitro* dissolution studies.

Tablet hardness [3, 10]

For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester. Hardness was determined by placing each tablet diagonally between the two plungers of tablet hardness tester and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in Kg/cm^2, and the average is calculated and presented with standard deviation.

Friability

The friability values of the tablets were determined using a Roche type friabilator. Accurately weighed 10 tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. The tablets were then re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets[10].

Percentage friability was calculated using the following equation.

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where; W_O = weight of the tablet at time zero before revolution.

W = weight of the tablet after 100 revolutions.

Drug content estimation

From each formulation of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 10 ml of 0.1N HCl was added and then the solution was subjected to sonication for about 20 min. The solution was made up to the mark with 0.1N HCl. The solution was filtered and suitable dilutions were prepared with 0.1N HCl. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 250nm by using UV-Visible spectrophotometer.

Buoyancy / Floating test [11-13].

All the formulated floating tablets are subjected to *In vitro* buoyancy studies. Here, the tablets were placed in a 1L glass beaker containing 900 ml of 0.1N HCl. The time taken for the tablet to emerge to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant was determined as Total Floating Time (TFT)

***In vitro* dissolution studies[14]**

The *In vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of 0.1 N HCL. The test was performed at $37^0C \pm 0.5^0C$ and at a rotational speed of 50 rpm. Five ml samples were withdrawn at predetermined time intervals and the volume was replaced with fresh medium. The filtered samples were suitably diluted with dissolution medium and the absorbance of the samples were analyzed at 250nm using double beam UV-Visible spectrophotometer against reagent blank.

Release Kinetics [3, 4, 5]

Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of Atazanavir sulphate from floating tablets**.** The dissolution data were analyzed on the basis of zero order rate (cumulative percentage amount of drug released vs. time), first order rate (log cumulative percentage amount of drug remaining vs. time), Higuchi model (cumulative percentage amount of drug released vs. square root of time), Hixon-Crowell (cube root of drug percentage remaining in matrix vs. time) and Korsmeyer and Peppas model (log cumulative percentage amount released vs. log time)**.**The model with highest correlation coefficient (R) was considered to be the more appropriate model for the dissolution data. The kinetic models used were zero-order equation (eq. 1), first-order equation (eq. 2), Higuhi equation (eq. 3), Korsmeyer - peppas equation (eq. 4), and Hixon- Crowell equation (eq. 5).

$Qt = Q_0 + K_0t$ ---------- (1)

$\log C = \log C_0 - K_1t/2.303$ ---------- (2)

$Q_t = K_H.t^{1/2}$ ---------- (3)

$(W_0^{1/3} - W_t^{1/3}) = K_{HC}\, t$ ---------- (4)

$Mt/M_\infty = K_K.t^{n}$ ---------- (5)

Qt: amount of drug released in time t, Q_0: initial amount of drug in the tablet, C_0:Initial concentration of drug, Q: active fraction released per unit of surface, W_0: initial amount of drug in the pharmaceutical dosage form, Wt: remaining amount of drug in the pharmaceutical dosage form at time t, Mt: The amount of drug released at time t and M_∞: Amount released at time ∞, thus the

Mt\M∞: Fraction of drug released at time t. K_0, K_1, K_H, K_{HC}, and K_k are release rate constants for Zero-order, First-order, Higuchi, Hixon-Crowell, and Koresmeyer-Peppas model respectively. Zero order represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs. First order is applicable to study of hydrolysis Kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. Matrix (Higuchi Matrix) is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water-soluble drug. Hixson-Crowell Equation applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. Peppas-Korsmeyer Equation is widely used; when the release mechanism is not well known or when more than one type of release phenomena could be involved. According to the Korsmeyer-Peppas equation, the release exponent 'n' value is used to characterize different release mechanisms. If the n value is 0.45, the release mechanism follows Fickian diffusion. If n value is $0.45 < n < 0.89$ (for cylindrical), the mechanism follows a non-Fickian (anomalous) diffusion and when n=0.89 it will be a non Fickian case II transport and if n>0.89 it will be a non-Fickian super case II transport.

Drug-polymer-excipient compatibility studies

The compatibility between Drug-polymer-excipient can be confirmed by Fourier transforms infrared spectroscopy (FT-IR). A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm^{-1}. A quality equivalent to 2mg of pure drug was used for the study.

Differential scanning calorimetry (DSC)

Thermal properties of pure drug and the formulation were evaluated by Differrential scanning colorimetry (DSC) using a diamod (DSC) (Mettler star sw8.10). The analysis was performed at a rate 5^0c min^{-1} to 200^0C temperature range under nitrogen flow of 25 ml min^{-1}.

RESULT AND DISCUSSION

Effect of sintering on physiochemical parameters of unsintered and sintered floating tablets of Atazanavir sulphate

All the unsintered and sintered tablets passed the physicochemical tests concerning hardness, friability, drug content uniformity. The results are presented in table 2.

Hardness

The measured hardness of all formulations (both sintered and unsintered) were in the range of 3.2 kg/cm ^{2} to 5.8 kg/cm ^{2}.The hardness was found to be increased with increase in sintering temperature and duration of sintering. The increase in hardness with increase in sintering temperature and sintering time might be due to the fusion of the polymer or formation of welded bonds among the polymer after cooling.

Friability

Friability of tablets was found to be decreased with increasing sintering duration. Therefore by using this sintering technique friability of tablets can be reduced. For both the sintered and unsintered tablets the percentage weight loss in the friability test was found to be less than 0.8% in all formulations, which ensures that tablets are mechanically stable.

Drug content uniformity

The percentage of Atazanavir sulphate content in all formulations was found to be in the range of 96% to 101% (table 2), which was within the official limits. It was also observed that sintering temperature and sintering time has no significant effects in percentage of drug content of all the formulations.

Table 2: Physiochemical parameters and Buoyancy characteristics of unsintered and sintered floating tablets of Atazanavir sulphate

Sintering temperature and time	Hardness* (Kg/cm^2)	Friability$^{\#}$ (%)	Drug content$^{@}$ (%)	Floating lag time** (Sec)	Total floating time** (hr)
Formulation F1					
Unsintered	3.2	0.72	98.12±0.51	228±3	10±1.0
50^0-1.5 hr	3.5	0.60	99.54±0.84	211±5	12±0.5
50^0-3 hr	4.0	0.57	97.68±1.08	197±8	14±1.0
60^0-1.5 hr	4.3	0.51	100.02±0.32	190±4	15±1.0
60^0-3 hr	4.5	0.46	97.53±0.98	178±6	16±0.5
Formulation F2					
Unsintered	3.5	0.70	96.87±1.09	180±4	10±1.0
50^0-1.5 hr	4.3	0.60	99.65±0.67	172±5	11±1.0
50^0-3 hr	4.5	0.54	97.26±1.12	161±2	12±1.0
60^0-1.5 hr	5.2	0.47	99.08±0.86	158±4	13±0.5
60^0-3 hr	5.5	0.42	98.86±0.45	141±7	15±0.5
Formulation F3					
Unsintered	4.0	0.64	100.68±0.74	141±5	09±1.0
50^0-1.5 hr	4.5	0.48	97.73±0.49	130±8	10±1.0

50^0-3 hr	5.0	0.41	98.90±0.38	114±5	12±1.0
60^0-1.5 hr	5.3	0.38	99.48±0.87	109±4	13±1.0
60^0-3 hr	5.8	0.32	100.88±0.29	96±6	14±1.0

***: n=5; #: n=10; @:Mean±S.D (n=3); **: Mean±S.D (n=5).**

Buoyancy studies

On immersion in solution of 0.1 N HCL the tablets floated and remained floated for longer periods. Floating lag times of all the formulations were in the range of 96 to 228 sec (table 2). Floating lag time was found to be decreased with increase in the sintering temperature, which may be due to decrease in porosity. When the tablets were exposed to sintering temperature, the porosity (void spaces between the particles) of the tablets might be decreased and tablet particles were exposed to the gastric fluid quickly, which leads to the decrease in the floating lag time. Total floating time of all the formulations was found to be in the range of 8-15 hrs (table 2).It was observed that total floating time was increased as the sintering temperature was increased. This is may be attributed to the formation of welded bonds between the particles by softening of polymer, which makes tablet intact for longer period. Hence floating lag time was inversely proportional to the sintering temperature and sintering time. Whereas total floating time was directly proportional to the sintering temperature and sintering time.

***In vitro* dissolution studies**

The dissolution profile (cumulative percentage drug released) of unsintered and sintered floating tablets of Atazanavir sulphate are presented in Figure 1-3.

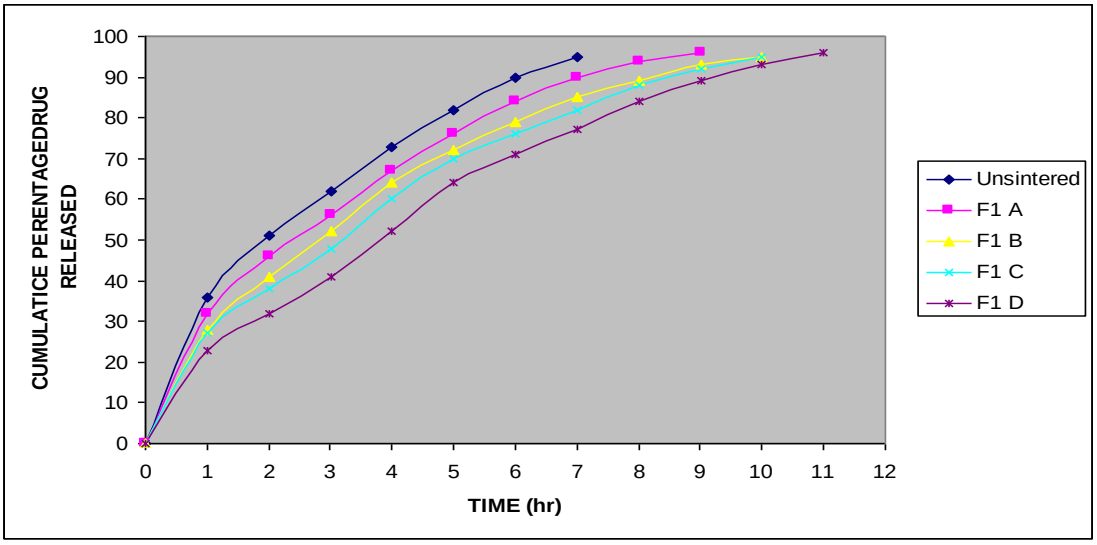

Figure 1: Dissolution profiles of unsintered and sintered floating of F1

A: Sintered at 50^0c for 1.5 hr; B: Sintered at 50^0c for 3 hr; C: Sintered at 60^0c for 1.5 hr D: Sintered at 60^0c for 3 hr

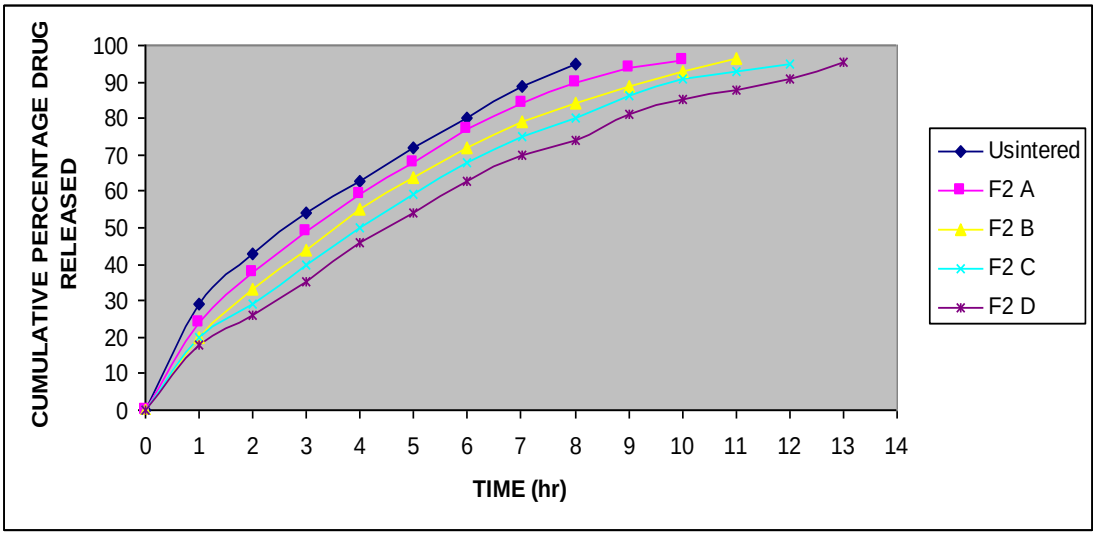

Figure 2: **Dissolution profiles of unsintered and sintered floating of F2**

A: Sintered at 50^{0}c for 1.5 hr; B: Sintered at 50^{0}c for 3 hr; C: Sintered at 60^{0}c for 1.5 hr D: Sintered at 60^{0}c for 3 hr

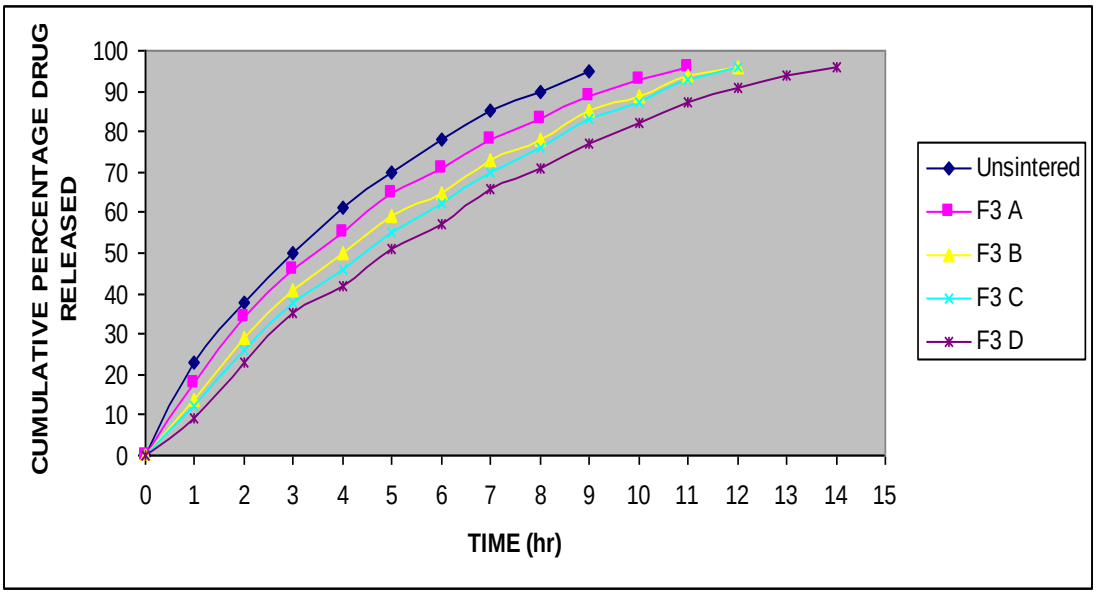

Figure 3: Dissolution profiles of unsintered and sintered floating of F2

A: Sintered at 50^{0}c for 1.5 hr; B: Sintered at 50^{0}c for 3 hr; C: Sintered at 60^{0}c for 1.5 hr D: Sintered at 60^{0}c for 3 hr

From the result it was observed that the formulation F1 without sintering condition was able to retard the drug for 7 hrs only and the maximum drug release was 95.1%. When the tablets were sintered at 50^{0}c for the time duration 1.5 and 3 hr, the maximum release and time taken to attain maximum release were 96.4%, 95.7% and 9 hr, 10 hr respectively, while their corresponding values at 60^{0}c for the time duration 1.5 and 3 hr were 95.3%,96.1% and 10 hr, 11 hr respectively.

Similarly the formulation F2 without sintering condition was able to retard the drug for 8 hrs only and the maximum drug release was 95.5%. When the tablets were sintered at 50^0c for the time duration 1.5 and 3 hr, the maximum release and time taken to attain maximum release were 96.3%, 96.2% and 10 hr, 11 hr respectively, while their corresponding values at 60^0c for the time duration 1.5 and 3 hr were 95.6%,96.7% and 12 hr, 13 hr respectively. Similarly the formulation F3 without sintering condition was able to retard the drug for 9 hrs only and the maximum drug release was 94.7%. When the tablets were sintered at 50^0c for the time duration 1.5 and 3 hr, the maximum release and time taken to attain maximum release were 96.5%, 96.1% and 11 hr, 12 hr respectively, while their corresponding values at 60^0c for the time duration 1.5 and 3 hr were 96.9%,95.2% and 12 hr, 14 hr respectively. From the results it was observed that the sintering temperature and the sintering time markedly affected the drug release properties. The release rate of the drug was inversely related to the sintering temperature and the sintering time. Increasing the temperature or time of exposure to a particular temperature often decrease the release rate. The drug retarding property might be due to the fusion of polymer granules and formation of welded bonds by softening of polymer to which drug particles may have been entrapped in the matrix formed which results in the controlled released of drug. From the results it was also observed that the release of drug retarded as the concentrations of polymer increased, which might be due to increased intensity of air pockets surrounding the jellified surface of tablets[4].

Selection of Optimized formulation

From the *in-vitro* dissolution data it was found that among all the formulations (both unsintered and sintered) the formulation F3 sintered at 60^0 for 3 hr and formulation F2 sintered at 60^0 for 3 h were able to retard the drug for longer period of 14 hr and 13 hr respectively. But due to the higher percentage of drug release and low proportion of the polymer and compare to formulation F3, the formulation F2 sintered at 60^0 for 3 h was selected as an optimized formulation. The optimized formulation followed Fickian diffusion mechanism with Korsmeyer-Peppas release kinetics.

Release Kinetics

The results of dissolution data fitted to various kinetic models are given in table 3. Korsmeyer-Peppas model was found to be the best fitted in all dissolution profiles having higher correlation coefficient (R) values except for formulation F3 sintered at 60^0 c for 1.5 hr and same at 60^0c for 3 hr. The formulation F3 sintered at 60^0 c for 1.5 hr and for 3 hr followed Higuchi model. The release exponents (n) value for Korsmeyer-Peppas model could be used to understand the drug release mechanism. The 'n' values were found to be < 0.45 for all the formulations (both unsintered and sintered) except the Formulation F3 sintered at 60^0c. For The Formulation F3

sintered at 60 ^{0}c the 'n' values were found to be 0.45 < n < 0.89. This indicates that drug release occurred from all the systems followed Fickian diffusion mechanism except the Formulation F3 sintered at 60 ^{0}c. Whereas the Formulation F3 sintered at 60 ^{0}c followed Non- Fickian diffusion mechanism.

Table 3: Drug Release Kinetic Studies from unsintered and sintered floating tablets of Atazanavir sulphate

Formulations	Zero Order (r)	First Order (r)	Higuchi (r)	Hixon Crowell (r)	Koresmeyer Peppas	
					(r)	(n)
F1 Unsintered	0.7209	0.9154	0.9198	0.8596	0.9995	0.2580
F1 50^0-1.5 hr	0.7432	0.9060	0.9322	0.8580	0.9995	0.2709
F1 50^0-3 hr	0.7706	0.9137	0.9523	0.8733	0.9987	0.3000
F1 60^0-1.5 hr	0.8003	0.9259	0.9602	0.8902	0.9929	0.2995
F1 60^0-3 hr	0.8391	0.9352	0.9723	0.9086	0.9823	0.3175
F2 Unsintered	0.7466	0.8923	0.9365	0.8485	0.9980	0.2847
F2 50^0-1.5 hr	0.7906	0.9104	0.9611	0.8748	0.9985	0.3270
F2 50^0-3 hr	0.8312	0.9283	0.9793	0.8998	0.9991	0.3669
F2 60^0-1.5 hr	0.8370	0.9779	0.9779	0.8981	0.9908	0.3440
F2 60^0-3 hr	0.8530	0.9269	0.9828	0.9049	0.9888	0.3500
F3 Unsintered	0.8062	0.9246	0.9694	0.8900	0.9979	0.3510
F3 50^0-1.5 hr	0.8253	0.9228	0.9769	0.8939	0.9907	0.4006
F3 50^0-3 hr	0.8477	0.9254	0.9845	0.9020	0.9880	0.4514
F3 60^0-1.5 hr	0.8573	0.9246	0.9860	0.9041	0.9857	0.4775
F3 60^0-3 hr	0.8673	0.9243	0.9848	0.9068	0.9757	0.5423

Drug-polymer-excipient compatibility studies

The FTIR Spectrum of pure Atazanavir sulphate (ATZ), Ethyl cellulose N100, HPMC K100M, ATZ-EC N100, ATZ-HPMC K100 M and optimized formulation were represented in Figure 4 to 9. Table 4 describes the FTIR spectrum peak points of pure Atazanavir sulphate (ATZ) and the prepared formulations. Thermally sintered optimized formulation showed the characteristic peaks of Atazanavir sulphate with minor shifts. The spectrum peak points of the optimized formulation were similar with that of the pure ATZ clearly indicating that there is no drug-polymer interaction

Table 4: FTIR spectrum peak points of pure Atazanavir sulphate (ATZ), Ethyl cellulose N100, HPMC K100M, ATZ-EC N100, ATZ-HPMC K100 M and optimized formulation

Pure ATZ	EC N100	HPMC K100 M	ATZ-EC N100	ATZ-HPMC K100 M	Optimised Formulation
462	577	572	465	460	586
503	655	610	503	503	663
546	718	662	587	546	702
585	853	804	662	588	784

646	880	849	703	620	805
702	926	946	744	644	850
744	999	1116	768	672	928
769	1032	1250	848	705	949
848	1110	1342	866	744	998
888	1189	1378	838	767	1033
951	1251	1419	928	847	1069
1030	1310	1465	998	892	1115
1068	1361	1585	1030	951	1181
1149	1444	1638	1068	1001	1251
1176	1585	1737	1149	1068	1311
1247	1638	2069	1251	1149	1396
1308	1669	2116	1311	1243	1448
1370	1735	2374	1370	1275	1490
1396	2852	2598	1451	1324	1532
1454	2919	2851	1465	1371	1554
1532	3432	2919	1533	1454	1585
1554	3662	3457	1553	1500	1636
1677			1651	1531	1676
1702			1677	1676	1735
1879			1701	1701	1840
1956			1938	1958	2313
2851			2629	2076	2851
2875			2851	2850	2919
2918			2875	2876	3271
2958			2918	2916	3369
3059			2956	2955	3415
3214			3059	3060	
3263			3214	3263	
3315			3262	3317	
3359			3359	3359	
3420			3421	3423	

Differential scanning calorimetry (DSC)

The DSC thermogram of Atazanavir sulphate (ATZ), ATZ-EC N100, ATZ-HPMC K100 M and optimised formulation were represented in Figure 10 to 13. DSC thermogram of ATZ shows sharp endothermic peak at 210.1^{0}C. Similarly endothermic peaks were obtained at 211.1^{0}C for physical mixture of ATZ-EC, at 208.3^{0}C for the physical mixture of ATZ-HPMC K100M, and at 210.6^{0}C for the optimized formulation. Table 5 summarizes the DSC melting points of different Atazanavir sulphate (ATZ), ATZ-EC N100, ATZ-HPMC K100 M and optimized formulation.

Table 5: DSC melting points of ATZ, ATZ-EC N100, ATZ-HPMC K100 M and optimised formulation

Formulations	DSC melting points in ^{0}c
Atazanavir sulphate(ATZ)	210.1^{0}C
Atazanavir-Ethyl cellulose	211.1^{0}C
Atazanavir-HPMC K100 M	208.3^{0}C
Optimized Formulation	210.6^{0}C

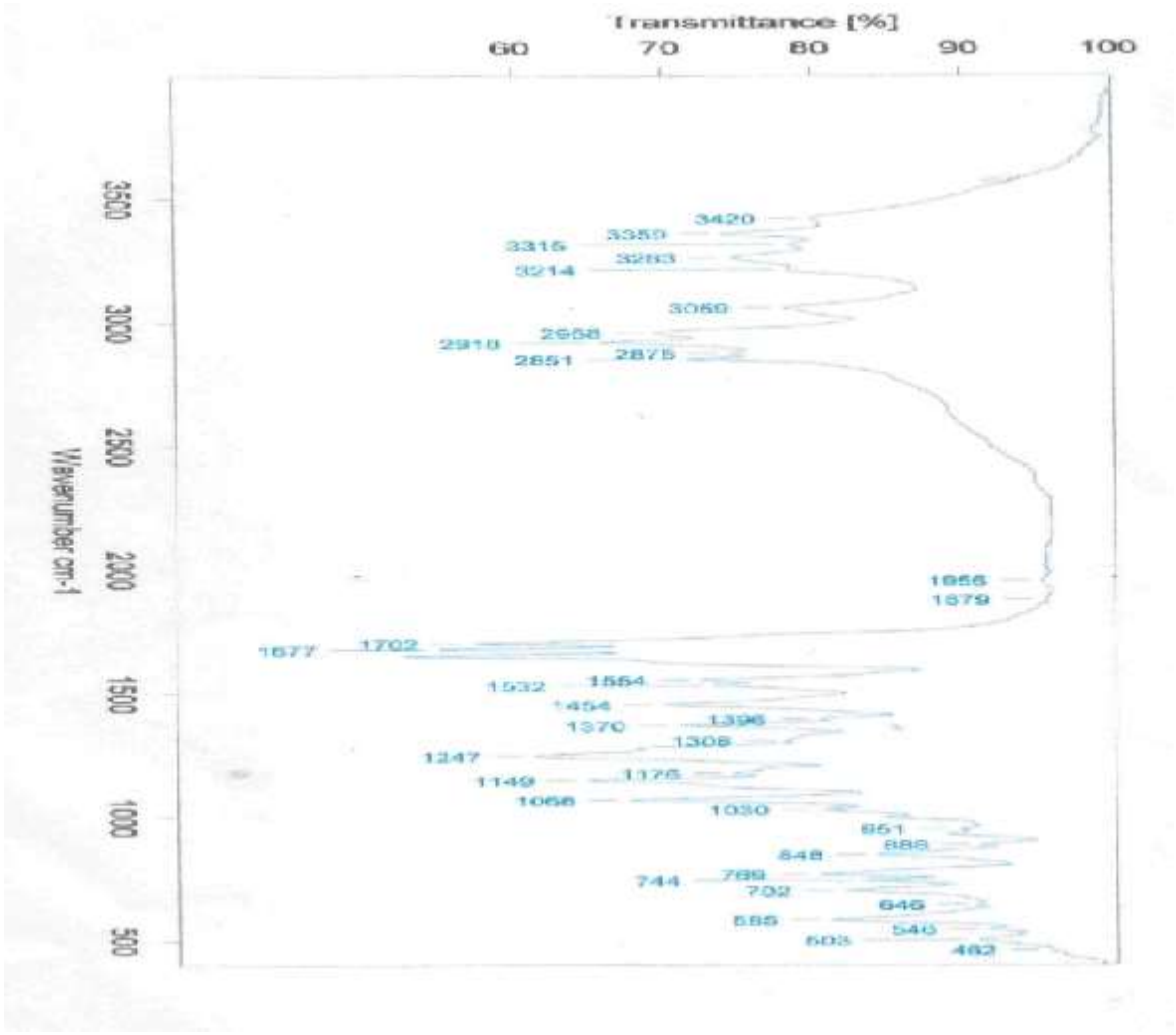

Figure 4: FTIR spectra of pure Atazanavir sulphate (ATZ).

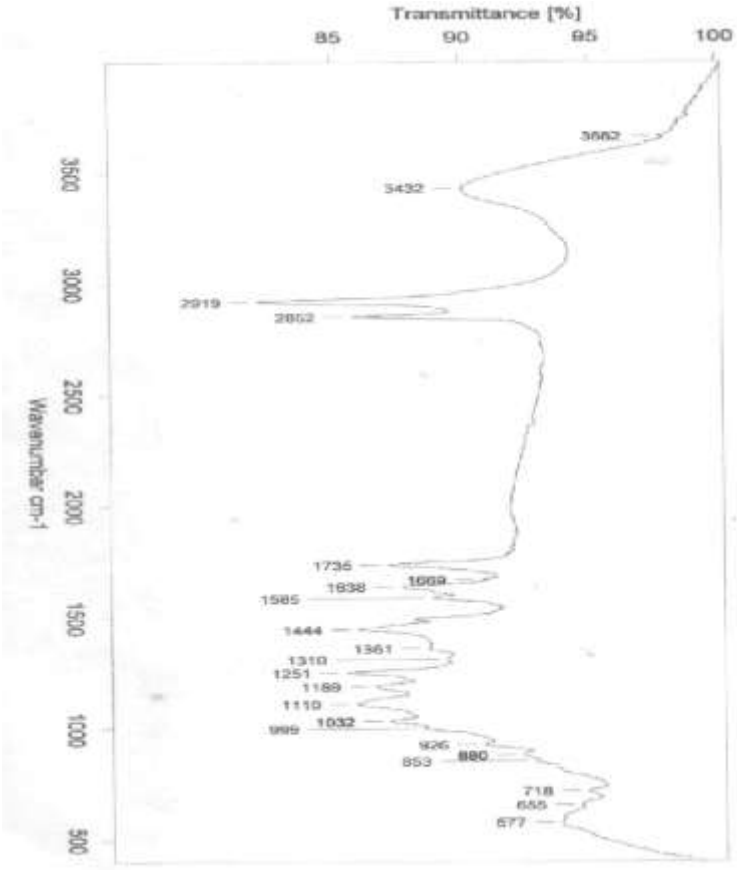

Figure 5: FTIR spectra of Ethyl Cellulose N100.

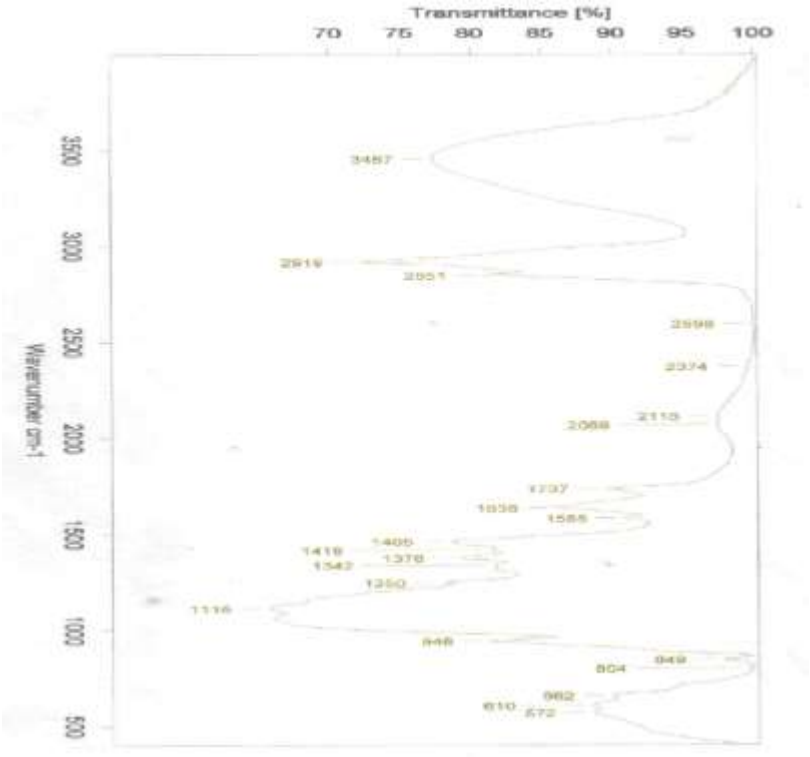

Figure 6: FTIR spectra of HPMC K100 M.

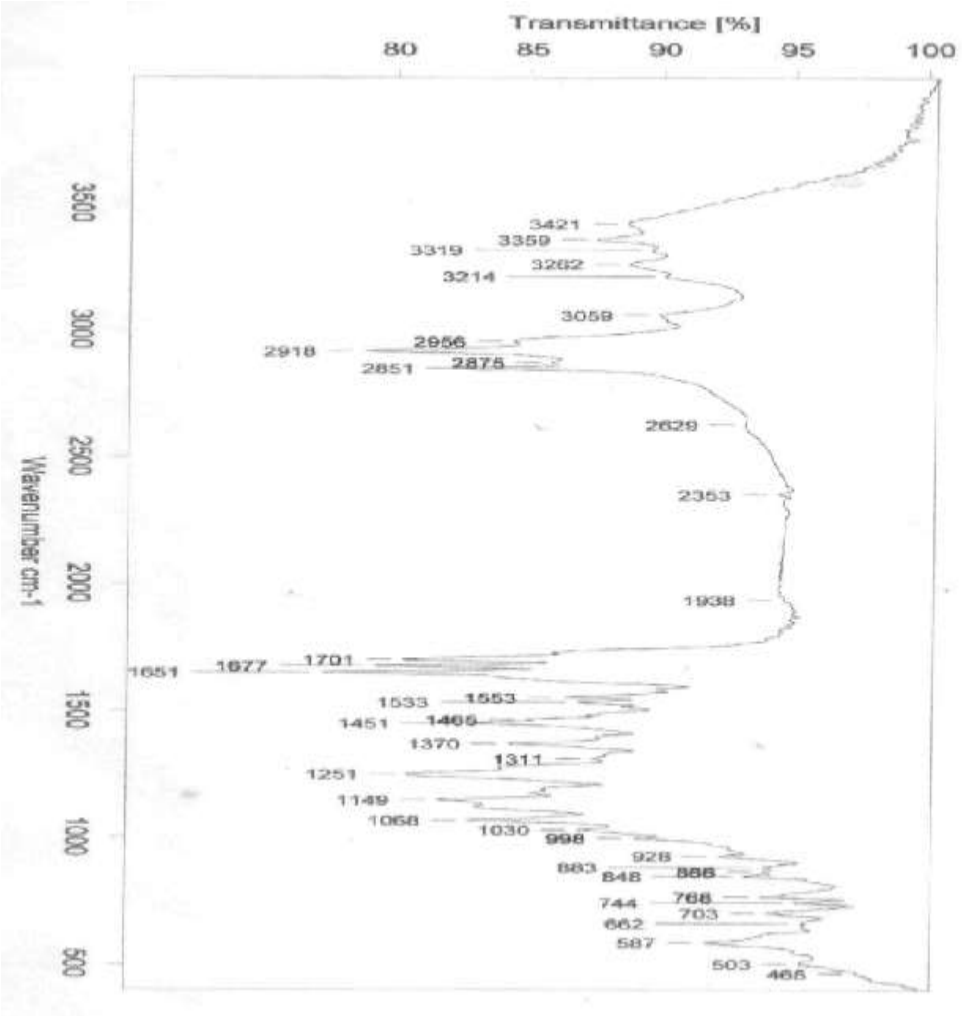

Figure 7: FTIR spectra of ATZ with Ethyl Cellulose N100

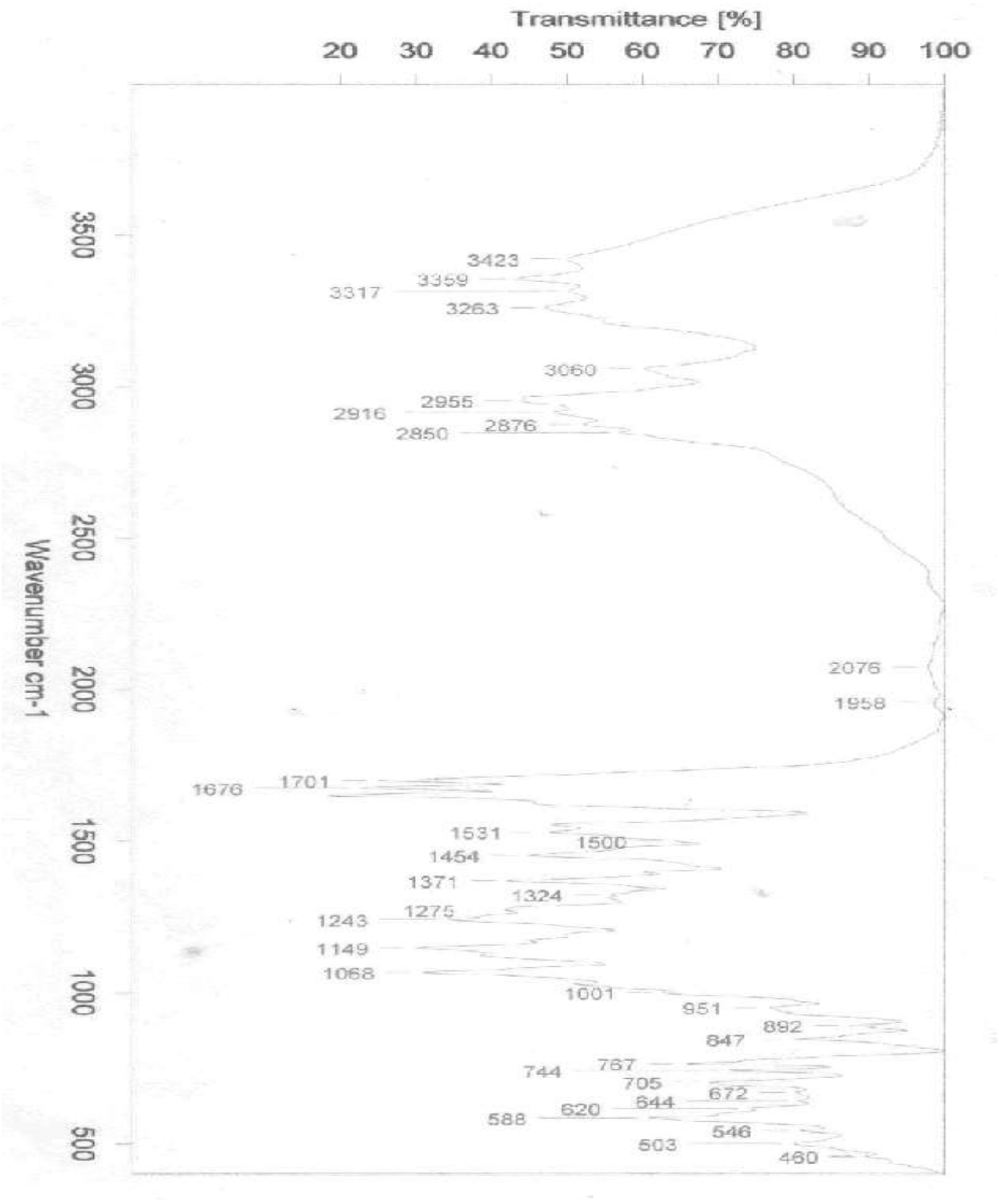

Figure 8: FTIR spectra of ATZ with HPMC K100M.

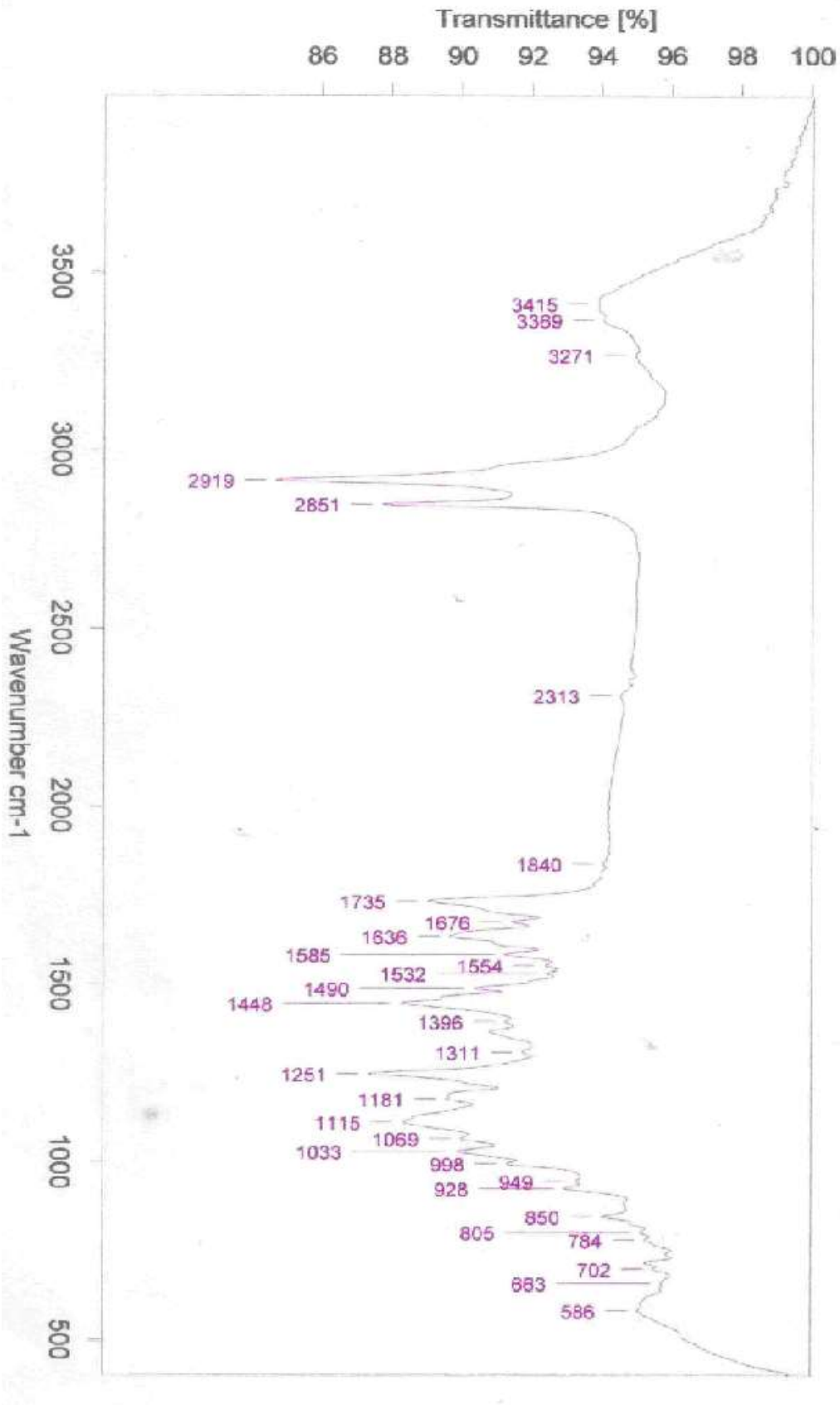

Figure 9: FTIR spectra of optimized formulation

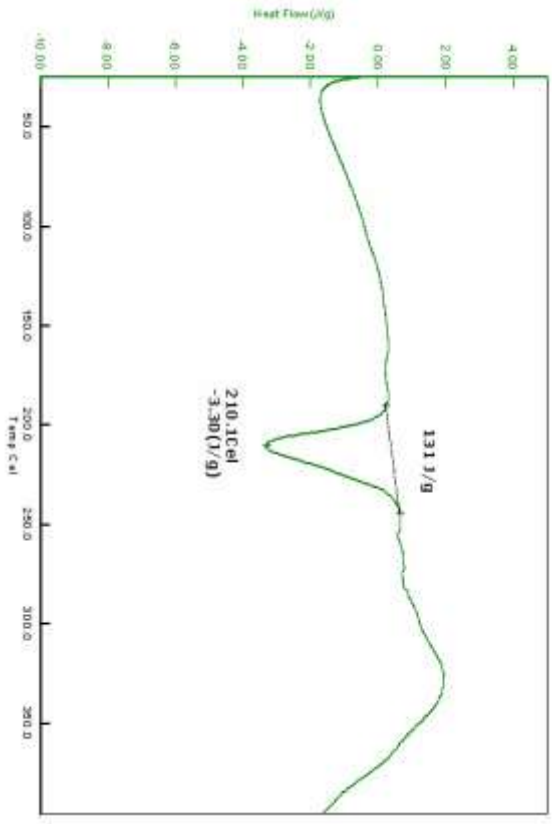

Figure 10: DSC thermograph of the Atazanavir sulphate.

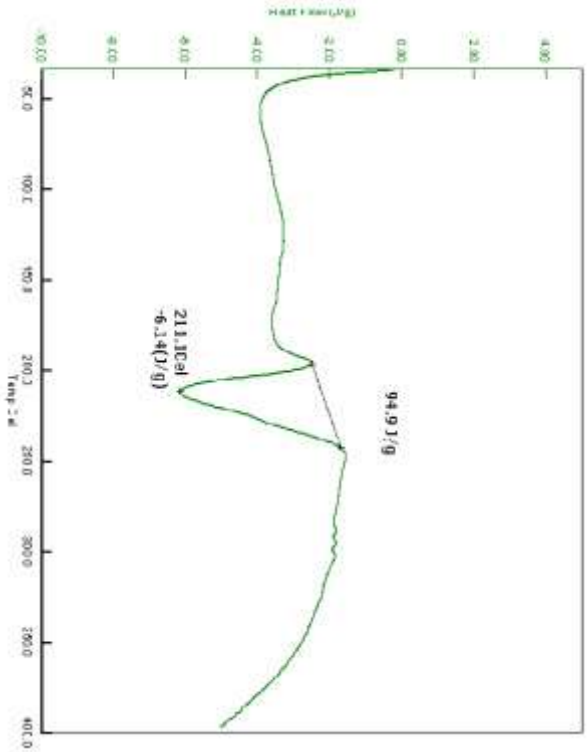

Figure11: DSC thermograph of the Atazanavir-Ethyl Cellulose.

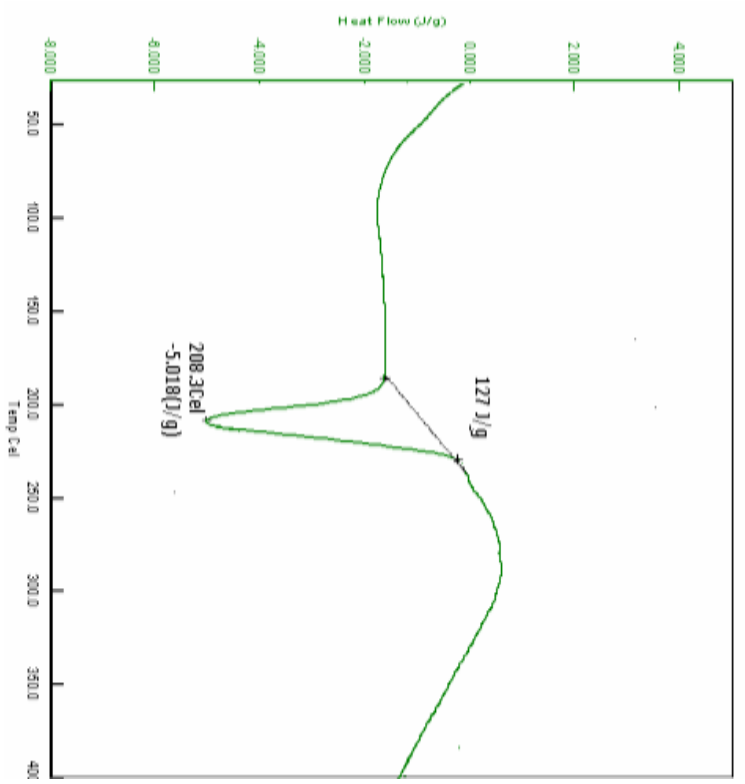

Figure 12: DSC thermograph of the Atazanavir-HPMC K100 M.

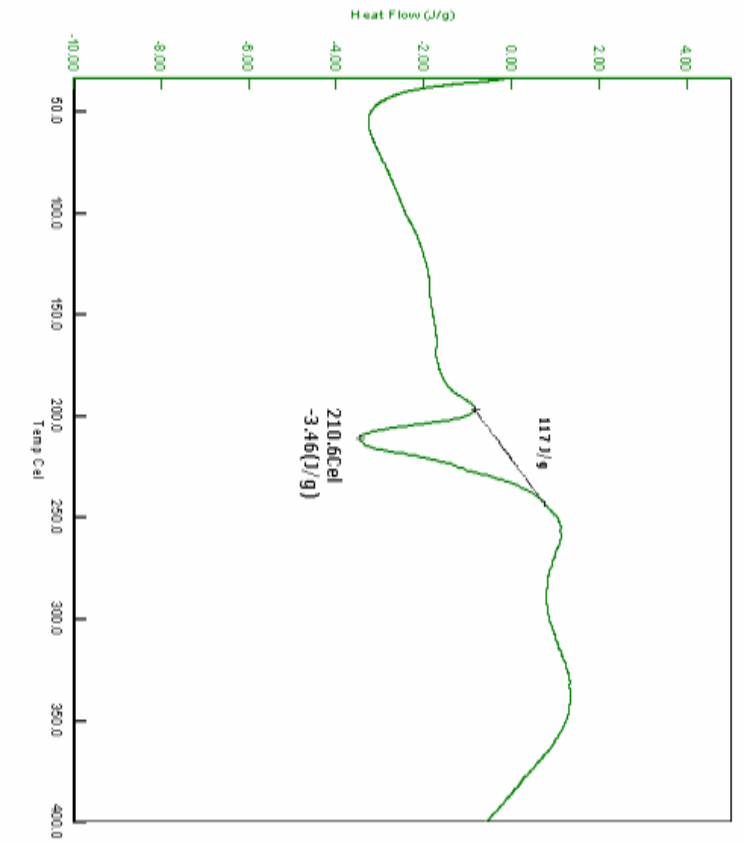

Figure 13: DSC thermograph of optimized formulation.

CONCLUSION

From the above study and its evaluation with mentioned parameters it is evident that the concept of thermal sintering can be used to reduce the polymer quantity with desired dissolution profile. From the experimental data it was found that the release rate of the drug was inversely related to the sintering temperature and the sintering time. Increasing the temperature or time of exposure to a particular temperature often retard the release rate. By using sintering technique floating lag time of tablets was found to be decreased with increase in the sintering temperature and total floating time was increased with increase in the sintering temperature. In addition the hardness was increased with increase in sintering temperature and duration of sintering, where as friability of tablets was found to be decreased with increasing sintering time. The changes observed in the thermogram of DSC and absence of any changes in the FTIR spectra for the selected formulations indicated that there was no evidence of interaction between drug and polymer when exposed to sintering temperature. Hence it can be concluded that a simple technique of thermal sintering may be used in the design of gastro retentive floating tablets (GRFT) of Atazanavir sulphate to sustain the drug release, decrease the floating lag time, increase total floating time, improve the local action and ultimately its bioavailability.

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