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Research article

Formulation and *In-vivo* Evaluation of Azatanavir Self-nanoemulsifying Drug Delivery System

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ABSTRACT

Atazanavir is a human immunodeficiency virus (HIV) protease inhibitor. Due to its intense lipophilicity, the oral delivery of atazanavir encounters several problems such as poor aqueous solubility, pH-dependent dissolution and rapid first-pass metabolism in liver by CYP3A5, which result in low and erratic bioavailability. The current study aimed to develop self-nanoemulsifying drug delivery systems (SNEDDS) of atazanavir in an attempt to circumvent such obstacles. Equilibrium solubility studies indicated the choice of peceol oil - acrysol EL135-capmul MCMC8 for formulating the SNEDDS. Ternary phase diagram constructed with surfactant (Acrysol EL135), co-surfactant (Capmul MCMC8) and oil (peceol oil) representing each apex of the triangle. The pharmacokinetics studies of SNEDDS formulation were investigated in wistar rats. The optimal formulation (F9) with best self-nanoemulsified and solubilization ability consisted of 20% (w/w) peceol oilas oil, 60% (w/w) acrysol EL135 as surfactant and 20% (w/w) capmul MCMC8 as cosurfactant. The formulation displayed maximum drug content of 99, 98% entrapment efficiency and drug release of >98% in 60 minutes. The particle size for the optimized formulation of SNEDDS (F9) was found to be 51.6 nm with PDI 0.468 and zeta potential of -20.6 mV. The formulation found to be stable after storage at accelerated conditions at 40 ± 2°C/75 ± 5% RH for a period of six months. The pharmacokinetic study in rats indicate that the C_{max} of the SNEDDS 0.33 ± 1.73 ng/mL was significant ($p < 0.05$) as compared to the pure drug 0.091 ± 0.39 ng/mL. T_{max} of both SNEDDS formulation and pure drug was 1.5 ± 0.53 and 3 ± 0.72 hours, respectively. The AUC indicated significant enhancement in the rate and extent of bioavailability by the SNEDDS formulation compared to pure drug. The studies, therefore, indicate the successful formulation development of SNEDDS with distinctly improved bioavailability of atazanavir.

Introduction

More than 60% of the discovered drugs have the problem of low aqueous solubility which leads to their poor dissolution and reduced bioavailability. There are many techniques to overcome this problem like cyclodextrin complexation, salt formation, particle size reduction, solid dispersion, lipid based formulations, etc. Self-nano emulsifying drug delivery system (SNEDDS) is one of the techniques which is gaining more attention for improving the solubility of the lipophilic drug. SNEDDS is an isotropic mixture of oil, surfactant, and co-surfactant which forms oil in water (o/w) nanoemulsion with slight agitation. Oil is selected based on their solubility capacity and both surfactant and co-surfactant is selected based on their emulsifying ability. To prevent the precipitation of the drug and to reduce the dosing frequency, suitable precipitation inhibitors can be used (maintains supersaturation state and blocks the formation and growth of the crystals). By introducing precipitation inhibitors into the formulation, the surfactant concentration can be minimized (reduce GI side effects).[1-7]

The drug, atazanavir, chosen in the present study is a biopharmaceutics classification systems (BCS) class II drug with poor water solubility and high permeability (log p of 4.11).[8] In adults, atazanavir-recommended therapeutic dose is 400 mg once a day. Besides these, it undergoes rapid first-

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pass metabolism in liver, leading eventually to marked reduction in the drug oral bioavailable fraction (i.e., 60%) in humans and animals such as rats, and so on.[9] To circumvent the aforementioned limitations, various formulation approaches of atazanavir have been reported such as, nanocrystals, nanoparticles,[10] tablets and capsules[11] but all with limited fruition. The current work endeavors to design an optimized SNEDDS system of atazanavir, resulting in improved oral bioavailability. It is anticipated that this study not only offers a good example of enhancing the oral bioavailability of atazanavir, by the use of SNEDDS, but also presents a promising oral formulation of atazanavir for clinical application.

The prime objective of the present study is to develop suitable SNEDDS for azatanavir for enhanced solubility and drug dissolution rate.

Material And Methods

Materials

Azatanavir drug was purchased from Aurobindo Pharma Ltd, Hyderabad. The formulation excepients were purchased from Gattefosse, Mumbai.

Solubility of Azatanavir in Vehicles

Azatanavir along with 1 g of vehicle (i.e., oil or surfactant or co-surfactant) was vortexed for 10 minutes followed by reciprocally shacking using for 48 hours at 25°C. Contents allowed to settle for 24 hours followed by centrifugation (3000 rpm, 10 minutes). The supernatant filtered, diluted using methanol and evaluated spectrophotometrically.[12,13]

Construction of Ternary Phase Diagram

Ternary phase diagram constructed with surfactant (Acrysol EL135), co-surfactant (Capmul MCMC8) and oil (peceol oil) representing each apex of the triangle. Varying ratios of oil: S_{mix} (surfactant + cosurfactant) were mixed with 100 mL of water and formulations with no phase separation and no turbidity, checked for transmittance using UV-spectrophotometer. The transmittance value >90 were used for plotting ternary phase diagram using CHEMIX software.[14] The area of nanoemulsion formation was studied on peceol oil-Acrysol EL135-Capmul MCMC8 compositions with S_{mix} in 3:1 ratio, with larger nanoemulsification region. About 17 formulations of varying ratios of peceol oil-Acrysol EL135-Capmul MCMC8 was incorporated with 300, 400 and 500 mg of azatanavir and evaluated for % transmittance.[15]

Preparation of Azatanavir SNEDDS

About 1-mL of the formulation filled in size '00' hard gelatin capsules, sealed, stored at ambient temperature (25°C) and evaluated (Table 1).[16]

Evaluations of Azatanavir SNEDDS

Physical Evaluation

All the SNEDDS were evaluated for time of self-emulsification, dispersibility, appearance, turbidity, robustness to dilution in distilled water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer as per the refereed methods. The diluted nanoemulsions were stored for 24 hours and observed for any signs of phase separation or drug precipitation.[17-20]

Percentage Drug Content and Entrapment Efficiency

Accurately weighed samples were dissolved in 10 mL of methanol and vortexed for 10 minutes. Contents filtered, and drug content estimated spectrophotometrically. A known quantity of SNEDDS mixed with 100 mL phosphate buffer (pH 6.8) and kept in dark for 24 hours.[21]

Entrapment efficiency was calculated by formula:

Drug entrapment efficiency= Experimental drug content /Theoretical drug content x 100

In-vitro Dissolution Studies

In-vitro dissolution studies performed in USP dissolution Apparatus II (Lab India DS 8000, Mumbai, India). The formulations were introduced into 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C at 50 rpm. At pre-determined time intervals, 5 mL samples withdrawn and equivalent amount of fresh medium replaced and evaluated.

Characterization of Optimized Azatanavir SNEDDS

The particle size, zeta potential of the diluted SNEDDS analysis carried out using Malvern zetasizer (Malvern, UK).[22]

The FTIR (Fourier-transform infrared spectroscopy) was performed between 4000 to 400 cm^{-1} using FT-IR instrument (FTIR- 8400S, Bruker, Germany). The scanning electron microscope (SEM) analysis carried out using Hitachi S-3000 N SEM.[23]

Stability Studies

The stability of the formulation evaluated as per ICH guidelines, namely, accelerated stability studies were conducted at 40°C ± 2°C/75% RH ± 5% for 6 months.[24]

In vivo Pharmacokinetic Studies in Rats [25,26]

The animal investigations were performed as per the requisite protocol approved by the Institutional Animal Ethics Committee [IAEC NO: 1477/PO/Re/S/11/CPCSEA-54A]. The committee is duly approved for the purpose of control and supervision of experiments on the animals by the Government of India.

Healthy male wistar rats were (weighing 150–180 g) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (temperature 25°C, relative humidity 45% and 12 hours alternate light and dark cycle) with 100% fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with standard diet and waterad libitum.

Rats were divided in to two groups at random. Each group containing six rats. The treatments as given below were administered to the rabbits.

The rats were fasted for 24 hours prior to the experiments.

Table 1: Composition of azatanavir SNEDDS

Formulation code	*Azatanavir drug (mg)*	*Ratios of Oil: Smix*	*Oil (Peceol oil)*	*Smix 3:1*	
				Surfactant (Acrysol EL135)	*Co-surfactant (Capmul MCMC8)*
F1	300	1:01	50	37.5	12.5
F2	300	1:02	33	49.5	16.5
F3	300	1:03	25	56.25	18.75
F4	300	1:04	20	60	20
F5	300	2:01	66	24.75	8.25
F6	300	2:03	40	45	15
F7	300	2:05	28.5	53.25	17.75
F8	300	2:07	22.2	58.2	19.4
F9	300	2:09	18	60.75	20.75
F10	300	3:02	60	30	10
F11	300	3:04	42.6	42.6	14.8
F12	300	3:07	30	52.5	17.5
F13	300	7:03	70	22.5	7.5
F14	300	5:03	62.5	28.12	9.3
F15	300	4:03	57.1	31.95	10.65

Table 2: % Drug content and % entrapment efficiency values

Formulation code	*%Entrapment efficiency*	*% Drug content*
F1	96.96 ± 1.43	97.01 ± 1.21
F2	97.52 ± 1.51	97.57 ± 1.19
F3	98.23 ± 1.69	98.35 ± 1.65
F4	98.75 ± 1.43	99.08 ± 1.59
F5	95.98 ± 1.22	96.53 ± 1.19
F6	97.38 ± 1.67	97.43 ± 1.49
F7	98.08 ± 1.53	98.13 ± 1.78
F8	98.79 ± 1.79	98.84 ± 1.15
F9	99.80 ± 1.73	99.85 ± 1.66
F10	96.69 ± 1.35	96.74 ± 1.45
F11	97.06 ± 1.39	97.11 ± 1.13
F12	97.87 ± 1.95	97.92 ± 1.62
F13	95.66 ± 1.84	96.11 ± 1.89
F14	96.31 ± 1.70	96.57 ± 1.39
F15	96.81 ± 1.71	96.97 ± 1.40

Above parameters are communicated as Average ± Standard Deviation; (n=3)

After 4 hours of dosing, foods were reoffered. First group was administered with pure atazanavir (as such) made suspension with 0.5% methocel and second group was administered prepared atazanavir optimised SNEDDS diluted in 0.5% methocel by oral route at a dose of 1.17 mg. 200 µL blood samples were collected at regular time intervals from the femoral artery at times 0, 0.50, 1, 1.50, 2, 2.50, 3, 4, 5, 6, 8, 12, 16, 20, 24 hours post dose and transferred into eppendrof tubes containing heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 minutes to 10 minutes and stored frozen at –20°C until analysis. Plasma samples were analyzed by HPLC. Non-compartmental pharmacokinetic parameters for extravascular input, that is, C_{max}, T_{max}, AUC, t1/2, Ke and MRT were computed by choosing Kinetica 5.0.11 version software (Thermo Fisher Scientific Inc. Waltham, USA).

Results And Discussion

Determination of Solubility and Construction of Ternary Phase Diagram

The peceol oil (0.042 ± 0.06 mg/mL), acrysol EL135 (50.14 ± 0.13 mg/mL) and capmul MCMC8 (44.423 ± 0.83 mg/mL) were selected for further studies based on higher solubilizing capacity towards azatanavir.

The peceol oil-acrysol EL135-triton SP- 135 system with S_{mix} ratio in 3:1 exhibited larger nanoemulsification region as compared to 1:1 and 2:1 S_{mix} ratio.The formulation containing peceol oil-acrysol EL135-Capmul MCMC8 system with 3:1 S_{mix} ratio and 300 mg of azatanavir displayed maximum emulsification region (Fig. 1).

Preparation and Evaluation of Azatanavir SNEDDS

About 15 formulation of SNEDDS with peceol oil (18-66% w/w), Acrysol EL135 (22-61% w/w) and Capmul MCMC8 (7-21% w/w) in 3:1 of oil:S_{mix} ratio with 300 mg of loaded atazanavir drug were prepared and evaluated. Visual observations indicated that at higher levels of surfactant, the self- emulsification process increased. The formulations with low turbidity (<20) gave a transmittance values > 90 indicating rapid and spontaneous emulsification within 1-minutes. All formulation was found robust to dilutions. The drug content of all formulations ranged between 95.66 to 99.80% with maximum value exhibited by F9.The entrapment efficiency of all formulations vary between

Table 3: Storage at 40 ± 2°C/75 ± 5% RH for 6 months

Retest time for optimized formulation F9	*%Entrapment efficiency*	*% Drug content*	*In-vitro drug release (%)*
0 days	99.80 ± 1.73	99.85 ± 1.66	99.69 ± 2.14
30 days	98.53 ± 0.45	99.56 ± 0.78	99.22 ± 1.56
60 days	98.35 ± 0.78	99.09 ± 0.23	98.90 ± 1.34
90 days	98.02 ± 0.84	98.93 ± 0.54	98.75 ± 1.95

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Table 4: Mean pharmacokinetic parameters of atazanavir pure drug and atazanavir optimised SNEDDS formulation

Pharmacokinetic parameters	*Atazanavir Pure drug*	*Atazanavir optimised SNEDDS*
C_{max} (µg/mL)	0.091 ± 0.39	0.33 ± 1.73
AUC_{0-t} (µg. h/mL)	0.45 ± 1.02	1.38 ± 0.21
AUC_{0-inf} (µg. h/mL)	0.52 ± 1.73	1.61 ± 2.48
T_{max} (h)	3 ± 0.72	1.5 ± 0.53
$t_{1/2}$ (h)	7.6 ± 0.02	5.8 ± 0.05

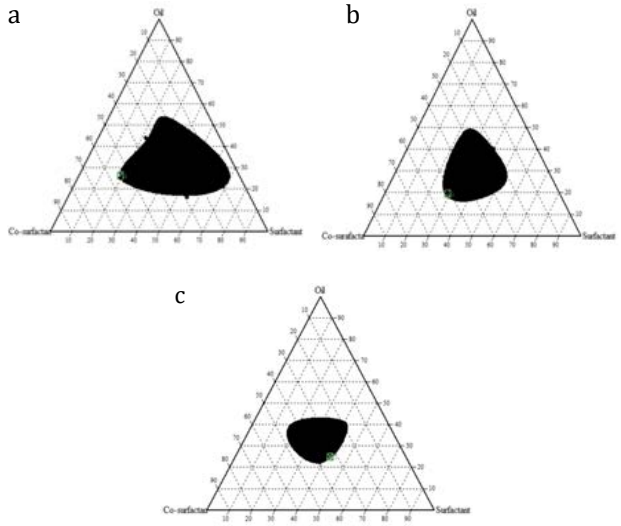


Fig. 1: Ternary phase diagram for azatanavir loaded in peceol oil - Acrysol EL135- Capmul MCMC8 system with Smix in 3:1 ratio a) 300 mg of drug B) 400 mg of drug c) 500 mg.

96.11 to 99.85 % with maximum value displayed by F9 (Table 2).

In-vitro Dissolution Studies

All the formulations (F1-F15) displayed >95% dissolution within 90 minutes whereas, pure drug released only 32% in 60 minutes. Formulation F9 exhibited highest drug release of 99.69 ± 2.14% within 30 minutes. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration (Fig. 2)

Characterization of Optimized SNEDDS

The FTIR spectrum of azatanavir displayed characteristic peaks at 3423 cm^{-1} (-OH stretching), 3358 cm^{-1} (NH stretching), 2964 cm^{-1} (C_N stretching), 1712 cm^{-1} (C=O stretching), peaks around 3800 cm^{-1} (aromatic C-H

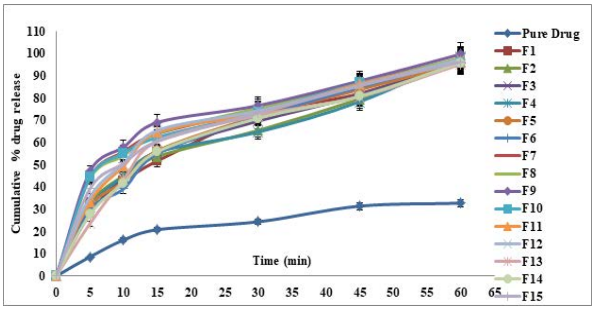


Fig. 2: Comparative dissolution profile of pure drug and SNEDDS formulation (F1-F15).

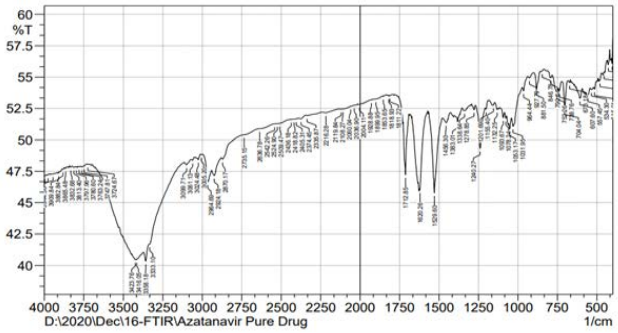


Fig. 3: FTIR spectrum of pure drug azatanavir.

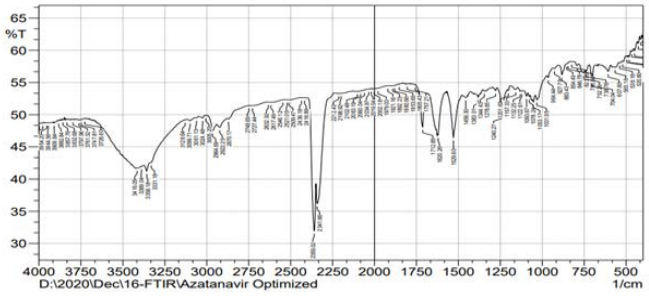


Fig. 4: FTIR of optimized formulation (F9).

stretching), 1620 cm^{-1} (CO-N stretching). The presence of prominent characteristic peaks in optimized formulation conform the compatibility of drug and excipients used (Figs 3 and 4).

Globule Size and Zeta Potential

The particle size for the optimized formulation of SNEDDS (F9) was found to be 51.6 nm with PDI 0.468. The negative value of zeta potential of -20.6 mV might be due to the presence of anionic groups of free fatty acids, and glycols present in the oil, surfactant and co-surfactant (Figs 5, and 6)

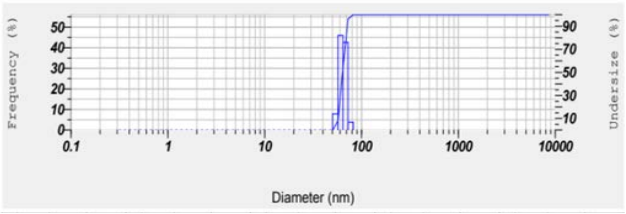


Fig. 5: Particle size of optimized SNEDDS formulation of azatanavir(F9).

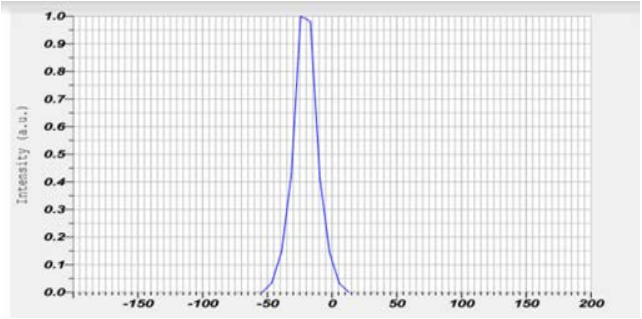
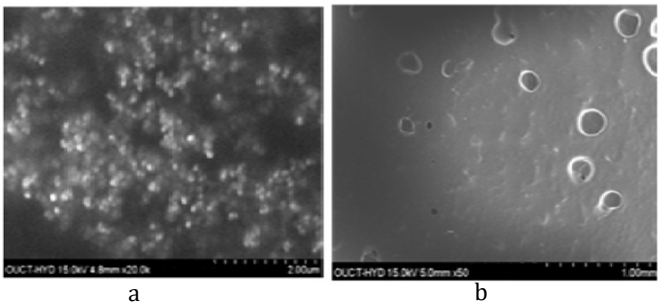


Fig. 6: Zeta potential of optimized SNEDDS formulation of azatanavir (F9).



a b

Fig. 7: SEM images of optimized formulation of azatanavir SNEDDS F9 (a and b).

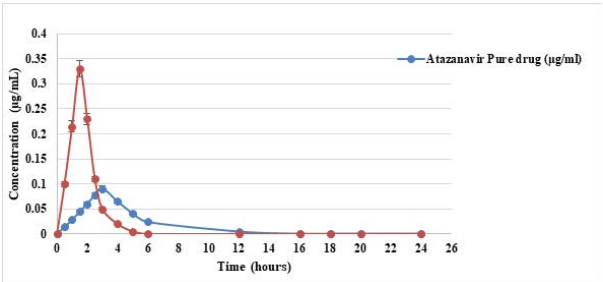


Fig. 8: Mean plasma concentration-time profiles for atazanavir pure drug and atazanavir optimized SNEDDS formulation in rats (n=6).

SEM Studies

The SEM results were in accordance to that of globule size analysis and were observed that the size of all droplets of SNEDDS F9 was less than 100 nm as furnished in Figs 7A and 7B. However, the shape of droplets was found to be spherical (Fig. 7).

Accelerated Stability Studies

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. No significant difference was observed% entrapment efficiency, % drug content and *in-vitro* drug release post storage (Table 3).

Fig. 8 shows the plasma concentration–time curve in Wister rats after a single oral dose of atazanavir SNEDDS formulation as compared to atazanavir pure. At all the indicated time points, the atazanavir plasma concentrations in rats treated with SNEDDS formulation was significantly higher than those treated with pure drug. Pharmacokinetic parameters of atazanavir after oral administration of the two formulations in wistar rats are shown in Table 4.

C_{max} of the SNEDDS 0.33 ± 1.73 ng/mL was significant ($p<0.05$) as compared to the pure drug 0.091 ± 0.39 ng/mL. T_{max} of both SNEDDS formulation and pure drug was 1.5 ± 0.53 and 3 ± 0.72 hours, respectively. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0-\infty}$ infinity for SNEDDS formulation was higher (20.5 ± 2.48 ng. h/mL) than the pure drug 6. 34 ± 1.73 ngh/mL. Statistically, AUC_{0-t} of the SNEDDS formulation (1.61 ± 2.48 ng h/mL) was significantly higher ($p < 0.05$) as compared to pure drug (0.52 ± 1.73 ng h/mL). Higher amount of drug concentration in blood indicated better systemic absorption of atazanavir from SNEDDS formulation as compared to the pure drug.

Conclusion

The current work entails the development of SNEDDS formulation of atazanavir and its subsequent pharmacokinetic evaluation for ratifying its biopharmaceutical superiority. Equilibrium solubility studies were carried out in an attempt to find out the maximum soluble fraction of atazanavir in different lipids and surfactants. Based upon maximal drug solubility, a peceol oil was selected as oil phase. The acrysol EL135 solubilizer and absorption enhancer, was found to be a very efficient solubilizer for atazanavir, and so was chosen as a surfactant in the development of SNEDDS formulation aiming to improve the drug-Loading capabilities along with capmul MCMC8 as cosurfactant. The particle size for the optimized formulation of SNEDDS (F9) was found to be 51.6 nm with PDI 0.468. The zeta potential of -20.6 mV might be due to the presence of anionic groups of free fatty acids, and glycols present in the oil, surfactant and co-surfactant. The drug release of about 98% in 60 minutes which is about 3-fold higher than that of pure drug (32%) was observed from SNEDDS. Based on in-vivo studies carried out in rats the AUC_{0-t} of the SNEDDS formulation was found significantly higher ($p<0.05$) as compared to pure drug. Higher amount of drug concentration in blood indicated better systemic absorption of atazanavir from SNEDDS formulation as compared to the pure drug.

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