Original Article

Development and *in vitro* Evaluation of Atazanavir Microcrystals for Intranasal Delivery

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ABSTRACT

Background: Nasal route of drug administration has gained popularity nowadays specially for drugs acting on nasopulmonary area. Atazanavir is an antiviral drug which has proved efficacy in different viral infection including COVID-19. Therefore the hypothesis is, if given through intra nasal route this formulation will be able to prevent the viral infection like COVID-19 by directly acting on the virus at its entry point. **Objectives:** This study aims to prepare a stable mucoadhesive microcrystal formulation of this antiviral drug with good permeation for intra nasal delivery. **Materials and Methods:** The formulation was prepared by high-speed homogenization process. Prepared microcrystals were estimated for *in vitro* drug release and permeation, drug excipient interaction study by DSC, FTIR and *in vitro* mucoadhesiveness study on agar gel plate. A short-term stability study was conducted on all formulations for 6 months. **Results:** The melting point and absorbance maxima of atazanavir were found as 200.9°C and 248 nm. The DSC and FTIR study results confirmed no drug excipient interaction was there in the formulation. The particle size of the formulations was found as 5-11 μm in range. Drug release was better and faster from the microcrystals as compare to pure powder drug. The flux for microcrystal formulation was found to be 100 whereas flux for the pure drug powder was 24. Formulations had sufficient mucoadhesive strength due to incorporation of HPMC 400 polymer and they were found stable after six months stability study. **Conclusion:** Lastly, it can be concluded that this formulation would be a promising system for the delivery through intra nasal route as it showed good drug release and permeation during a short time span in *in vitro* nasal condition with a particle size range suitable for intranasal delivery. However, further *in vivo* studies are required to confirm the hypothesis.

Key words: COVID-19, Atazanavir, Protease inhibitor, Naso-pulmonary, Intranasal, Antiviral.

INTRODUCTION

Atazanavir was the first antiviral having protease inhibitor activity approved as once-daily formulation for the management of HIV-1. It was one of the nine protease inhibitor (6^{th}) approved by FDA.[1] It specifically obstructs the HIV virus by preventing of viral gag and gag-pol polyproteins, thus development of mature virions is blocked. Formulation of suitable liquid dosage form of this drug is a challenge due to its poor water solubility. Further rapid absorption of Atazanavir with a T_{max} approximately 2.5 hr after oral administration is another problem. Because rapid elimination of drug from body requires frequent administration which is therefore associated with side effects like cardiac conduction abnormalities, nephrolithiasis, hyperbilirubinea, etc. therefore another route of administration for this drug could be considered.[2]

The administration of the drugs to nasopulmonary region can be possible through two modes: first is administration through Intranasal while the second is the administration through oral inhalative. The oral inhalative administrations are further divided into intratracheal instillation and intratracheal inhalation. The intratracheal instillation type method is generally used in

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labs. With the help of special syringe the less amount of the drug is administered in the lungs, as it is effective and fast method of the drug administration. The various benefits of intratracheal instillation are: it is not expansive, easy method, it allow the distribution of non-uniform drug. The intratracheal instillation is generally used in the preclinical studies of animals to evaluate systemic bioavailability and pulmonary absorption in contrast with dosing and effectiveness of drug.[3] There are certain routes which have no records for application like intratrachral route, hence cannot be used for aerosol administration. On the other hand aerosol phenomenon gives apt result. This phenomenon is expensive and difficult to administer. There are 3 mechanisms through which the drug deposition takes place in pulmonary airways, these are: gravitational sedimentation, inertial impactation and the diffusion.[4] The deposition of large particles generally happens by gravitational or by inertial impactation method but the deposition of small particles happens by diffusion method, which generally depends on Brownian motion. The particle size and its geometry also play an important role as that of pulmonary morphological feature.[5]

Nasopulmonary route have gained attention in last few years for treating different diseases specially brain and lung diseases. The virulence of COVID19 forces all the researchers for an instantaneous intervention. Numerous studies have revealed positive observations with protease inhibitors like lopinavir, ritonavir and atazanavir against SARS-CoV-2 Mpro.[6] Further, Atazanavir alone or with ritonavir could hinder COVID virus reproduction in cell culture models. They also reported to prevent the release of cytokine storm-associated mediators. Further reported data proved that SARS-CoV-2 is vulnerable to atazanavir in different cell types.[7,8]

WHO has already confirmed that the virus of COVID-19 enters into the human body through the respiratory tract followed by intervention into the alveolar blood vessels and then spread by blood.[9] Therefore a drug delivery system through nasal route would be beneficial to prevent the virus at the entry point. This route is chosen for its direct accessibility with porous cribriform plate, devoid of systemic side effects, required low dose as rapid drug absorption occurs through alveolar blood vessel. Moreover drugs in nano or micro sized can be given through this route for better absorption and drug release at the viral site of action.[10] Nasal powder formulation is always better than liquid formulation in terms of formulation development, microbial stability, storage time, dose delivery and others.

It is hypothesized that delivering atazanavir directly into nasal area by powder inhalation would lower the dose, lower the oral side effects, and provide direct faster activity. Several *in silico* study reports already have established the fact that HIV protease inhibitors including Atazanavir could target SARS-CoV-2 Mpro.[7] It is also described that ATV could reach the lungs successfully after i.v injection.[11,12] Further, its secondary use in the treatment of pulmonary fibrosis also proved its accessibility to the lungs. This study aimed at delivering atazanavir in a microformulation using safe and conventional excipients through nasal route which can be used for the treatment of COVID-19.

A microcrystal is a particle having one or more particular dimensions having size range in micron. These unique particles considered to have advantages including solubility enhancement of poorly soluble drug due to higher surface: volume ratio which leads to promote permeability and bioavailability.[13] In the present study, the aim was to prepare mucoadhesive microcrystals of Atazanavir to deliver through intra nasal route.

MATERIALS AND METHODS

Materials

Atazanavir powder was received as a gift sample from Cadila Health care (Zydus), Ahmedabad, India. Other ingredients including sodium lauryl sulphate, PVP K 30 and PVA were purchased from S.D fine Chemical Ltd., India.

Methods

Preformulation studies of atazanavir

Preformulation studies of the drug molecule are necessary to carry out at the very beginning before developing a new delivery system. To develop as table, elegant, safe and effective delivery system physicochemical properties are need to be studied for understanding the characteristics of the drug. In this study we checked melting point, solubility, drug and excipient interaction study and UV absorption.

Melting point is one of the simple methods to check the drug purity. The melting point of the atazanavir was checked by capillary tube process. The open end of the capillary tube was packed with the atazanavir and tapped inversely to settle the drug at the bottom of closed end of the tube. Then the tube was placed in the melting point digital apparatus which was preheated at a rate of 10°C/min. After placing the tube it was heated by 1°C/min till the expected melting point. The melting temperature of the drug was noted by repeating the process three times and average value was calculated.

UV-wavelength (λ_{max})

Accurately weighed pure atazanavir (100 mg) was dissolved in 50% methanol and volume was made upto 100 with distilled water in volumetric flask to prepare 1000 µg/ml of stock solution. It was diluted with distilled water to get the standard solution with concentration of 5-40 ug/ml. These aliquots were analyzed spectrophometrically in the range of 400 nm to 200 nm to get the absorbance maxima by a UV Spectrophotometer (Shimadzu, UV-1800, Japan).[14]

Preparation of Standard Curve

From the atazanavir stock solution 10 ml was withdrawn and mixed with simulated nasal fluid (PBS of pH 5.6) in 100 ml volumetric flask. To get a 100 µg/ml concentration in the buffer medium volume was suitably diluted. From this stock solution, different aliquots were withdrawn and diluted with the same buffer solution to produce 2-20 µg/ml concentration respectively. After filtering the solution through Whatman filter paper # 41 absorbance was measured at maximum absorbance of atazanavir by spectrophotometrically (Shimadzu, UV-1800, Japan).

Solubility Studies

Solubility is a very important preformulation parameter which helps in choosing the best solvent for the therapeutic agent and enables formulator to prepare suitable dosage form. The solubility of atazanavir was checked by taking extra amount of drug in 1ml of individual solvent including distilled water, 0.1N HCl solution, phosphate buffer of pH 5.6, phosphate buffer of pH 7.4, methanol and DMSO in a glass vial and subjected to shaking for 12 hr. The vials were retained sideways till the undissolved drug settle down. After collecting the supernatant drug content was determined spectrophotometrically.

Drug and excipients interaction study by Fourier Transform Infrared (FTIR) Analysis

FT-IR analysis of pure atazanavir powder, mixture of drug, SLS and other ingredient was executed in the range of 4000-500 cm^{-1}. The powder mixture was pressed into thin pellets with KBr for studying with FTIR spectrophotometer, Perkin-Elmer BX II. The obtained peaks were studied and compared for functional groups to determine the drug excipient interaction.[15]

Preparation of atazanavir microcrystals

Atazanavir microcrystals were prepared by using high-speed homogenization method described earlier by Das *et al.*, 2019.[16] At first, atazanavir was dissolved in 10% of acetone and methanol solution (1:1). Then different concentration of the sodium lauryl sulphate and stabilizer (PVP K 30) was prepared. The drug solution was poured drop wise into this aqueous solution (0.5% w/v) of surfactant and stabilizer under magnetic stirring at a temperature of 25±2°C till a suspension produced. This suspension is further placed under a high-speed homogenizer (T 25 digital ULTRATURRAX IKA® WerkeStaufen/Germany) at high speed for 7 hr. The resulting microcrystals were separated by centrifugation followed by vacuum drying. The collected microcrystals were mixed with previously milled PVA and HPMC (viscosity grade 400) to act as a stabilizer and mucoadhesive filler respectively. 1 g microcrystals were mixed with 0.8g PVA and 1 g HPMC. Then the product was stored in a well closed container.

Characterization of Formulations

Determination of Particle Size

Particle size is an important criteria for the systems delivered through nasal route. Particles have 40-100 µm deposit well in the nasal cavity and particles having median aerodynamic diameter of less than 10 µm can access the lower airways.[17] For this purpose the crystal size of the microcrystals was studied by using Leica microsystem image processing device (Leica Q500MC, Wetzlar, Germany). For crystal size characterization around 300 crystals were studied for their width, length, area, and district/convex perimeter.

Study of Adhesiveness on Agar Gels

The mucoadhesive potential of the prepared microcrystals was measured by displacement of powder on pure agar gels. This was a method earlier reported by Bertram and Bodmeier.[18] 1.5% agar solution was prepared in phosphate buffer, pH 6.4. Then it was allowed to settle on a petri dish (diameter 12 cm) and left for overnight for gelation. Next day25 mg of microcrystals (sieve fraction 8–10 µm) were positioned on the gel plate in a spot with a diameter of approximately 10 mm. The petri dishes were kept in an angle of 45◦, and the displacement value of the samples was calculated as a function of time. The maximum calculable displacement on the plates was 10 cm, value above it were listed as >10 cm.

Differential scanning calorimetry (DSC)

The thermal behaviour of microcrystal formulation and pure drug was detected by differential scanning calorimeter (Mettler Toledo TG 821e DSC; Mettler Inc., Schwerzenbach, Switzerland). For this study 5 mg of powder was taken into DSC sample pans and hermetically sealed. Each sample was exposed to the temperature range of 50–300°C at a heating rate of

5°C/min and at a rate of 5°C/min under constant argon flow of 150 mL/min. Further data analysis done through the STARe software (Version 9.30, Mettler Toledo; Mettler Inc., Schwerzenbach, Switzerland).

In vitro Dissolution Study

USP dissolution apparatus, type II was used to examine the dissolution rate of microcrystals and determine the drug release profile. The test was performed under nasal conditions. 100 mL phosphate-buffered saline (PBS) of pH 5.60 was selected as a medium at 30°C for 1hr. The paddle rotation speed was 50 rpm. At 5 min interval point 2 mL of sample was withdrawn and tested by UV spectroscopy at 248 nm. The tests were carried out in triplicates.

In vitro Permeability Study

The Side-Bi-Side™ diffusion test was performed in nasal conditions (30°C at a pH of 5.6) for 1 hr. The method is earlier described by Ambrus *et al.*, 2020.[19] To determine the permeability cellulose ester membranes with 0.45 µm pore diameter were used after soaking in isopropyl myristate. At particular time interval 2 mL of samples were withdrawn from the acceptor chamber and instantly substituted by fresh buffer. The concentration of the permeated drug was spectrophotometrically measured at 248 nm after suitable dilution in triplicate. The formula for calculating flux and permeability coefficient is given below.

$$\text{Flux (J)} = Q/(A \times t)$$

Where, Q is the quantity of drug diffusing through the membrane at time t, A is area of the membrane in cm^2.

$$\text{Permeability coefficient (Kp)} = Q/[A \times t \times (Co\text{-}Ci)]$$

Where, Q is the amount of sample travelled across the membrane in time t (min), Co-Ci is the concentration difference of the sample from the donor side to the receptor side of the membrane, and A is area of the membrane in cm^2.

Stability Studies of Prepared Microcrystals

The prepared microcrystals were subjected to six month short term stability studies to determine their physical and chemical changes. For this purpose the microcrystals were kept in stability chamber at different temperatures and humidity**:** 5°C, 25°C/60% RH; 30°C/65%RH; 40°C/ 75% RH.[20] After six months, they were studied with FTIR to find the changes in functional groups as a result of chemical instability. They also studied for crystal size measurement, drug release and permeability.

Statistical Analysis

A one-way analysis of variance (ANOVA) was performed for analysis of the experimental data. Graph Pad Prism software-5, San Diego, CA, USA was used for statistical analysis of the data. All the data were determined by the mean ± standard deviation (SD) and mean variations were considered to be significant at $P < 0.05$.

RESULTS AND DISCUSSION

Total four formulations were prepared by different surfactants ratio and speed of homogenization. Table 1 represents different formulation variables used in the preparation of microcrystals. F1 formulation contains 2:1 SLS (surfactant) and drug ratio and prepared under speed of 15000. F2 formulation contains drug and SLS in a ratio 1:4 prepared under same condition and same ingredients as F1. F3 formulation contains drug and SLS ratio 1:2 same as F1 but prepared under homogenizer speed of 25000. F4 formulation is same as F2 as per ingredients but a variation in homogenizer speed of 25000.

Preformulation studies

Melting Point

M. P. of atazanavir was found a 200.9°C. The evaluation was carried out three times and average value is reported here.

Determination of Absorbance Maxima (λ_{max})

The atazanavir was dissolved in methanol and diluted subsequently with distilled water to a final concentration of 10 µg/ml which was analyzed spectrophotometrically at UV range 400 -200 nm. The absorbance maxima were obtained at 248 nm as shown in Figure 1A. Therefore 248 nm wavelength was selected as λ_{max} for the all-further study.

Preparation of Standard Curve

The stock solution of atazanavir was suitably diluted with PBS 5.6 in a concentration range of 2 to 20 *µg*/ml and absorbance was checked at 248 nm. The obtained value of absorbance was plotted and calibration curve of atazanavir was constructed as shown in Figure 1 B. This data were plotted to check linearity. The correlation

Table 1: Formulation variables of microcrystals.

Formulation code	Drug: SLS	Homogenizer Speed
F1	1:2	15000
F2	1:4	15000
F3	1:2	25000
F4	1:4	25000

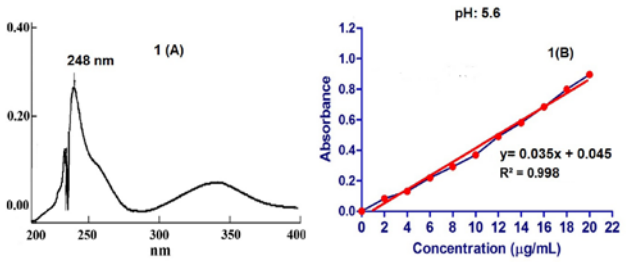

Figure 1: Absorption maxima of atazanavir pure drug solution 1(A) and calibrated standard curve 1(B).

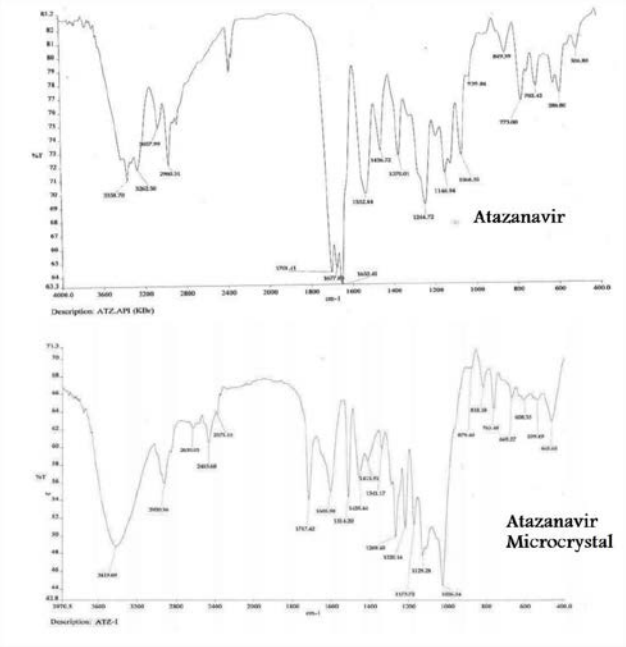

Figure 2: FTIR images of pure drug and microcrystal formulation.

coefficient (R^2) was found as 0.998. From this R^2 value it can be concluded that the concentration range of 2 to 20 μg/ml of drug obeys beer's lambert law.

FTIR

FTIR spectroscopy was employed to describe possible interactions between the drug and the excipients. The FTIR spectrum of atazanavir pure drug and other ingredients like sodium lauryl sulphate were obtained and compared with spectrum of microcrystal formulation. After comparing the spectrum, no major shifting or loss of peaks was found. Further, no marked difference was found in the position and trend of the absorption bands (Figure 2).

Solubility Studies

The solubility of atazanavir in different solution was given in Table 2.

Table 2: Solubility study of mesalamine in different solvents.

Solvents	Solubility
Distilled water	Slightly soluble
Methanol	Soluble
Phosphate buffer of pH 5.6	Insoluble
Phosphate buffer of pH 7.4	Insoluble
Acetone	Soluble
DMSO	Freely soluble
Acetone	Freely soluble

Determination of Particle Size

The particle size of microcrystal was in the range of required size for nasal administration that is between 5 and 45 µm.[21] The raw powder particles of drug were in the range of 50-72 µm, but in aggregated form. This size and aggregation form could make the drug administration uncertain. However in the microcrystal formulations, the particle size of the product was found as 5-11 µm in range. It was further observed that formulations prepared with higher milling speed (25000 rpm) had smaller particle size (5.2-7.6 µm) compare to those prepared with lower milling speed (15000 rpm). FormulationF1 and F2 had particle size in the range of 8-10.4 µm.

Study of Adhesiveness on Agar Gels

To test the contact stage of dry particles in the actual conditions of nasal area this test was performed in which the dry microcrystal particles were placed on the surface of agar gel (as wet mucosa). When dry microcrystals come in contact with nasal mucosa, the mucoadhesive polymer (HPMC) gets hydrated and attached with mucosa. The result showed good adhesion of particles on gels which indicated definite interactions between the formulation and the agar due to its mucoadhesive property. HPMC is a neutral short chain polymer it helped to move the particles faster because of low viscosity after wetting. Displacement was calculated in cm in a hourly gap of upto 5 hr. At first hr 1.5 cm displacement was obtained but after 2 hr it was about 4.2 cm. However after 3 hr more than 10 cm displacement was found and it was continued upto 5 hr. The result indicated adequate adhesiveness of the formulation for delivering through nasal mucosa.

Differential Scanning Calorimetry (DSC)

The DSC thermograms (Figure 3) showed characteristic peak of atazanavir pure drug at 200.91°C. In microcrystal formulation the peak was less intense due to the milling effect and the presence of surfactant. However no

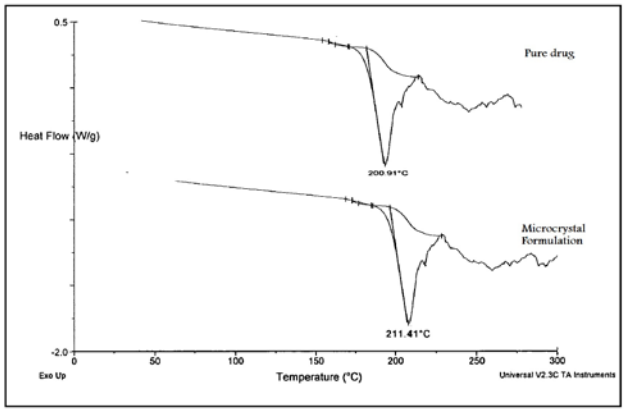

Figure 3: DSC thermograms of pure atazanavir and microcrystal formulation.

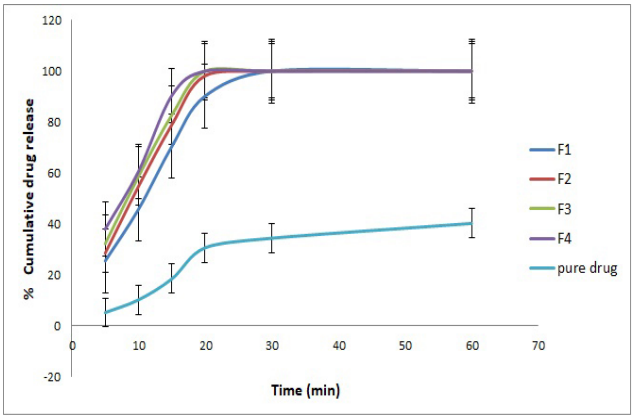

Figure 4: Drug release study of pure atazanavir solution and microcrystal formulations

Table 3: Release Kinetic data of atazanavir microcrystals

Formulations	Zero order kinetic		First order kinetic		chi'skinetic		meyer's kinetic	
	R^2	*k*	R^2	*k*	R^2	*k*	R^2	*n*
F1	0.8637	4.1235	0.8966	0.0312	0.8414	13.326	0.9581	0.9408
F2	0.8640	3.6426	0.8843	0.0454	0.7923	15.405	0.8963	1.8932
F3	0.8732	4.4679	0.8956	0.0241	0.8822	16.753	0.9815	1.6730
F4	0.8965	3.5793	0.8939	0.0346	0.8981	18.892	0.9137	1.8420

change was found in area under the curve and same endotherm was found at 211.41°C. This refers no interaction between drug and other excipients present in the formulation. The changed in crystallinity degree along with decrease in particle size, increased surface and the presence of surfactant may cause improved solubility of the drug (0.0899 ± 0.0014 mg/mL vs. 0.1425 ± 0.0164 mg/mL) in water at 25°C after 24 hr. The obtained results suggested improved dissolution and permeability rates since microcrystals offers better aqueous solubility than the insoluble pure drug.

In vitro Dissolution Study

Release study revealed that microcrystals released the drug in a controlled manner as compare to pure drug (Figure 4). The released amount of pure powder drug was the lowest. Whereas, the microcrystals had released32.26% of drug after 5 min and 58.68% after 10 min, respectively. However, 100% of drug dissolved after 20 min from the microcrystals due to the small particle size and high surface area. Further, it was also noted that drug release was faster from formulation F3 and F4 than F1 and F2. F1 and F2 was prepared with slower milling speed as compare to F3 and F4. Therefore the particle size was lesser in F3 and F4 as compare to F1 and F2. Small particle size with high surface area released the drug faster as compare to large particle size formulation.

Drug Release Kinetics

Different kinetic equations were subjected to interpret the release of atazanavir from different matrices which has been represented in Table 3. The formulations followed Korsmeyer's Peppas model having R^2=0.9946 and diffusion exponent value n= 1.562. So it can be concluded the release mechanism of atazanavir from microcrystals was super Case-II transport and *Non-fickian* pattern.

In vitro Permeability Study

It was found that the concentration of drug was much higher in the acceptor phase for the microcrystals than from the pure drug powder. This may be the result of difference in solubility of the pure drug and microcrystals. Pure drug atazanavir is less soluble therefore drug permeation in aqueous media was less. Further particle size of pure drug was higher than microcrystal which is another reason of low permeability. However microcrystals with small size and high solubility permeate the membrane better and found in good concentration at donor chamber. Formulation F2 and F4 had shown better permeation than F1 and F3. Formulation F2 and F4 contained higher surfactant which might help to permeate the drug through the membrane (Figure 5). The flux for microcrystal formulation was found to be 100 whereas

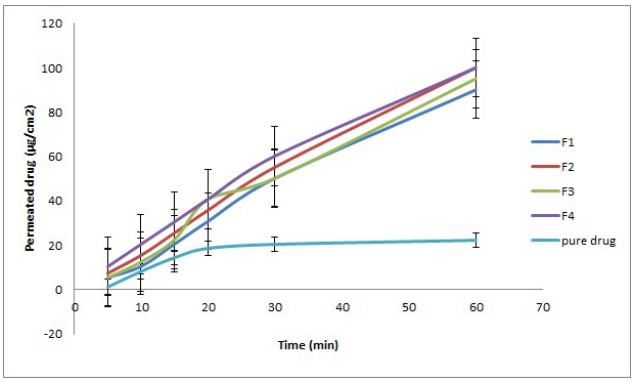

Figure 5: Drug permeation study of atazanavir solution and microcrystal formulations.

Table 4: Drug permeation study of atazanavir solution and microcrystal formulations

Formulation code	Drug release after 1h		Drug permeability coefficient		Particle size	
	Initial	After 6 months	Initial	After 6 months	Initial	After 6 months
F1	90%	72.6%	0.024	0.022	8.3±2.1	8±2.5
F2	100%	80%	0.040	0.035	9.5±2.5	9.8±2.2
F3	95%	76.8%	0.036	0.028	5.2±1.4	6.5±2.4
F4	100%	80.4%	0.038	0.027	6.5±1.8	7.2±2.1

flux for the pure drug powder was 24. Permeability coefficient was 0.040 and 0.005 respectively for the prepared formulation and pure drug powder.

Stability Studies

The physical appearance was unchanged after six months of the stability study. The microcrystals were white, odourless and crystalline as earlier. FTIR spectroscopy confirmed no drug and the excipients interaction after the stability studies as no major changes of peaks were found. Particle size of the formulation was in the range of 8-11 µm. Drug release rate was slower than earlier however more than 80% of drug was released from all the formulations after 1 hr. Similarly drug permeability study revealed slow permeation of drug as compare to fresh formulations. The flux for microcrystal formulation was 98 whereas flux for the fresh formulation was 100. Permeability coefficient was 0.040 and 0.035 respectively for the fresh formulation and formulation after stability study. All the data of stability studies (table 4) at different temperature were subjected to t-test and obtained as insignificant at 95% level and $P < 0.05$. From these result it can be concluded that after short term stability study the microcrystals were stable.

CONCLUSION

Nasal delivery of antivirals has been studied by limited researchers and less *in vivo* data are available on this. Further atazanavir intra nasal delivery have not explored yet. Therefore in this study, atazanavir microcrystals were developed by high-speed homogenization method to improve its dissolution and permeation through nasal route. The results obtained in this study were promising in terms of drug release, permeation, stability and particle size. Thus in conclusion, two main objectives were served: microcrystas of atazanavir was successfully prepared by simple high speed homogenization method for intra nasal delivery and improvement of the drug release and permeation in nasal condition. Therefore, we expect that controlled release of atazanavir using this technology will be a promising approach for improving the local treatment of viral infection including COVID-19. However, further *in vivo* studies are required to establish its complete efficacy in COVID infection.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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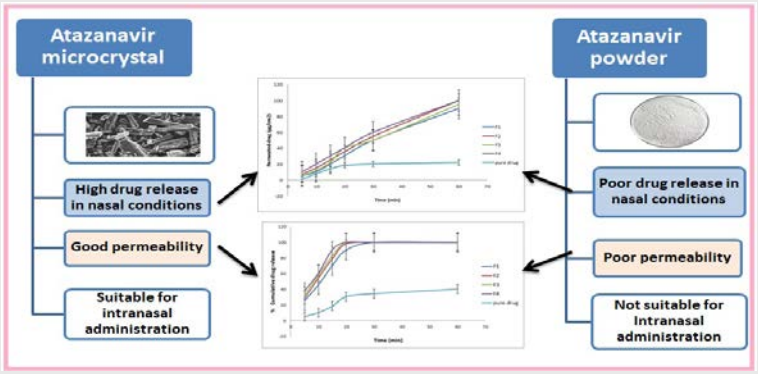
PICTORIAL ABSTRACT



SUMMARY

Nasopulmonary route have gained attention in last years for treating different diseases specially brain and lung diseases. The virulence of COVID19 forces all the researchers for an instantaneous intervention. Numerous studies have revealed positive observations with protease inhibitors like lopinavir, ritonavir and atazanavir against SARS-CoV-2 Mpro(6). It is hypothesized that delivering atazanavir directly into nasal area by powder inhalation would lower the dose, lower the oral side effects, and provide direct faster activity. This study aims to prepare a stable mucoadhesive microcrystal formulation of this antiviral drug with good permeation for intra nasal delivery. The formulation was prepared by high-speed homogenization process. Prepared microcrystals were estimated for *in vitro* drug release and permeation, drug excipient interaction study by DSC, FTIR and *in vitro* mucoadhesiveness study on agar gel plate. A short-term stability study was conducted on all formulations for 6 months. The melting point and absorbance maxima of atazanavir were found as 200.9°C and 248 nm. The DSC and FTIR study results confirmed no drug excipient interaction was there in the formulation. The particle size of the formulations was found as 5-11 μm in range. Drug release was better and faster from the microcrystals as compare to pure powder drug. Formulations had sufficient mucoadhesive strength due to incorporation of HPMC 400 polymer. The results obtained in this study were promising in terms of drug release, permeation, stability and particle size. Thus in conclusion, two main objectives were served: microcrystals of atazanavir was successfully prepared by simple high speed homogenization method for intra nasal delivery and improvement of the drug release and permeation in nasal condition. Therefore, we expect that controlled release of atazanavir using this technology will be a promising approach for improving the local treatment of viral infection including COVID-19.

About Authors

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