Original Article

Enhancement of Solubility and Dissolution Rate of Atazanavir Sulfate by Nanocrystallization

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ABSTRACT

Objectives: The current objective of the present study was to enhance the solubility and dissolution rate of the antiviral drug atazanavir sulphate by employing nanocrystallization technique. **Materials and Methods:** The method employed for increment of solubility was nanocrystallization which is based on the reduction of particle size of the drug thereby increasing its solubility and also its dissolution property. Various polymers in different ratios were used like HPMC K15M, PVP K30 and PEG 6000. **Results:** Drug and polymers were firstly tested for their interaction between each other's and it was found that the drug and polymers are compatible with each other. From the solubility study it was seen that the solubility of the optimized batch was increased to 40.068mg/ml in distilled water and 160.182mg/ml in phosphate buffer while the pure drug shows the solubility of 4.174mg/ml in distilled water and 20.547mg/ml in phosphate buffer. The percent drug release of the optimized formulation was seen of 87.91% in 2 hrs which was maximum from all the other batches. The stability study revealed that the prepared nanocrystal does not show any insignificant changes and therefore it can be concluded as stable. **Conclusion:** The prepared nanocrystals are the proof that this method of nanocrystallization may prove to be an efficient method in increasing the solubility and dissolution rate of the drug which are having low solubility and low bioavailability.

Key words: Atazanavir Sulphate, Nanocrystallization, Solubility Enhancement, Dissolution Enhancement, Antiviral.

INTRODUCTION

Lower solubility of an active drug substance may hinder the dissolution rate and absorption of the drug which can lead to lower bioavailability initiating the use of high amount of dose of the drug. Higher amount of drug can cause various adverse effects leading to damage to the body. Therefore it becomes essential to improve the solubility of the drug so that it will increase the dissolution of the drug. For oral administration, conventional formulations of poorly water-soluble drugs are associated with erratic absorption in the GI tract and low/variable bioavailability.[1-4] Thus, bioavailability of poorly water-soluble drugs will be affected positively when their dissolution rate is increased.

Nanocrystallization is a method to scale back the particle size of the drug as nanosized particle which can be made into a powder or suspension in liquid which will cause an efficient area increment within the diffusion layer, which can eventually increases the dissolution rate of the drug. Nanonization of non-water loving drugs generally involves the manufacturing nanocrystals through either disintegration or chemical precipitation.[5-7] The nanosuspensions prepared for crystallization will need solvent elimination process to induce a redispersible powder.[8] Atazanavir acts by selectively prohibiting the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the positioning of HIV-1

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protease. This prevents the formation of mature virions. But atazanavir is not active against HIV-2. Atazanavir gets extensively metabolized in humans, primarily within the liver. Mono-oxygenation and dioxygenation are the major biotransformation pathways of atazanavir in humans. Atazanavir is rapidly absorbed and has T_{max} of roughly 2.5 hrs. It has been reported that bioavailability of atazanavir gets enhanced when administered with food and reduces pharmacokinetic variability. Oral bioavailability is found to be 60-68%.[9-12]

In the current method the method applied was nanocrystallization and this method is employed here to overcome with the physical instability of drug when converted to various polymorphic forms.

MATERIALS AND METHODS

Materials

Atazanavir Sulphate was supplied by Yarrow Chem, Mumbai India. HPMC K15M was obtained as a gift sample from Colorcon India, Goa. PVP K30 and PEG 6000 were procured from S.D. Fine Chem Pvt. Ltd. Mumbai, India. All other reagents and chemicals were used as obtained and were of analytical grades.

Methods

Drug- Excipients Interaction Study

The drug-excipient interaction study was carried out by employing FT-IR and DSC study. The study by FTIR of the drug and excipient was carried out by conventional KBr plate method in order to study the interaction of the drug and polymer so as to determine the physical as well as chemical changes that can occur during the formulation. For this the mixture of powder of excipient and pure was mixed in a ratio of 1:1 with potassium bromide and the small pellet was formed by pressing the mixture in a hydraulic press and the FT-IR was carried out in the frequency range 400-4000 cm^{-1}. The predominant peaks were recorded and were matched with standard FTIR.[13]

DSC Study

The DSC study was carried out by studying thermograms of pure drug and its physical mixture with polymers was carried out to investigate any possible interaction between the drug and the utilized polymer. The selected heating rate is from 50°C to 400°C at an increase of 20°C per minute using Differential Scanning Calorimeter.[14]

Standard Calibration Curve

The standard calibration curve of Atazanavir Sulphate was carried out on UV spectrophotometer by using phosphate buffer of pH 7.4 as the solvent. From the solution which is now having a concentration of 100 µg/ml samples of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 ml were pipette out into 10ml volumetric flasks. The volume was made up to the mark with Phosphate buffer 7.4 to get the final concentration of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml respectively.[15] The absorbance of concentration was measured at 250nm.

Preparation of Atazanavir Sulphate Nanocrystals

From the results of preformulation studies the 3 types of polymers were chosen i.e. HPMC K15M, PVP K30 and PEG 6000. The nanocrystals of atazanavir sulphate were prepared by the steps i.e. Formulation of atazanavir sulphate nanosuspensions and Lyophilization of nanosuspensions. Accurately weighed amount of drug sample was added (200 mg) to methanol (10 ml) to prepare the drug solution. The prepared drug solution is then added into required quantity (10ml) of water which contains various concentrations of stabilizers with continuous stirring on mechanical stirrer for 2 hrs at 1000 rpm. After this the organic solvent is removed by stirring it again for 4-5 hrs at 500 rpm. After the preparation of nanosuspensions the cryoprotective agent i.e. mannitol is added into it and the nanosuspensions are lyophilized by using deep freeze technique to enhance the chemical stability of nanocrystals.[16-18] Atazanavir sulphate nanosuspensions were then rapidly cooled down to -20°C for up to 2 hrs. The formulation chart is depicted in Table 1.

Table 1: Formulation Chart of Nanocrystals.

Batch	Drug (mg)	HPMC K15M (%)	PVP K30 (%)	PEG 6000 (%)
A1	200	0.1	-	-
A2	200	0.2	-	-
A3	200	0.3	-	-
A4	200	0.4	-	-
A5	200	0.5	-	-
B1	200	-	0.1	-
B2	200	-	0.2	-
B3	200	-	0.3	-
B4	200	-	0.4	-
B5	200	-	0.5	-
C1	200	-	-	0.1
C2	200	-	-	0.2
C3	200	-	-	0.3
C4	200	-	-	0.4
C5	200	-	-	0.5

Characterization of Nanocrystals

Percent Drug Content

Samples containing 100mg of atazanavir sulphate crystals were accurately weighed and dissolved in phosphate buffer of pH 6.8 and sonicated for 10 min. The solution is then filtered using a whatman filter paper from the above solution 10 ml is pipette out and made up to 100 ml using phosphate buffer of pH 6.8. The resultant solution is then analyzed spectrophotometrically at 250nm and then the percent drug content is estimated.[19]

In-vitro Dissolution Study

USP dissolution apparatus Type I (basket type) was used to study the drug release behavior of pure drug and nanocrystals. Dissolution behavior of pure Atazanavir sulphate and nanocrystals was studied using phosphate buffer pH 6.8 as dissolution medium. Drug (1000 mg) in muslin cloth which was tightly tied was placed in basket containing 900 ml of solution of pH 6.8 for 2 hrs. After each regular interval of time 5ml of solution was withdrawn and diluted with buffer 6.8 solution. After each withdrawal of the samples the fresh dissolution medium was added into the apparatus in order to maintain the sink condition. The diluted samples were then analyzed at 250.0 nm using UV-spectrophotometer.[20] The cumulative drug release (% CDR) was then calculated for every batch of nanocrystals containing different polymers.

Kinetics Study

The drug release data were fitted to zero order (cumulative vs. % drug release versus time), first order (log of cumulative vs. % drug retained versus time), and Higuchi models (cumulative vs. % drug released versus square root of time) and Korsmeyer-Peppas model (log of %cumulative drug release vs. log of time) to calculate the kinetics of drug release and determine the release mechanism of the drug from the prepared nanocrystals.

Determination of Particle size and Zeta potential

The mean particle size and zeta potential of atazanavir sulphate nanocrystals formulations are determined by dynamic light scattering technique using a zeta size analyzer. The freeze dried nanocrystals are re-dispersed with water to obtain a proper scattering intensity before analysis.

Solubility Studies

Solubility of atazanavir sulphate nanocrystals were studied in different solvents such as distilled water and phosphate buffer pH (6.8). Pure drug and an excess amount of nanocrystal formulation were added in 10 ml of the chosen solvents. The mixtures are mixed in a mechanical stirrer for 24 hrs. Visual inspection is carefully made to ensure there are excess atazanavir sulphate solids in the mixture, indicating saturation have been reached.[21,22] The mixtures are then filtered and the resultant solution was diluted suitably to determine the solubility of atazanavir sulphate in each solvent by using UV spectrophotometer at 250nm.

X-ray Diffraction Study (XRD)

X-ray diffraction spectra of atazanavir sulphate and prepared nanocrystals were recorded with x-ray diffractometer employing a voltage of 45 Kv and a current of 40 mA. The instrument was operated in continuous scan mode over 2θ range at 20°– 80°. The relative intensity I/I0 and interplanar distance (d) like the 2θ values were reported and compared.[23]

Head Space Gas Chromatography

For the determinations of content of methanol in the prepared nanocrystals that may be get entrapped in the preparation HS-GC was employed in order to determine the amount of methanol that should be in least amount and safe for human consumption. For this accurately weighed optimized nanocrystals were suspended in methanol and shaken in orbital shaking incubator for 24 hrs at 100 rpm. Subsequently, the dispersion was filtered and filtrate was analyzed using HS-GC with column Rtx- 5MS and Helium as carries gas. The reference solution (1000 ppm) and sample solution were injected alternatively to HS-GC and area of peak obtained was used to calculate the solvent concentrate in the optimized formulation.[23] The permitted daily exposure methanol according to ICH is 300 ppm.[24]

Scanning Electron Microscopy (SEM)

Scanning electron microscopy of atazanavir sulphate and prepared nanocrystals were taken using scanning electron microscope. The form and surface morphology were observed using SEM. The nanocrystals were observed at various magnifications so as to research the effect of additives on surface morphology and crystallization efficiency.[25]

Stability Study

The stability of the optimized formulation was carried out accordingly as per the guidelines of International Council for Harmonization (ICH). The stability study was carried out as accelerated study at 40°C ± 2°C / 75 % RH ± 5% RH for 90 days. The optimized formulation was studied for the parameters such as solubility study and dissolution rate.[26]

RESULTS AND DISCUSSION

Drug- Excipients Interaction Study

The study of FT-IR spectrum of pure drug exhibited characteristic peaks at 3357.84, 3060.82 and 2873.74 cm^{-1} corresponding to the stretching vibrations of N-H, aromatic C-H and asymmetric and symmetric aliphatic C-H stretching respectively. The presence of amide group in the structure was also confirmed by C=O stretching at 1699.17 cm^{-1} and N-H deformation band at 1650.95 cm^{-1}. Though the fingerprint region of drug and nanocrystals were not super imposable due to the presence of polymer in nanocrystals, but almost identical prominent absorption bands were obtained from FTIR spectrum of optimized nanocrystals but with somewhat lower intensity. From the study it was concluded that the drug and excipients used were compatible with each other and does not have any interaction between them. The results can be seen in Figure 1.

DSC Study

DSC thermograms of atazanavir sulphate showed a single sharp characteristic endothermic peak at 211.7°C corresponding to its melting point, indicating its crystalline nature. This sharp peak confirmed the purity of drug with no noticeable impurities present. Atazanavir sulphate was found to be stable to heat up to 200°C without any signs of moisture and phase transition. In the DSC thermogram of nanocrystals, endothermic peak correspond to atazanavir sulphate at 210.96°C with a significant reduction in heat of fusion/enthalpy (ΔH) of 19.08 J/g. This occurrence might be attributed to the dispersion of crystalline atazanavir sulphate into amorphous polymer. Partial amorphization of crystalline atazanavir sulphate in nanocrystals might also be a reason. Partial amorphization of drug might provide comparatively more stability than their complete amorphous counterparts. Further, a small endothermic peak at 61.71°C in DSC thermogram of nanocrystals might be because of the evaporation of methanol solvent which was entrapped in crystals during formulation. These findings from Figure 2 clearly indicated a strong possibility of the transformation of atazanavir sulphate to its nanocrystals which might be responsible for improved dissolution.

Standard Calibration Curve

The standard calibration curve of pure atazanavir sulphate shows that it obeys the beers lamberts law as the equation obtained was linear. The equation obtained was y = 0.014 x +0.139 and the value of R^2 was found to be 0.997 as seen in Figure 3.

Percent Drug Content

From the drug content study it was seen that the drug content in the batch of A1-A5 the drug content range was between 88.00±1.8644 - 93.63±1.6226%. B1-B5 shows the drug content range in between 90.33±1.0237 - 93.66±1.1547%. The last batch of C1-C5 shows the drug

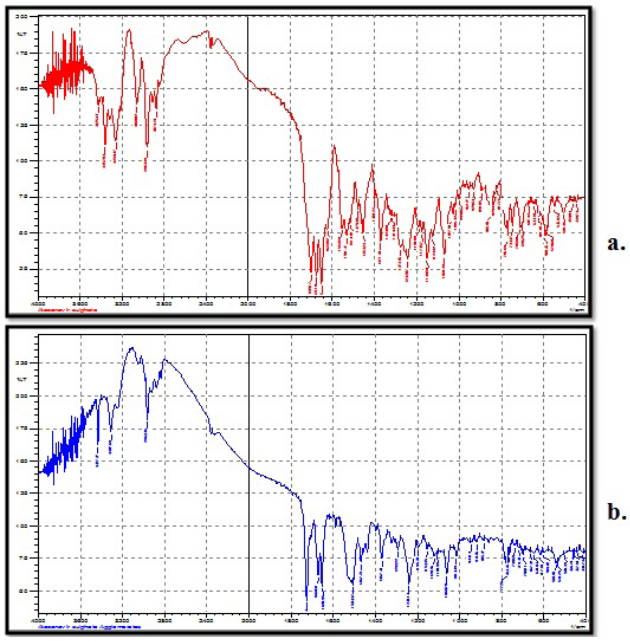

Figure 1: a) FTIR of Pure Drug Atazanavir Sulphate. b) FTIR of Optimized Formulation.

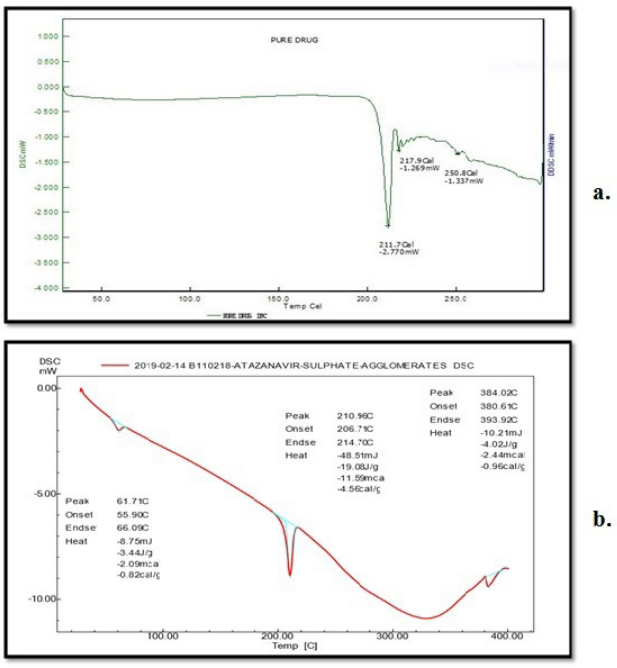

Figure 2: a) DSC of Pure Drug Atazanavir Sulphate. b) DSC of Optimized Formulation.

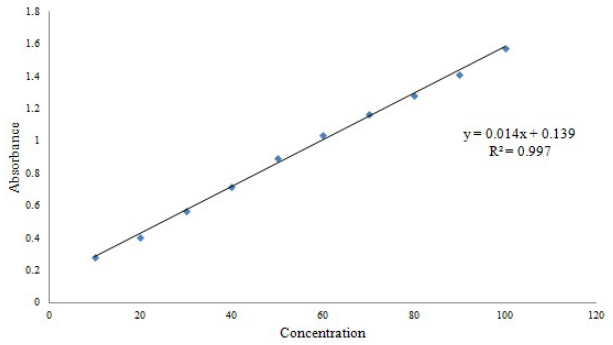

Figure 3: Standard Calibration Curve of Atazanavir Sulphate.

Table 2: Percent Drug Content Study.

Sr. No.	Batch	Percent Drug Content (%)
1.	A1	93.63±1.6226
2.	A2	89.63±1.9561
3.	A3	89.70±1.3856
4.	A4	88.00±1.8644
5.	A5	89.50±2.0621
6.	B1	92.86±1.8013
7.	B2	92.00±1.6055
8.	B3	90.33±1.0237
9.	B4	93.66±1.1547
10.	B5	93.00±1.4641
11.	C1	93.66±1.2748
12.	C2	95.33±0.5166
13.	C3	96.98±1.2784
14.	C4	95.33±1.5166
15.	C5	96.00±1.7320

n=3*

content in the range of 93.66±1.2748 - 96.98±1.2784%. Form all the results in the Table 2 it was seen that the maximum drug content in all the batches was of C3 which was 96.98±1.2784%.

In-vitro Dissolution Study

The *in-vitro* dissolution studies of all formulations were compared with pure drug. The drug release of pure drug in the time span of 2hr was found to be 61.78%. The percent cumulative study of the prepared nanocrystals revealed that the *in-vitro* release profiles of all the formulations are significantly greater than that pure drug atazanavir sulphate. The nanocrystals prepared from the stabilizer HPMC K15M in various ratios showed the drug release of 53.39%, 68.24%, 67.97%, 71.12% and 74.21%. The drug release from PVP K30 as a stabilizer in various ratios showed the drug release of 73.29%, 74.04%, 75.68%, 75.67% and 78.78%. Lastly the drug release from PEG 6000 as a stabilizer in various ratios showed the drug release from 60.46%, 72.49%, 78.69%, 81.02% and 87.91% respectively. From all the data obtained from the dissolution study it was concluded that the batch of C5 from PEG 6000 was having the maximum drug release rate of 87.91% which is higher than compared with the other batches. The batch of C5 can be considered as the optimized batch because the increased percentage drug release of stabilizer (PEG 6000) having formulation (C1-C5) indicates that, stabilizer PEG 6000 had long hydrophilic chain and it captured the water molecule through hydrogen bonding, which were formed between the hydroxyl group and ether bond of PEG and water molecule, in order to improve the drug dissolution rate. The results can be seen in Figure 4.

Kinetics Study

From the results of kinetics study as shown in Table 3 it can be seen that the prepared optimized formulation possesses a drug release by korsmeyers-peppas model of diffusion with the R^2 value of 0.9711.

Determination of Particle size and Zeta potential

Particle size, size distribution and zeta potential were important characterizations of the nanocrystals because they govern the other characterizations, such as saturation solubility and dissolution. In the present study the average diameters and polydispersity index of atazanavir sulphate nanocrystals was found to be in the range of 80.3nm to 300.6 nm. The average particle size of the optimized formulation i.e. C5 was found to be 100.8 nm as shown in Figure 5.

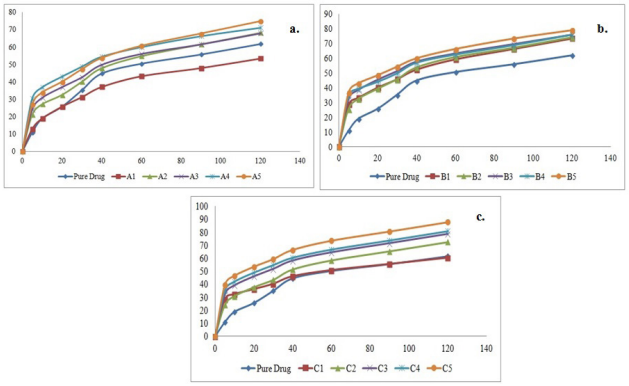

Figure 4: Percent Cumulative Drug Release of the prepared Nanocrystals.
a) Percent Drug Release of Nanocrystals using HPMC K15M.
b) Percent Drug Release of Nanocrystals using PVP K30.
c) Percent Drug Release of Nanocrystals using PEG 6000.

Table 3: Kinetics Study of the Optimized Formulation.					
Batch	**Zero Order (R^2)**	**First Order(R^2)**	**Higuchi (R^2)**	**Korsmeyers-Peppas (R^2)**	**Best Fit Model**
C5	**0.6969**	**0.8726**	**0.9146**	**0.9711**	**Korsmeyers-Peppas**

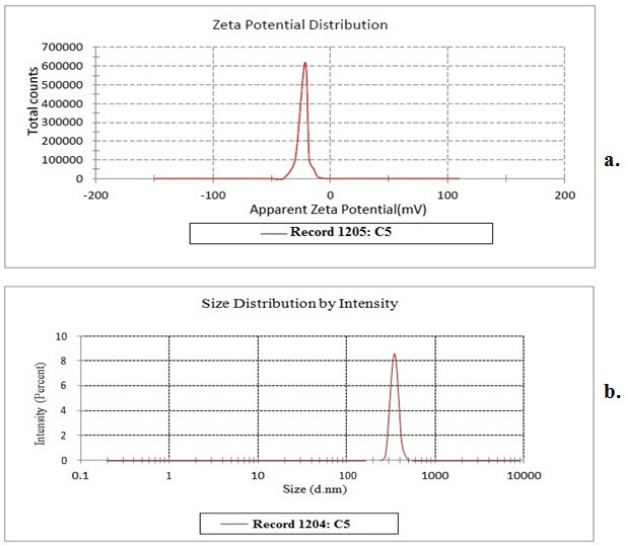

Figure 5: a) Zeta Potential of the Optimized Formulation. b) Particle Size Analysis of Optimized Formulation.

The atazanavir sulphate nanocrystals were characterized to evaluate the effect of stabilizers at different ratios and different on surface charge of nanocrystals. Zeta potential values of the formulations prepared with different stabilizers showed negative zeta potential (-19.7mV to -24.7mV) which indicated a stable preparation. The zeta potential of the optimized formulation was found to be -21.4 mV and the results were depicted in Figure 5.

Solubility Studies

The solubility study of the prepared nanocrystals and the pure drug was studied in distilled water and in phosphate buffer of pH 6.8. The formulations showing highest amount of drug release was chosen for the study with the optimized formulation. From the results it was clear that the optimized formulation was having the highest solubility of drug in the solvents selected for the test. The pure drug atazanavir sulphate showed the solubility of 4.174±0.02mg in distilled water and 20.547±0.05mg in phosphate buffer while the optimized formulation C5 showed the solubility of 40.068±0.09mg in distilled water and 160.182±0.14mg in phosphate buffer. The solubility of the prepared nanocrystals increased up to ten folds when compared to pure drug. The reason behind the solubility increment of atazanavir sulphate may be due to the decreased particle size and increased surface area. This solubility data is shown up in the Figure 6.

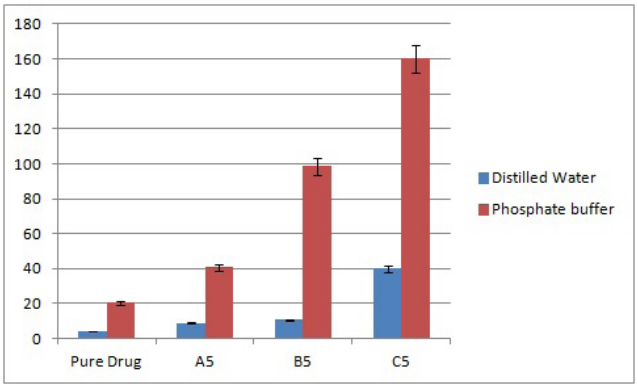

Figure 6: Solubility Study of the Prepared Nanocrystals.

X-ray diffraction study (XRD)

The XRD pattern of atazanavir sulphate exhibited intense, sharp well resolved peaks whereas XRD pattern of prepared nanocrystals exhibited less intense and denser peaks compared to atazanavir sulphate. The XRD pattern of atazanavir sulphate showed its characteristics peaks at 2θ of 5.77, 10.88, 12.09, 13.03, 16.79, 18.02, 18.60, 19.47, 20.26, 21.00, 22.90 and 23.36 which are the characteristic of a crystalline compound. This result from Figure 7 confirmed that the characteristic peaks were still preserved indicating the crystalline state was not changed.

Head Space Gas Chromatography

A residual solvent peaks of optimized atazanavir sulphate nanocrystals were observed at same retention times as that of standard i.e. 2.862 min methanol respectively with extremely low intensity. It depicted that the most of the solvents were evaporated and very small amount of solvents retained in nanocrystals. The results of this study as shown in Table 4 and Figure 8 revealed that the entrapped methanol was having a concentration of 10ppm and was in an insignificant extent and hence it does not produce toxicity in humans.

Scanning electron microscopy (SEM)

An examination of the SEM from Figure 9 of atazanavir sulphate confirmed that the pristine atazanavir sulphate was significantly smaller in particle size and blade shaped with fines. Improved solubility of modified

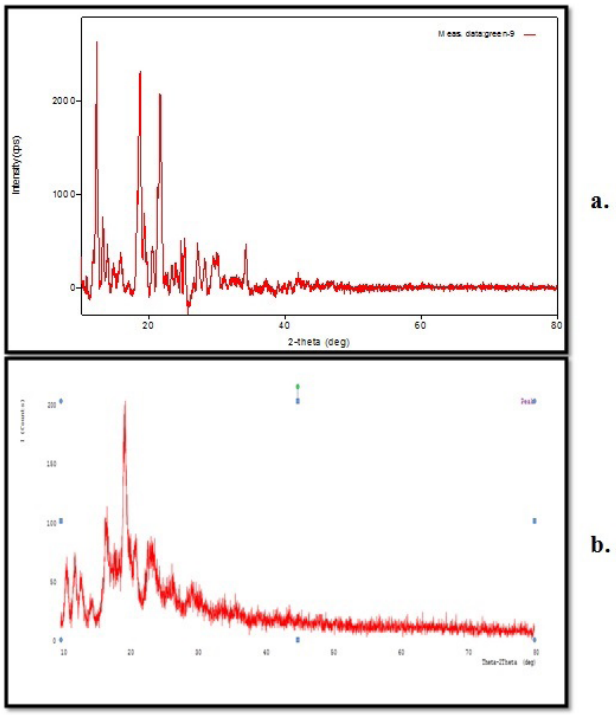

Figure 7: a) XRD Study of Pure Drug Atazanavir Sulphate. b) XRD Study of Optimized Formulation.

Table 4: Results of Residual Solvent Determination for Methanol.

Peak	Component Name	Time [min]	Area [uVsec]	Height [uV]	Area [%]
1	Methanol	2.250	105.08	39.74	1.41
2		2.876	7325.64	2705.33	98.59
			= 7430.72	= 2745.07	= 100.00

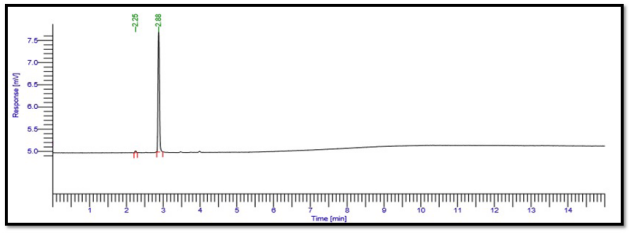

Figure 8: Results of Head Space Gas Chromatography for the Estimation of Methanol in Nanocrystals.

crystals obtained by nanocrystallization was an evidence of cylindrical shape of crystals.

Stability Study

From the results of stability study it was seen that the solubility of the prepared nanocrystals were having an insignificant change during the time period. There was

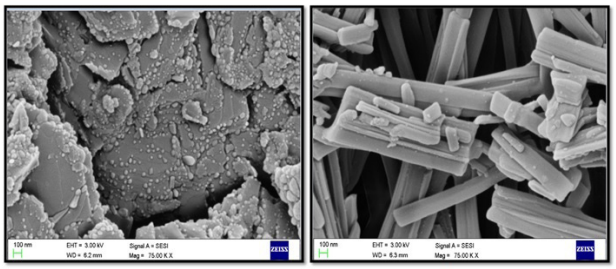

Figure 9: a) SEM study of Pure Drug. b) SEM of Optimized Formulation.

Table 5: Stability Study of the prepared Nanocrystals at Accelerated Study (40°C ± 2°C/75 % RH ± 5% RH).

Day	Batch	Solubility Study (mg/ml)		*In-vitro* Drug Release (%)
		Distilled Water	Phosphate Buffer (6.8)	
0	C5	40.068±0.009	160.068±0.14	87.91
15		40.068±0.258	160.068±0.25	87.91
30		40.068±0.067	160.068±0.11	87.59
60		40.015±0.017	159.197±0.12	87.55
90		38.195±0.248	159.186±0.87	87.55

n=3

a slight change in the solubility was can be negligible i.e. 40.068mg/ml-38.195mg/ml in distilled water and 160.068mg/ml-159.186mg/ml from 0 to 90 days and the percent drug release in 2hrs was decreased from 87.91% - 87.55%. All the changes found during the stability study were insignificant as shown in Table 5 and hence it can be concluded that the prepared formulation was stable.

CONCLUSION

The nanocrystals of atazanavir sulphate were prepared by employing emulsion solvent diffusion method. It was concluded that nanocrystallization was an excellent approach to enhance the solubility and dissolution property of atazanavir sulphate. The solubility and *in vitro* dissolution studies suggested that the nanocrystal formulations can improve the solubility and as well as the bioavailability of the atazanavir sulphate rate when compared to pure drug. Thus the adaptation of this method of nanocrystallization in the drug delivery system can increase the solubility and dissolution rate of poorly soluble drug like atazanavir sulphate to enhance their solubility and also it will enhance its absorption in the body giving maximum bioavailability in the body.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PVP: Polyvinyl Pyrollidine; **HPMC:** Hydroxypropyl Methyl Cellulose; **GI:** Gastro-Intestinal; **HIV:** Human Immunodeficiency Virus; **FTIR:** Fourier Transmission Infra-red; **DSC**: Differential Scanning Calorimetry; **UV:** Ultra Violet; **USP:** United States Pharmacopoeia; **CDR:** Cumulative Drug Release; **XRD:** X-Ray Diffraction; **HSGC:** Head-Space Gas Chromatography; **SEM:** Scanning Electron Microscopy; **RH:** Relative Humidity.

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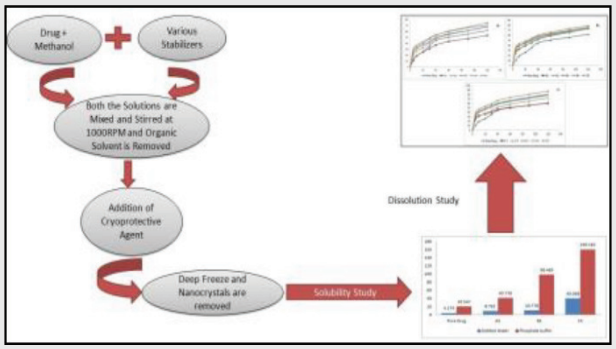
PICTORIAL ABSTRACT



SUMMARY

The current study was performed in order to carry out the solubility enhancement and dissolution rate of atazanavir sulphate by nanocrystallization technique. In this method various polymers were used as stabilizing agents in various ratios. As the drug is water insoluble the nanocrystals were prepared in order to increase its solubility. The prepared nanocrystals were tested in various solvents and it was found that the solubility is increased at a good percentage. Now as the solubility is increased this factor also lead to its increased drug release property i.e. dissolution rate is increased when compared with the drug release with pure drug only. PEG 6000 was seen as the best stabilizer for solubility enhancement as the hydroxyl group and ether bond of PEG and water molecule may be responsible for its solubility enhancement. The stability study shows that the prepared optimized formulations were stable under the testing conditions as there were not any significant changes seen.

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