In vitro dissolution study of atorvastatin binary solid dispersion

Abstract

The aim of the present study was to improve the solubility and dissolution rate of atorvastatin (ATV), a slight water-soluble drug, by solid dispersion (SD) technique using a hydrophilic carrier Poloxamer 188 (POL188). Physical mixing (PM) and solvent evaporation (SE) method were used to prepare ATV-SD where different drug-carrier ratios were used. Prepared formulations were characterized in their solid state by solubility study; differential scanning calorimetry, scanning electron microscopy, and Fourier transform infrared spectroscopy which demonstrated changes in the formulations supporting the improved solubility. Percent content of POL188 in the SD matrix was found to play the pivotal role in the improvement of dissolution property of ATV. In case of PM, highest enhancement in drug release was found for 1:3 ratio (P < 0.05, ANOVA Single factor) whereas in case of SE, 3:0.5 ratio of ATV-POL188 resulted the maximum enhancement in ATV release (P < 0.05, ANOVA Single factor). Analysis of dissolution data of optimized formula indicated the best fitting with Peppas-Korsmeyer model and the drug release kinetics was fickian diffusion. In conclusion, binary SD prepared by both PM and SE technique using POL188 could be considered as a simple, efficient method to prepare ATV solid dispersions with significant improvement in the dissolution rate.

Key words: Atorvastatin, physical mixing, poloxamer 188, solid dispersion, solvent evaporation

INTRODUCTION

Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only the existing drugs that cause problems, but it is the challenge of pharmaceutical scientists to ensure that new drug molecules are not only pharmacologically active but also have enough solubility to ensure faster dissolution at the site of administration, often gastrointestinal tract.[1]

Attempts for increasing the solubility of these poorly water-soluble drugs have been taken and the techniques have been proven successful to do so.[2] Among them, solid dispersion (SD) technique has attracted considerable interest as an efficient means of improving the dissolution rate, which increases the bioavailability of a range of poorly aqueous soluble drugs.[3,4] For last few decades, SD techniques become the common choice of selection for increasing the solubility of poorly soluble drugs because of its ease of preparation, ease of optimization and reproducibility.[5-9]

SD are usually prepared with water-soluble low melting point synthetic polymers such as polyvinylpyrrolidone (PVP),[10,11] polyethylene glycol,[12,13] lactose,[14] β-cyclodextrine,[15] and hydroxypropyl methylcellulose.[8,16] But in recent years, poloxamers have attracted remarkable attention for application in SD formulations because of its low melting point (about 56-57°C), surfactant properties and oral safety. Poloxamers are a group of block copolymer that are nonionic surfactants in nature.[17,18] These polymers
are available in different grades and all of these grades have been proven effective in SD techniques.\[8,9,19\] In this study, Poloxamer 188 (POL188) was used to prepare SD formulations of atorvastatin.

Atorvastatin (ATV), a \(\text{[R-(R*, R*)]-2-(4-fluorophenyl)-\beta, 6\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid}}\) [Figure 1], is a selective inhibitor of HMG-CoA reductase and a widely prescribed drug in case of hyperlipidemia. Nevertheless, poor solubility of ATV has been the major constrain in the attainment of good absorption property. The solubility of ATV in aqueous solution of pH 2.1 is about 20.4 mg mL\(^{-1}\), while the solubility is only 1.23 mg mL\(^{-1}\) in aqueous solution of pH 6.0.\[20\] Although the \(T_{\text{max}}\) of ATV is quite rapid, 1-3 h, it suffers from very poor bioavailability and this is only 14%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and hepatic first-pass metabolism.\[21,22\]

Literature survey reveals that only a few approaches of SD techniques have been reported to increase the solubility of ATV such as SD of PEG 6000 using microwave energy,\[23\] SD by dropping method using PEG 4000, PEG 6000\[24\] and lyophilization technique.\[25\] But no work was done using solvent evaporation technique (SE) while SE technique has been proven successful in solubility enhancement of poorly water-soluble drugs.\[26\] This ultimately directed us toward the fabrication of some SD formulations of ATV. For this, we used simple but reproducible physical mixing and solvent evaporation technique to prepare ATV-SD formulations.

**MATERIALS AND METHODS**

**Materials**

Atorvastatin calcium was a generous gift from Biopharma Laboratories (Dhaka, Bangladesh). Poloxamer 188 (BASF, Bangladesh), Potassium dihydrogen phosphate (Merck, Germany), methanol (Merck, Germany) were also obtained as gift samples. All other materials used were of analytical grade.

**Preparation of Atorvastatin Solid Dispersions**

ATV and POL188 at 1:1, 1:2 and 1:3 weight ratios were mixed in a mortar and pestle to obtain a homogeneous physical mixture (PM). The mixture was sieved through 40 mesh screen and then stored in a desiccator at room temperature until further use. SD of ATV with POL188 at weight ratios of 1:1, 1:2, 1:3, and 3:0.5 were prepared by solvent evaporation (SE) technique. Solution of ATV in methanol (300 mg/5 ml) was prepared and appropriate amount of POL188 was added in it. The solvent was evaporated under reduced pressure at 50°C for 48 h and then kept in a desiccator for next 48 h to ensure the complete removal of residual solvent. SD formulations were then pulverized, passed through a 40 mesh screen and stored in a vial at room temperature until further use.

**Optical Microscopy**

The samples of SD formulation were placed on a glass slide and then were exposed to phosphate buffer. Images were taken with 10x or 20x objective (Olympus, China) to observe morphological changes that occurred due to formulation variation.\[27\]

**Solubility Study**

The amount of SD powder containing 2.5 mg equivalent ATV was weighed accurately in screw cap vials and was dissolved in 5 ml distilled water by sonication (3 times) for 15 minutes. Samples were then filtered through a 0.45-\(\mu\)m filter paper and analyzed spectrophotometrically in a UV-VIS spectrophotometer (UVmini-1240, Shimadzu Corporation, Japan) at 247 nm. This was performed in triplicate.

**Differential Scanning Calorimetry**

Thermal analysis was performed using differential scanning calorimeter (DSC-60 A, Shimadzu). Under nitrogen flow of 20 ml/min, approximately 4-4.5 mg of sample was placed in a sealed aluminium pan and heated at a scanning rate of 10°C/min from 30°C to 300°C. An empty aluminium pan was used as reference.

**Fourier Transform Infrared Spectroscopy**

FT-IR spectra were obtained on a FT-IR spectrometer (Shimadzu, IR Prestige, Japan) using attenuated total reflectance method. The scanning range was 750-4000 cm\(^{-1}\) and the resolution was 8 cm\(^{-1}\). Number of reference scans was 20.

**Scanning Electron Microscopy**

The scanning electron microscopy (SEM) analysis was carried out using scanning electron microscope (JSM 6490 LA, Jeol, Japan). Samples of pure drug and the optimized formula of SD formulation were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of platinum (150-200A°) with auto-fine coater (JFC-1600). The scanning electron microscope was
operated at an acceleration voltage of 15 KV, working distance (12-14 mm).

**In vitro Dissolution Studies**

Dissolution studies were performed in 900 ml phosphate buffer (pH 6.8) at 37 ± 0.5°C, using 8 station USP type-I apparatus (Shimadzu, Japan) rotating at 50 rpm. SD formulations containing 10 mg of ATV and 10 mg of pure ATV powder were filled in hard gelatine capsule shell (size # 1) and these capsule shells were subjected to dissolution media where release of pure ATV powder was considered as standard. At predetermined time intervals (5, 10, 15, 25, 35, 45, 55, 60 min), 10 ml of sample was withdrawn from each basket, filtered through a 0.45-μm filter paper and then analyzed spectrophotometrically at 247 nm in a UV-VIS spectrophotometer. Each test was performed in triplicate (n = 3) and calculated mean values of cumulative drug release were used to plot the release curve.

**Statistical Correlation Test**

Analysis of variance (ANOVA) test considering single factor was used to the statistical significance of the obtained results. ANOVA was performed for 95% confidence level (P value 0.05) e.g., P value less than 0.05 level will be considered statistically significant.

**RESULTS AND DISCUSSION**

Figure 2 shows the microscopic images of the optimized ATV-SD formulations. Distinct sharp crystals were seen while pure ATV was observed [Figure 2a]. Crystals of ATV disappeared in the images of PM at higher POL188 ratio [Figure 2b]. ATV crystals were also absent in case of SE where ATV-POL188 was 1:1 and also in the higher POL188 content. But as POL188 was used at six times less than the drug content, drug crystals disappeared quite surprisingly [Figure 2d]. This might be due to the transformation of ATV molecule from crystal to the amorphous state at that particular concentration of POL188 which was clearly seen in DSC thermogram described in the later section. However, this is a very common phenomenon of SD formulations comprising POL188. POL188, while is used at the optimum concentration in case of SD, transforms the drug crystals in to amorphous state where as at higher or lower level of the optimum concentration, drug remains in crystal form.[8]

Figure 3 shows the solubility (in distilled water) properties of ATV. In case of PM, as the POL188 was increased in the formulations, solubility of the drug was increased accordingly. But in case of SE, solubility of the drug was found to be increased in reverse order, e.g., solubility was increased with decreased amount of POL188 and maximum solubility was found for the lowest amount of POL188 (drug-carrier ratio, 3:0.5) (P < 0.05). This solubility was approximately 8 μg/mL which was almost twice of that of pure ATV, 4 μg/mL. However, in case of PM, maximum solubility was approximately 6.3 μg/mL for maximum amount of POL188.

DSC thermograms of pure ATV, POL188 and optimized SD formulations are shown in Figure 4. Sharp peak at 161.35°C was found in case ATV which indicates the melting of the drug [Figure 4a] and heat of fusion was -256.28 J/g. DSC thermogram of PM showed sharp peak at 52.79°C (1:1) and 52.55°C (1:3) [Figure 4c and d] and heat of fusion were -61 J/g and -102 J/g, respectively. However, disappearance of ATV peak in these SD formulations might be due to the formation of eutectic mixture.[8] In case of SE, peaks were around 52°C to 55°C [Figure 4f] with an exception of little broadening of the peak which was observed in case of 3:0.5 [Figure 4e]. Disappearance of the endothermic peaks of ATV at a low concentration can be elucidated as a result of dissolution of ATV crystals in the dissolved POL188. The same phenomenon has also been reported previously.[28,29] In addition, this result was in accordance with Mura et al. who

![Figure 2: Microscopic image of (a) Pure atorvastatin (b) Physical mixing 1:3 (c) Solvent evaporation 1:1 (d) Solvent evaporation 3:0.5](image)

![Figure 3: Solubility of atorvastatin in solid dispersion formulations; PM: Physical mixing, SE: Solvent evaporation](image)
reported that the total disappearance of the drug peak in the dissolved carrier indicates about the drug amorphization.\(^\text{30}\)

FTIR spectroscopy was used to examine the possible interactions between ATV and POL188 inside SD matrix. The IR spectra of SE (1:1, 3:0.5) were compared with the standard spectrum of ATV. In the IR spectrum, peak at 748.38 cm\(^{-1}\) indicates presence of C-F, peak at 1111 cm\(^{-1}\) indicates the presence of O-H bending, peak at 1242.16 cm\(^{-1}\) indicates presence of C-O-H stretching, peak at 1311.59 cm\(^{-1}\) indicates the presence of C-N group [Figure 5]. Peak in the range of 1512-1658 cm\(^{-1}\) indicates the presence of N-H bending (secondary amide). The POL188 exhibits characteristic peaks at 2885.51 \(^{-1}\) and 1107.14 cm\(^{-1}\) due to stretching of C-H and C-O groups. The FT-IR spectra of SDs of ATV showed a slight shift and broadening of O-H bending vibration peak (at 1107.14 cm\(^{-1}\)), C-H stretching vibration peak (at 2885.1 cm\(^{-1}\)), C-N vibration peak (at 1307.74 cm\(^{-1}\)). The absence of major shift in peak positions, retention of drug peak and the equivalent addition spectra (of ATV and POL188) for SE suggested the absence of interactions in solid state between ATV and POL188. The spectrum of SE of ATV revealed a slight shift in few characteristics peaks with no difference in overall spectrum which indicates possibility of intermolecular hydrogen bonding between ATV and POL188. These results indicate that there was no significant chemical interaction found in the FT-IR spectra of pure drug and SD formulations. No interaction was found even at higher concentration level of the polymer tested.

In vitro release data are shown in Figures 6 and 7. Pure ATV showed approximately 50% drug release after 60 min. In case of PM, maximum dissolution was found when SD contained the highest amount POL188 [Figure 6, PM 1:3]. In contrast, maximum dissolution for SE was found while the SD contained the lowest amount of POL188 [Figure 7, SE 3:0.5]. However, this may be explained in the following ways. Increased dissolution rate of ATV from PM might be due to the close contact of the drug with the hydrophilic polymer, brought about by the dry mixing process and higher concentration of polymer. This eventually led to increased wettability and dispersibility of the drug which eventually led in increased dissolution rate of the drug.\(^\text{31}\)

Drug release was approximately 55%, 28% and 23% for SE 1:1, SE 1:2 and SE 1:3 respectively [Figure 7] within first 15

**Figure 4:** DSC thermogram of (a) pure ATV (b) POL188 (c) PM of 1:1 (d) PM of 1:2 (e) SE of 3:0.5 (f) SE of 1:1 (g) SE of 1:2 (h) SE of 1:3
minutes of dissolution. Release was approximately 78% within 15 minutes and complete drug release was found within 35 minutes of dissolution when ATV-POL188 ratio was 3:0.5 or 6:1. That is higher ratios of POL188 (1:3 and 1:2) retarded the drug release (P < 0.05) and this might be due to the gel forming property of POL188 at higher concentrations.\[33\] Besides, thermoreversible gelling property of POL188 at higher concentrations might also contribute to this.\[33\]

However, this effect was not observed in SE of 3:0.5. Because, POL188 was present at lower concentration in this binary system. So, it can be inferred from the above findings that ATV-POL188 ratio played the pivotal role while they were used in SE technique. SE at a ratio of 3:0.5 was found superior to the other formulations and may be considered as the best combination of ATV-POL188 for maximum dissolution enhancement of ATV.

Release data were also used to study the kinetic parameters [Table 1]. Release of ATV from SD formulations was found to follow Peppas-Korsmeyer model where drug release followed diffusion process.

SEM micrographs are shown in Figure 8. Characteristic rod-shaped crystals were observed in the photomicrograph of pure ATV. SEM of SD prepared by SE revealed about the irregular particles with several microscopic cracks and crevices.
Table 1: Dissolution rate of Atorvastatin from different SD formulations

| Solid dispersion (SD) | Ratio of substance | N value | Dissolution rate (%/min) |
|----------------------|-------------------|---------|--------------------------|
|                      | PM                | SE      |                          |
| ATV:POL188           | 1:1               | 0.64    | 1.15                     |
|                      | 1:2               | 0.59    | 1.16                     |
|                      | 1:3               | 0.54    | 1.19                     |
| ATV:POL188           | 1:1.1             | 0.44    | 0.98                     |
|                      | 1:1.2             | 0.39    | 0.56                     |
|                      | 1:1.3             | 0.45    | 0.57                     |
|                      | 3:0.5             | 0.43    | 1.4                      |
| Pure ATV             | -                 | -       | 0.8045                   |

CONCLUSION

In the present investigation, poloxamer 188 has significantly improved the dissolution rate of atorvastatin. Physical studies demonstrated the absence of chemical interactions between the drug and polymer, the possibility of the presence of the amorphous form of the drug in SD systems. Among the ratios used, 3:0.5 ratio of SD was found to be optimal due to its superior performance in dissolution enhancement. This indicates that an increase in the mass fraction of polymer does not always offer any advantage for dissolution enhancement, rather optimal combination of drug and polymer needs to be used. Based on these results, it can be concluded that solid oral dosage forms of atorvastatin using SD technique with poloxamer 188 may be formulated having a high dissolution rate which will ensure faster onset of action and improved bioavailability.

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