Original Research Paper

Preparation, characterization, and in vitro/vivo evaluation of polymer-assisting formulation of atorvastatin calcium based on solid dispersion technique

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Due to low solubility and bioavailability, atorvastatin calcium is confronted with challenge in conceiving appropriate formulation. Solid dispersion of atorvastatin calcium was prepared through the solvent evaporation method, with Poloxamer 188 as hydrophilic carriers. This formulation was then characterized by scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction and fourier transform infrared spectroscopy. Moreover, all these studies suggested the conversion of crystalline atorvastatin calcium. In addition, the drug solubility studies as well as dissolution rates compared with bulk drug and market tablets Lipitor were also examined. Furthermore, the study investigated the pharmacokinetics after oral administration of Lipitor and solid dispersion. And the \( \frac{AUC_{0-8}}{AUC_{\infty}} \) and \( C_{\text{max}} \) increased after taking ATC-P188 solid dispersion orally compared with that of Lipitor. All these could be demonstrated that ATC-P188 solid dispersions would be prospective means for enhancing higher oral bioavailability of ATC.

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1. Introduction

Atorvastatin calcium (ATC) is indicated in the treatment of atherosclerosis and coronary disease alone or along with other lipid-lowering medicine [1]. It reduces plasma cholesterol levels since it inhibited the synthesis of HMG-CoA reductase and cholesterol [1,2]. ATC is also helpful in increasing the receptor of low density lipoprotein receptor on cell surface and decrease triglyceride levels in serum, meanwhile it can increase the level of high density lipoprotein (HDL) [1,3]. Owing to its low solubility and first-pass metabolism, the oral bioavailability is only around 14% [4,5]. Therefore, development of ATC formulation in virtue of low solubility and oral bioavailability is challenging [6]. Among those technologies including particle size reduction [7], solid dispersion (SD)

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technique [8–12], salt formation [13,14], nanosuspension [15] and other techniques, solid dispersion technology has received popularity as it increases solubility of insoluble drugs [16–18]. The most important feature of solid dispersion technology is that drug was highly dispersed in suitable carriers [19]. The techniques include twin screw extrusion, melting method, spray-dried dispersion, solvent evaporation method and other methods [20]. Solid dispersion could enlarge the surface of the drug particles, which results in enhancing the drug release based on Noyes–Whitney equation [10,21]. Moreover, the existence of P188 not only ensures the high dispersion of the drug, but also could effectively prevent the aggregation of the atorvastatin calcium. On the other hand, oral bioavailability of crystalline ATC could be enhanced by converting the crystalline state and particle property of drug [6].

Poloxamer 188 (P188) is a kind of non-ionic surfactant approved by FDA, commonly used with insoluble drugs as solubilizer and surfactant, based on high drug loading, low melting point, hydrophilicity and safety. For example, it has been used in thermoreversible gels for topical drug delivery as compatibility with skin which could increase skin permeability and promote the absorption of external agents. It has been reported that P188 can play efficient role on anti-tumor mechanism when used as carriers for drug delivery [22,23]. This study is mainly aimed at enhancing the solubility, dissolution rates and oral bioavailability of ATC by conventional solvent evaporation method with P188 as the carrier. Quite a few reports have formulated SDs of ATC using PEG 6000/4000, PVP K30, Soluplus [21,24–26] and so on as carriers. However, they have limitations compared with P188 due to the high viscosity, which lead the solution difficult to be desiccated. P188 is widely used in various formulations as pharmaceutical excipient based on promoting drug absorption and non-toxic effects. The limitation of the above mentioned methods (hot-melt method, spray-dried method) is that these methods require extra instruments and a large amount of drugs or carriers. The spray-dried method includes interaction of the machine configuration and formulation variables, which could affect drying efficiency and therefore impact the solid states property of SD. However, the hot-melt method commonly operates at high temperatures (more than 100 °C), which could affect the stability of drugs. By comparison, the conventional solvent evaporation method has the advantages of low cost, operating and reproducing conveniently. In addition, it is reported that P188 and PEG 4000 can increase the release of the ATC when they as the carriers of solid dispersion simultaneously and it has not found solid dispersion of ATC using P188 as carriers alone updated. Compared with the two carriers, the prescription in this work is simpler and the process is easier to reproduce. In this work, the physiochemical characterization of SD were detected by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR) after preparation. Some studies have shown improvement of solubility and drug release of ATC through solid dispersion method relative to bulk drug (API) and physical mixture. Finally, a pharmacokinetic study was conducted in rats by oral administration. In the existing literature, many formulations including solid dispersion prepared by atorvastatin calcium has only increased bioavailability.

2. Materials and methods

2.1. Materials

Atorvastatin calcium bulk drug was purchased from Zhejiang New Donggang Pharmaceutical Co., Ltd. (China). P188 was given by BASF Co., Ltd. (Shanghai, China). The commercial product (Lipitor, 10 mg dose) was purchased from Pfizer Co., Ltd (Dalian, China). Methanol was bought from Tianjin Concord Technology Co., Ltd. (China).

2.2. Preparation of the solid dispersion

Different atorvastatin calcium bulk drug: polymer (P188) combinations (1:1, 1:3, 1:5, 1:8; w/w) were dissolved in methanol (25 ml), ultrasonically for 5 min and sturred for 30 min at 40 °C by using water bath. The rotary evaporator was used to evaporate methanol at 35 °C after complete dissolving. Then it was transferred to a vacuum drying apparatus to remove residual solvent for 24 h. The resultant was pulverized, filtrated through 80 mesh sieve and stored in a desiccator at about 25 °C.

2.3. Preparation of physical mixture

Different weight ratios of drug: P188 (1:1, 1:3, 1:5, 1:8; w/w) were prepared in mortar until symmetrical mixture were formed. The resulting mixture was also filtrated through 80 mesh sieve and stored in a desiccator at about 25 °C.

2.4. Optimization of solid dispersion

In order to evaluate the feasibility of solid dispersion technique, it is unavoidable to investigate the dissolution behavior [28]. Hence, the appropriate dissolution medium is critical. The solubility of atorvastatin calcium increased with the enhancement of pH and pH 1.0 buffer was used as a tool for selecting formulation of solid dispersion according to relevant literature [29]. Ultraviolet-visible spectroscopic method was development to analyze the dissolution study. It was carried out with dissolution apparatus (RC806D dissolution apparatus, Tianta Tianfa Technology Co. Ltd., Tianjin, China) using the paddle method. Solid dispersion (equivalent to 10 mg of atorvastatin) was placed into 900 ml of dissolution medium (pH 1.0) at 37 ± 5 °C and paddle rotation speed was 50 rpm. 10 ml of solution was sampled at a predetermined interval (5, 10, 20, 30, 45, 60 min) and an equivalent volume (10 ml) of pre-warmed fresh media (37 °C) was added in each vessel to keep equivalent of volume. The concentration of ATC was analyzed.
by an ultraviolet spectrophotometer (UV1102 II spectrophotometer, Tianmei Technology Co. Ltd.; Shanghai, China) at a wavelength of 244 nm. All samples were performed in triplicate and no adsorption of ATC to the filter membranes could be detected.

2.5. Solubility of solid dispersion

Excessive of the physical mixture (PM), and the SD powder was added in test tube containing 10 ml dissolution medium: 0.1 M HCl, acetate buffer solution (pH 4.5), phosphate buffer solution (pH 6.8 and 7.2) and water. These samples were placed in water bath at 37 ± 0.5 °C for 48 h with vortex mixing. The suspensions were centrifuged at 13,000 rpm for 5 min and filtrated through a 0.45 μm membrane filter. After dilution, the samples were analyzed at a wavelength of 244 nm by an ultraviolet spectrophotometer [21]. No effect of polymer on UV measurement could be detected.

2.6. Characterizations of solid dispersion

2.6.1. Fourier-transform infrared spectroscopy

FTIR spectrum of sample was obtained on IFS-55 system (Bruker Corporation, Switzerland) using KBr disc method. The sample was recorded over wave number range of 4000–400 cm⁻¹ at the resolution of 2.0 cm⁻¹.

2.6.2. Powder x-ray diffraction

The powder X-ray diffraction patterns of the samples were recorded using Rigaku Miniflex diffractometer (Rigaku Corporation, Tokyo, Japan), a voltage of 40 kV and a 30 mA current. The sample were analyzed over a 2θ range of 5–45°, with a scanning rate of 2°/min and a CuKα radiation source.

2.6.3. Differential scanning calorimetry

Differential scanning calorimetry measurement was conducted by DSC-1 (Mettler-Toledo International Inc., Switzerland) with cooling equipment. The temperature program was performed form 30 to 250 °C at a heating rate of 10 °C/min.

2.6.4. Scanning electron microscopy

Scanning electron microscopy (S-3400, Hitachi, Tokyo, Japan) was applied to observe the morphology of bulk drug, P188, physical mixture and solid dispersion. The samples were fixed using mutual conductive adhesive tape on aluminum stubs and sputter-coated with a gold layer at 20 mA for 30 s in an ion sputter coater (S-570, Hitachi, Tokyo, Japan) at a pressure of 8–10 Pa prior to the observation at an accelerating voltage of 20 kV.

2.7. Pharmacokinetics studies

Ten Wistar rats (male, 220–250 g), which were provided by the Animal Center in Shenyang Pharmaceutical University, were kept under standard laboratory conditions at a temperature of 25 ± 2 °C and relative humidity (55% ± 5%). The rats were divided into two groups: A (Lipitor, 10 mg) and B (solid dispersion) at a dose of 25 mg/kg, randomly.

The Lipitor and solid dispersion were grinded into powder which dispersed in 0.4% Carboxymethylcellulose sodium (CMC-Na) before administration. Blood samples (0.3 ml) were collected within 8 h from orbital plexus and added into heparinized tubes at 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 8 h after oral administration. The samples were centrifuged at 13,000 rpm for 10 min instantly and the separated plasma was stored at −20 °C for analysis.

2.8. Plasma sample analysis

First, 50 μl acetonitrile and 50 μl Gliclazide solution (4 μg/ml) were added into 100 μl plasma sample and vortex-mixed for 3 min. After that, 2 ml acetonitrile was added to vortexed for about 5 min and centrifuged at 3500 rpm for 10 min. The supernatant was evaporated to dryness at 37 °C under nitrogen. The residue was reconstituted with 100 μl of acetonitrile. The samples (20 μl) were chromatographed on a reverse phase Phenomenex Ultradex C18 (250 mm × 4.6 mm, 5 μm) at a wavelength of 244 nm. Chromatographic analysis was carried out on a HPLC system (HITACHI, Japan), consisting of a quaternary pump, an autosampler, detector and a column oven. The mobile phase consisting of acetonitrile and 0.5% formic acid-water solution in the ratio of 48:52 (v/v) was filtered through a 0.22 μm membrane filter and degassed under vacuum before use. The concentration of each sample was calculated referred to a calibration curve with the concentration range from 0.075 to 2 μg/ml. The related pharmacokinetic parameters were analyzed using DAS 2.0 software [30].

3. Result and discussion

3.1. Optimization of solid dispersion

Dissolution behavior is a significant mean to guide the development of new formulation and could be used as a distinguishing method in formulation selection [31,32]. According to related literature, the dissolution was carried out in pH 1.0 media solution. The results were calculated from standard calibration curve (A = 0.048C – 0.042, R² = 0.999, the range of 2–20 μg/ml) of ATC and the cumulative percentage release of the drug was plotted against time. Based on the dissolution profile (Fig. 1), the release of ATC increase subsequently as the proportion of P188 increased (1:1, 1:3 and 1:5). However, there was no significant difference between the releases of solid dispersion with drug: polymer ratio of 1:8 and the ratio of 1:5. In view of solvent quantity and the ratio of carrier, solid dispersion with drug: polymer ratio of 1:5 was selected for further study. To evaluate this formulation, dissolution test was also carried out at different dissolution medium (pH 1.0, pH 4.5, pH 6.8 and water) to compare dissolution profile between bulk drug and Lipitor. As depicted in Fig. 2, The release of bulk drug was 40% in pH 1.0 media over 60 min. Nevertheless, either market tablets or the solid dispersion exhibited a significant enhancement in drug release than that of bulk drug. In other media, about 100% ATC were released from solid dispersion and Lipitor, higher than bulk drug within 30 min. It is worthy of note that the release rates was quite slower in Lipitor compared to solid dispersion, which could be seen within 5 min.

The enhancement of dissolution rates could be due to molecularly dispersion of ATC within P188 and drug
3.2. Solubility of SD

Based on the results (Fig. 3), the improved solubility of ATC in physical mixture might be result from the hydrophilic nature of P188. However, the results of further increase solubility in SD revealed that the solid dispersion techniques caused further increase in ATC solubility compared to the bulk drug and PMs.

3.3. Characterizations of SD

3.3.1. Fourier-transform infrared spectroscopy

If the drugs have different crystal form, there may be difference in chemical bond length and angle, which could affect vibrational-rotational transitions and some characteristics such as IR absorption band frequency, peak shape,

Fig. 1 – Dissolution profiles of different weight ratios (1:1, 1:3, 1:5, 1:8) of drug: P188. Each value represents the mean ± SD (n = 3).

Fig. 2 – Dissolution profiles of different medium pH 1.0 (A), pH 4.5 (B), water (C) and pH 6.8 (D) of bulk drug, solid dispersion and Lipitor. Each value represents the mean ± SD (n = 3).
peak position and intensity. Remarkably, IR spectrum could provide this information about chemical bonds, characteristic function groups and generally detect possible molecular interaction between drugs and carriers in the solid dispersion system [21]. In this study, FTIR was applied to determine possible interactions between P188 and ATC through solvent evaporation method. FT-IR spectrum of ATC, P188, PM, SD are depicted in Fig. 4. The bulk drug exhibits characteristic peaks at 3670 cm\(^{-1}\) (free O–H stretching vibration), 3364.8 cm\(^{-1}\) (N–H stretching), 2970.4 cm\(^{-1}\) (C–H stretching), 1650.6 cm\(^{-1}\) (asymmetric C=O stretching), 1579.1 cm\(^{-1}\) (symmetric C=O stretching), 1316.1 cm\(^{-1}\) (CH\(_3\)/CH\(_2\) deformation), 1241.4 cm\(^{-1}\) (C–N stretching), 1217.3 cm\(^{-1}\) (C–F stretch). The spectrum of P188 shows important function groups at 2889.6 cm\(^{-1}\) (C–H stretching), 1110.9 cm\(^{-1}\) (C–O groups). As can be seen, the characteristic of free O–H stretching vibration at 3670 cm\(^{-1}\) was absent in SD but appeared in PM, which might be due to the formation of amorphous nature of ATC [5]. On the basis of FTIR spectrum, some characteristic function groups of 3364.8 cm\(^{-1}\), 3056.0 cm\(^{-1}\) in the spectrum of SD disappeared but there are characteristic peaks at 3364.7 cm\(^{-1}\), 1650.6 cm\(^{-1}\), 1579.9 cm\(^{-1}\) in the spectrum of physical mixture, which might be due to interaction between ATC and P188. Meanwhile, in view of chemical structure of P188 and ATC, it could form hydrogen bond which can effectively prevent re-crystallization of amorphous
3.3.2. Powder X-ray diffraction

Powder X-ray diffraction could provide further verification of drug crystal conversion. The PXRD patterns of bulk drug, P188, physical mixture and solid dispersion were depicted in Fig. 5. The untreated bulk drug exhibited sharp and intense diffraction peaks at 2θ values of 9.1, 9.4, 10.2, 10.5, 11.8, 12.1, 17.0, 19.4, 21.5, 21.9, 22.6, 23.3, 23.7, 24.3, 28.8 and 29.1, which are consistent with the characteristic diffraction peaks of the crystalline Form I described in the patent [36]. The bulk P188 shows intense characteristic peaks at diffraction angle (2θ) of 19.1, 23.3. Physical mixtures showed peaks coincident with P188, and some diffraction peaks at 2θ values of 9.1, 9.4, 10.2, 10.5, 11.8, 12.1, 17.0, 21.6, 29.0 are similar to bulk drug although at low intensity (considering the P188 dilution effect, the drug peaks almost disappear due to the high percentage of P188). However, no characteristic peaks corresponding to bulk ATC were found in solid dispersion. These results indicated that the drug have been transformed from crystalline Form I to amorphous states.

3.3.3. Differential scanning calorimetry

Fig. 6 shows differential scanning calorimetry of bulk drug, P188, physical mixture and solid dispersion. The DSC curve of P188 displayed a sharp endothermic peak at 53 °C due to its melting point. DSC curve of ATC shows two endoerhermic peaks, a broad peak at 80–120 °C is related to water loss or dehydration (demonstrates the presence of tri-hydrate bulk drug), followed by another broad peak at 160 °C corresponding to the melting point of the atorvastatin calcium. Meanwhile, the third broad peak at 210–250 °C may be attributed to degradation product of ATC [37]. Physical mixture of ATC:P188 with the ratio of 1:5 show endothermic peaks at 53 °C, 80–120 °C, 160 °C origin from the melting point of P188, water loss or dehydration and the melting point of ATC respectively. No endothermic peaks related to the bulk drug appeared in the SD suggested the conversion of drug crystallinity. According to Fourier-transform infrared spectroscopy, PXRD studies, the ATC has transformed to amorphous state.
Table 1 – Inter-day, intra-day precision and accuracy results for QC samples of atorvastatin in rats plasma (n = 6).

| QC samples(μg/ml) | Accuracy (%) | Inter-day Mean ± SD(μg/ml) | RSD (%) | Intra-day Mean ± SD(μg/ml) | RSD (%) |
|-------------------|--------------|-----------------------------|---------|-----------------------------|---------|
| 0.075             | 90.6         | 0.068 ± 0.006               | 9.43    | 0.067 ± 0.002               | 3.47    |
| 0.2               | 90.5         | 0.181 ± 0.01                | 5.29    | 0.185 ± 0.008               | 4.63    |
| 0.6               | 104.8        | 0.524 ± 0.009               | 1.78    | 0.521 ± 0.008               | 1.64    |
| 1.6               | 94           | 1.504 ± 0.106               | 7.02    | 1.466 ± 0.101               | 6.91    |

Table 2 – Pharmacokinetic parameters of ATC in rats after oral administration of Lipitor and solid dispersion at a dose of 25 mg/kg (mean ± SD, n = 5).

| ATC0-6 (ng/h/ml) | T1/2 (h) | Tmax (h) | Cmax (ng/ml) |
|------------------|----------|----------|--------------|
| Lipitor          | 534.5 ± 278.3 | 2.99 ± 2.38 | 338.74 ± 80.38 |
| SD               | 919.0 ± 315.1  | 1.14 ± 0.17  | 972.2 ± 174.5  |

3.3.4. Scanning electron microscopy
The surface morphology of bulk drug, P188, physical mixture and solid dispersion was examined by SEM analysis, as depicted in Fig. 7. The bulk drug demonstrated needle-like crystallites with smooth surface and various particle sizes. Carriers existed as various size of spherical with smooth surfaces. In physical mixture, ATC crystals were clearly showed together with P188 particles which were the same as bulk drug micrograph. Meanwhile, the microscopy of carrier was converted to irregularly shape particles result from shattering and sieving. On the other hand, no visible needle-like crystallites were witnessed such as bulk drug micrograph in solid dispersion. In micrograph of solid dispersion, we can observe the irregularly shaped particles of carrier. And the smooth surface of carrier was covered by many small lamellas and particles result from bulk drug. All these suggested that ATC has converted to amorphous form through solid dispersion technique.

3.4. In vivo pharmacokinetics
Ten rats administrated with Lipitor and solid dispersion in a dose of 25 mg/kg, respectively. The methodology was confirmed and the tested linearity was ranging from 0.075 to 2 μg/ml with correlation coefficient of 0.9971 and the standard curve was Y = 2.886X + 0.1515. The results for the inter-day, intra-day precision and accuracy are depicted in Table 1. The mean extraction recoveries for atorvastatin at 0.2, 0.6, 1.6 μg/ml were 94.08%, 85.31%, 96.94%, respectively. In summary, the method is suitable for the determination of atorvastatin in plasma.

The pharmacokinetics parameters are shown in Table 2 and Fig. 8. It was found that the AUC0-6 of solid dispersion (919.0 ng/h/ml) represents greater improvement than that of Lipitor (534.5 ng/h/ml). In addition, it was also observed that AUC0-6 of solid dispersion was almost 1.71-fold compared with Lipitor. It was obtained that Cmax of solid dispersion formulation was 972.2 ng/ml and thus the difference was highly significant (P < 0.05) compared with Cmax of Lipitor. The Tmax of solid dispersion—the time that the plasma concentration of atorvastatin reaches the maximum after administrating with solid dispersion and Lipitor was faster than that of Lipitor. The hydrophilicity of ATC increases through solid dispersion technique, which is easier to diffuse to hepatocytes. The metabolism of atorvastatin occurs principally in the liver via cytochrome P450 (CYP) system. All these could explain that the T1/2 of solid dispersion formulation was shorter than that of Lipitor [38]. As the plasma concentration and AUC0-6 increasing when administered solid dispersion, which indicated that the pharmacological activities of ATC may be increased [39]. In short, these results suggested that solid dispersion could be applied as an effective formulation for enhancing the oral bioavailability of ATC [20].

4. Conclusion
The present study demonstrated the preparation of ATC-P188 solid dispersion by conventional method successfully. After comparison of dissolution profile between various carriers, P188 was selected as the final hydrophilic carrier. The physiochemical characterization indicated that the drug has dispersed in carriers and transformed to amorphous state. Solubility and dissolution rates were enhanced significantly compared with bulk drug. Meanwhile, the dissolution profile
of solid dispersion reached the degree of market tablets Lipitor. The pharmacokinetic study indicated that the $C_{\text{max}}$ and $AUC_{0-\infty}$ of solid dispersion were improved nearly 2.87-fold and 1.71-fold compared with Lipitor, separately. It’s therefore reasonable to point out that ATC-P188 solid dispersion using solvent evaporation method could be an effective method for increasing the oral bioavailability of ATC.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2018.08.010.

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