ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 10, 2022

FORMULATION AND CHARACTERIZATION OF MICROEMULSION OF ATORVASTATIN

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ABSTRACT

It is difficult to create a suitable formulation for atorvastatin calcium because of its limited solubility and bioavailability. Using Poloxamer 188 as a hydrophilic carrier, a solid dispersion of atorvastatin calcium was produced using the solvent evaporation technique. Afterwards, powder X-ray diffraction, differential scanning calorimetry, scanning electron microscopy, and fourier transform infrared spectroscopy were used to describe this formulation. Furthermore, every one of these investigations proposed the calcium conversion of crystalline atorvastatin. Furthermore, the medicine's solubility tests and dissolving rates in comparison to market and bulk drug Lipitor tablets were also looked at. Additionally, the research looked at the pharmacokinetics of solid dispersion and oral Lipitor delivery. Additionally, when comparing the oral ATC-P188 solid dispersion to that of Lipitor, the AUC0–8 h and Cmax increased. It can be shown from all of these that ATC-P188 solid dispersions are a potential way to increase ATC's oral bioavailability.

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 increas ing 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) 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

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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 relative to the API. Only one report is found update, pharmacokinetics (PK) results revealed thatthe ATC–Nanoparticles (ATC–NPs) formulations were of significantly lower bioavailability compared to Lipitor although pharmacodynamics (PD) results revealed that Lipitor and ATC–NPs formulation were equally effective in reducing levels of low density lipoproteins and triglycerides [27]. In order to validate the formulation, the dissolution and bioavailability of solid dispersion was compared with Lipitor (10 mg) in this work.

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;

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w/w) were dissolved in methanol (25 ml), ultrasonic for 5 min and stirred 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, Tianda 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 prewarmed 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.

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

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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 re-crystallization during preparation [21,28]. Similar results have been reported for celecoxib [29], diazepam [33], and felodipine [34]. Hence, the preparation of solid dispersion essentially enhanced the dissolution rate of ATC taking advantage of the increased surface area, amorphous state and effective wettability of P188.

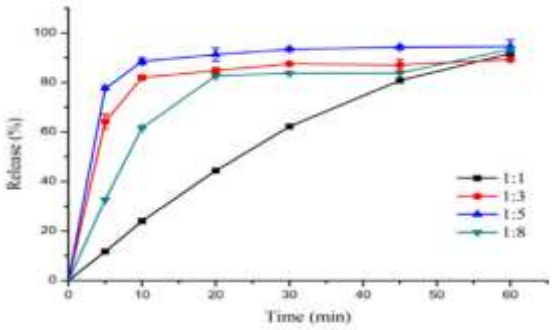


Fig. 1 – Dissolution profiles of different weight ratios (1:1, 1:3, 1:5, 1:8) of drug: P188. Each value represents the mean ± SD (n = 3).

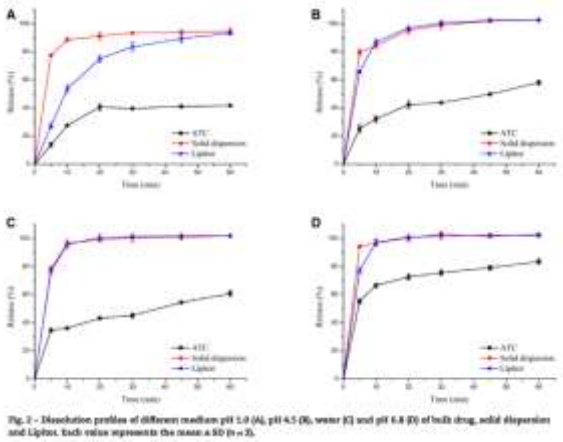
3.2. Solubility of SD

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,



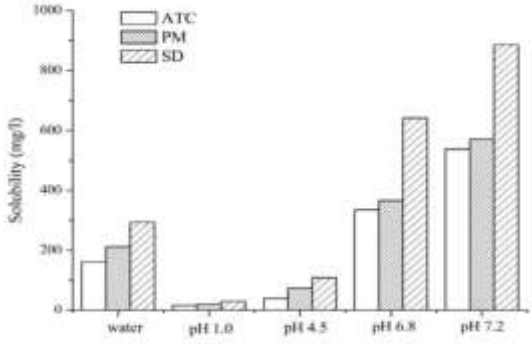


Fig. 3 – Solubility of bulk drug, physical mixture-bulk drug: P188 = 1:5 and solid dispersion in dissolution medium.

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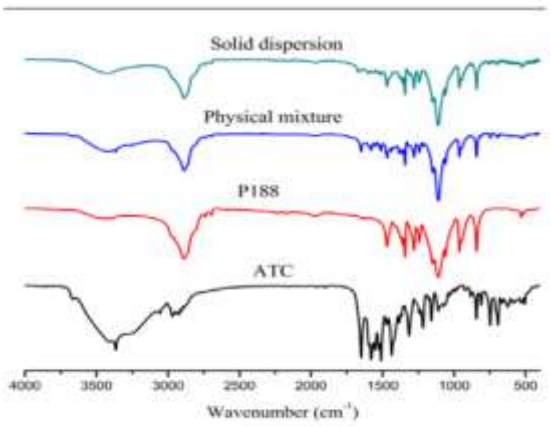

Fig. 4 – FTIR spectrum of physical mixture-bulk drug: P188 = 1:5, solid dispersion, P188, ATC.

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, FITR 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), 3056.0 cm−1 (symmetric O–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(CH3/ CH2 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

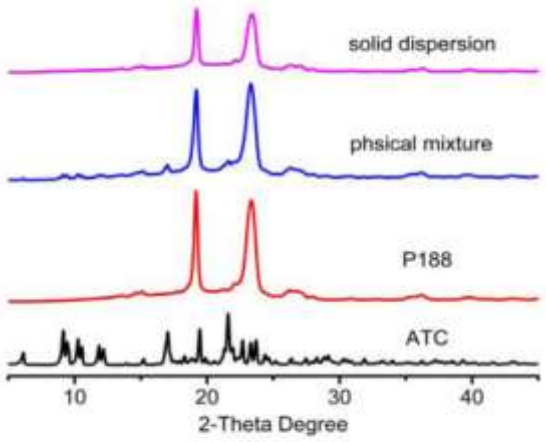

Fig. 5 – Powder X-ray diffraction patterns of physical mixture-bulk drug: P188 = 1:5, solid dispersion, P188, ATC.

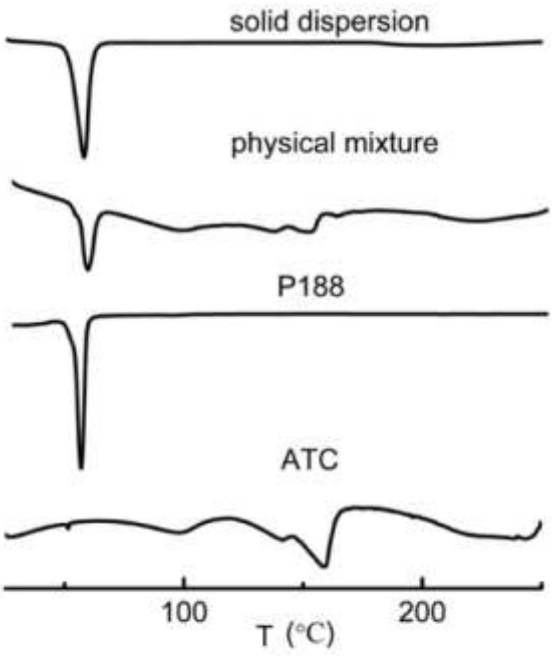

Fig. 6 – Differential scanning calorimetry of physical mixture-bulk drug: P188 = 1:5 (A), solid dispersion, P188, ATC.

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

ISSN PRINT 2319 1775 Online 2320 7876

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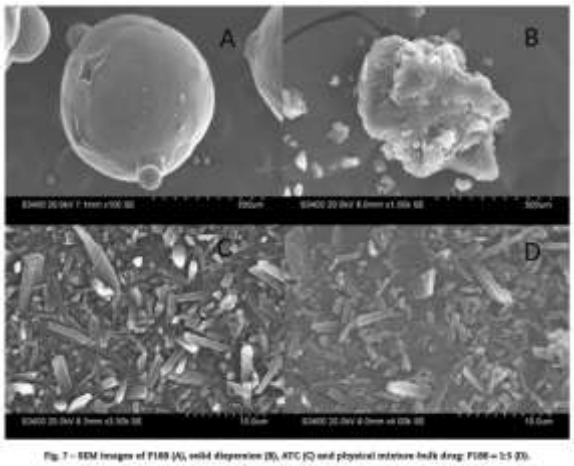
between ATC and P188. Meanwhile, in view of chemical structure of P188 and ATC, it could form hydrogen bond which can effectively prevent re-crystallization of amorphous



drugs and increase stability [21]. No additional new peaks is formed in SD suggested that there was no chemical interaction occurring during the preparation process [35].

4. CONCLUSION

The current investigation effectively showed the usual approach of preparing ATCP188 solid dispersion.

P188 was chosen as the ultimate hydrophilic carrier after a study of the dissolution profiles of the different carriers. According to the physiochemical characterisation, the medication has become amorphous and diffused in carriers.

Significant improvements were seen in solubility and dissolution rates as compared to the bulk medication. In the meanwhile, the solid dispersion's dissolving profile approached that of Lipitor tablets sold on the market. The results of the pharmacokinetic analysis showed that, in comparison to Lipitor, the Cmax and AUC0–8 h of solid dispersion were improved by over 2.87 and 1.71 times, respectively. Thus, it makes sense to mention that using the solvent evaporation approach to disperse ATC-P188 solid might be a useful strategy for raising ATC's oral bioavailability.

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