Asian Journal of Pharmaceutical Sciences 13 (2018) 546–554

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Original Research Paper

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

*Wenxiang Dong, Xitong Su, Meng Xu, Mingming Hu, Yinghua Sun, Peng Zhang**

Shenyang Pharmaceutical University, Shenyang 110016, China

ARTICLE INFO

Article history:
Received 25 April 2018
Revised 4 August 2018
Accepted 17 August 2018
Available online 12 October 2018

Keywords:
Atorvastatin calcium
Poloxamer 188
Solid dispersion
Dissolution rate
Oral bioavailability

ABSTRACT

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 $AUC_{0-8\,h}$ and C_{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.

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)

* Corresponding author. Shenyang Pharmaceutical University, No.103, Wenhua Road, Shenyang 110016, China. Tel.:+86 24 43520509
E-mail address: zhangpengspu@163.com (P. Zhang).
Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2018.08.010

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 relative to the API. Only one report is found update, pharmacokinetics (PK) results revealed that the 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; 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.

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 diffractmeter (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 CuK_{α} 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 Ultremex C_{18} (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 ($A = 0.048C–0.042$, $R^2 = 0.999$, 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

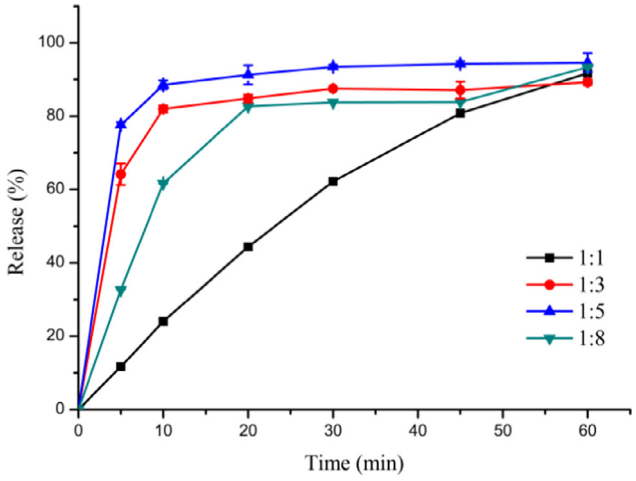

Fig. 1 – Dissolution profiles of different weight ratios (1:1, 1:3, 1:5, 1:8) of drug: P188. Each value represents the mean ± SD ($n = 3$).

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.

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,

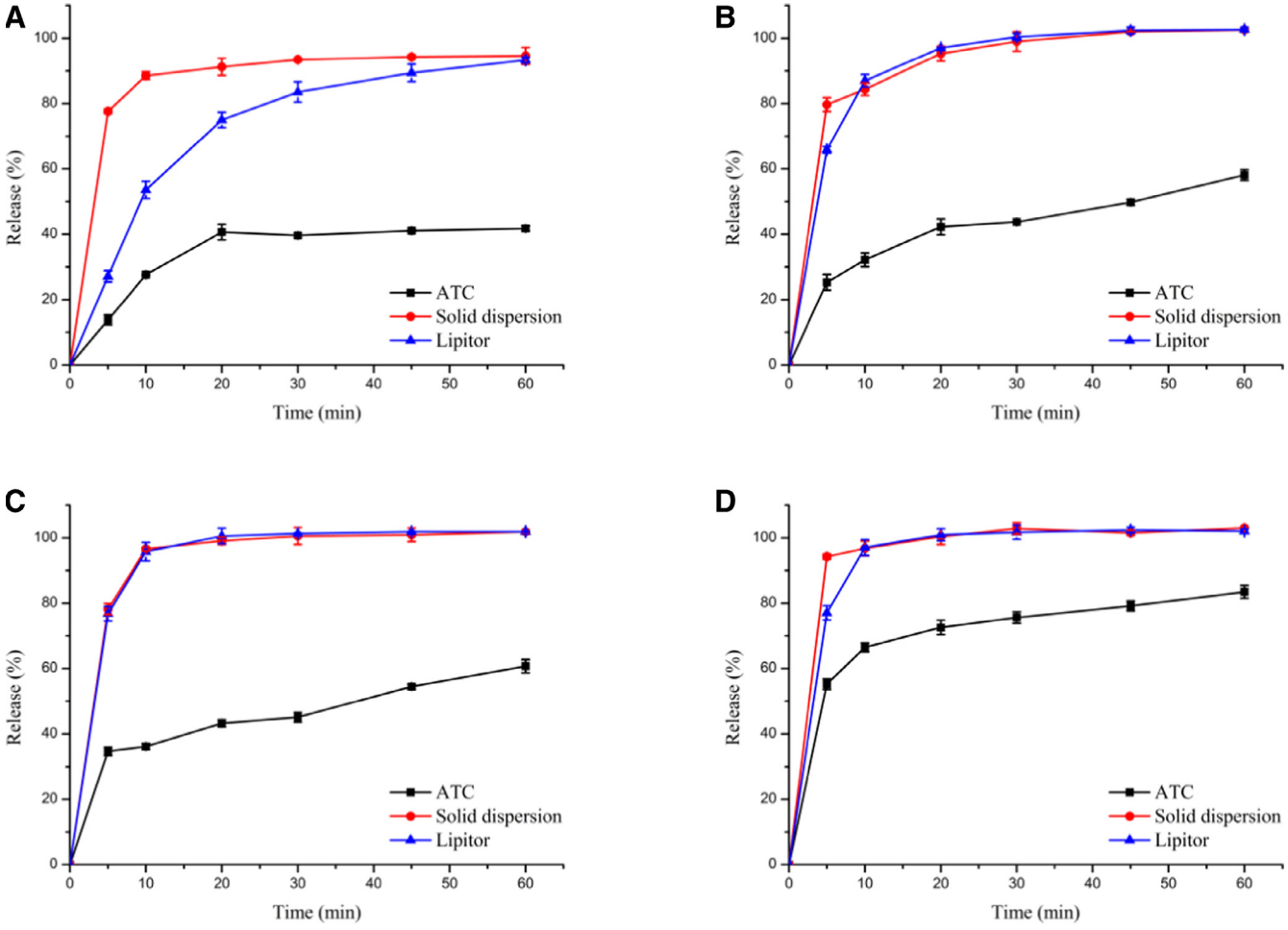

Fig. 2 – Dissolution profiles of different medium pH 1.0 (A), pH 4.5 (B), water (C) and pH 6.8 (D) of bulk drug, solid dispersion and Lipitor. Each value represents the mean ± SD ($n = 3$).

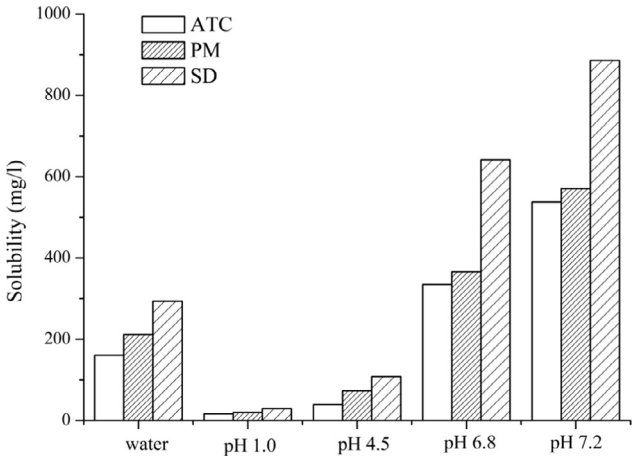

Fig. 3 – Solubility of bulk drug, physical mixture-bulk drug: P188 = 1:5 and solid dispersion in dissolution medium.

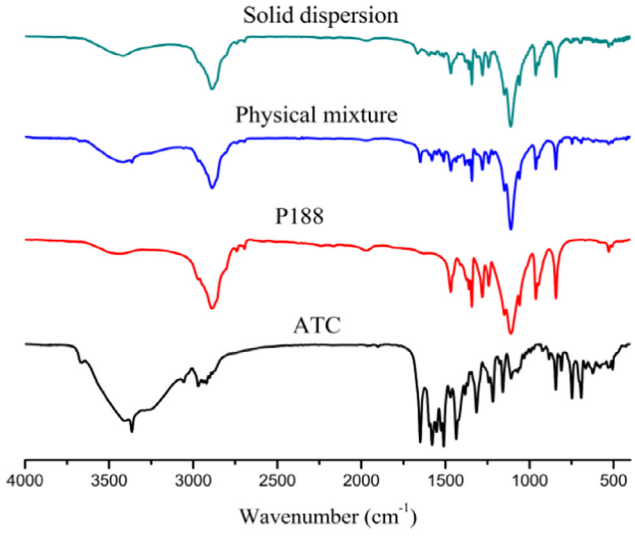

Fig. 4 – FTIR spectrum of physical mixture-bulk drug: P188 = 1:5, solid dispersion, P188, ATC.

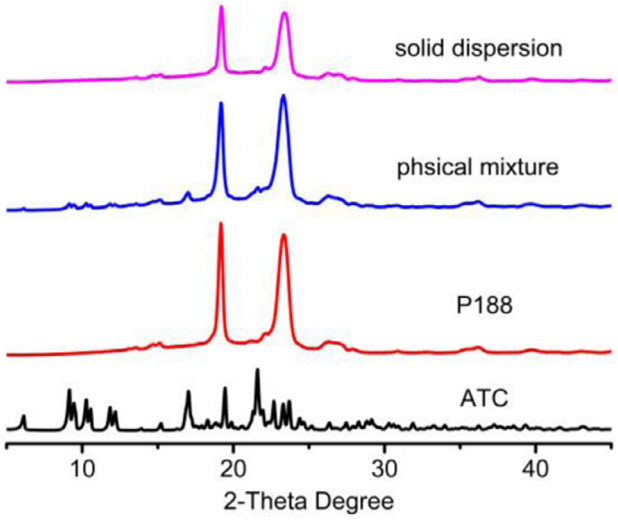

Fig. 5 – Powder X-ray diffraction patterns of physical mixture-bulk drug: P188 = 1:5, solid dispersion, P188, ATC.

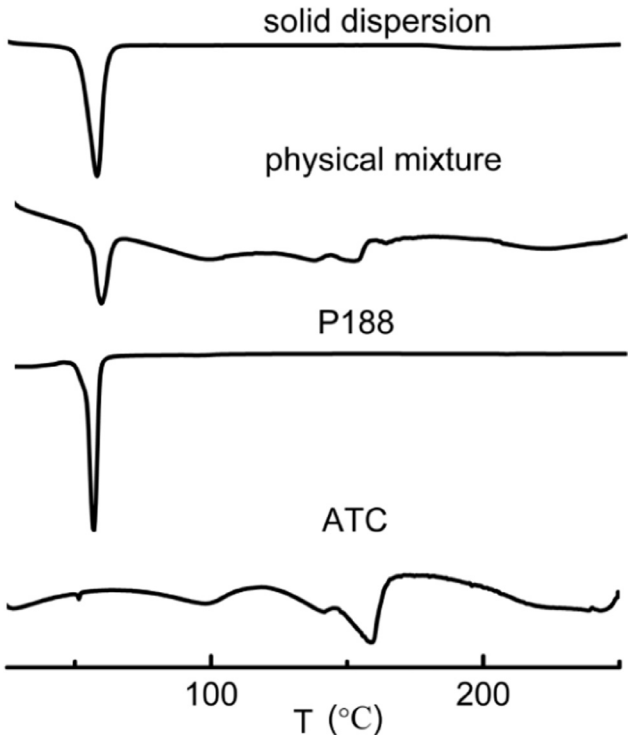

Fig. 6 – Differential scanning calorimetry of physical mixture-bulk drug: P188 = 1:5 (A), solid dispersion, P188, ATC.

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}(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

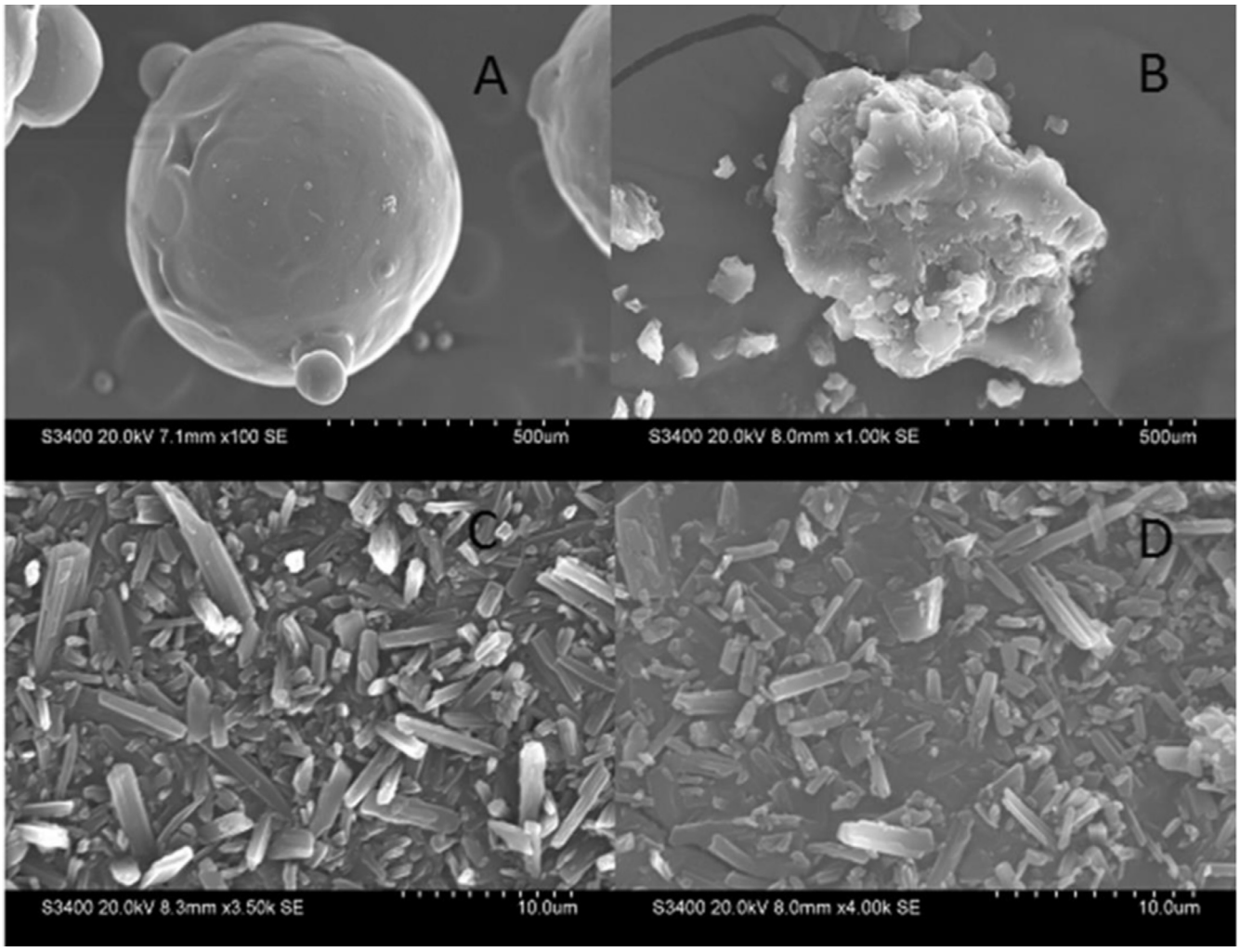

Fig. 7 – SEM images of P188 (A), solid dispersion (B), ATC (C) and physical mixture-bulk drug: P188 = 1:5 (D).

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].

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 disappears 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 endothermic 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 endotherm 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		Intra-day	
		Mean ± SD(μg/ml)	RSD (%)	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).

	AUC_{0-8} (ng/h/ml)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/ml)
Lipitor	534.5 ± 278.3	2.99 ± 2.38	0.65 ± 0.224	338.74 ± 80.38
SD	919.0 ± 315.1	1.14 ± 0.17	0.567 ± 0.181	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 conformed 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 $AUC_{0-8\,h}$ 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 $AUC_{0-8\,h}$ of solid dispersion was almost 1.71-fold compared with Lipitor. It was obtained that C_{max} of solid dispersion formulation was 972.2 ng/ml and thus the difference was highly significant ($P < 0.05$) compared with C_{max} of Lipitor. The T_{max}

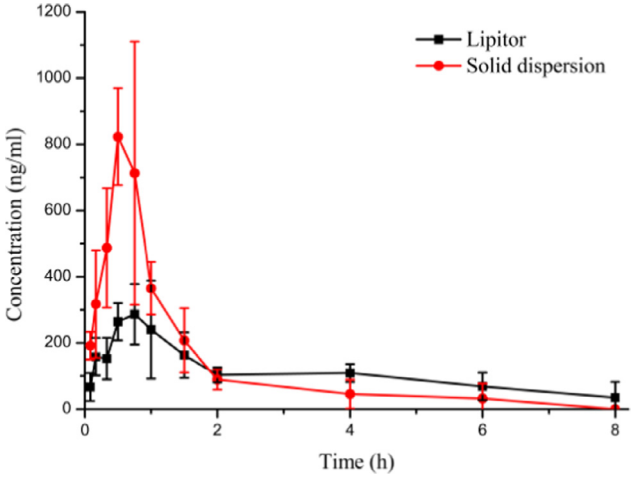

Fig. 8 – Mean plasma concentration – time curves of ATC in rats after oral administration of Lipitor and solid dispersion at a dose of 25 mg/kg AC (mean ± SD, n = 5).

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 $T_{1/2}$ of solid dispersion formulation was shorter than that of Lipitor [38]. As the plasma concentration and $AUC_{0-8\,h}$ 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_{max} and $AUC_{0-8\,h}$ 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.

REFERENCES

[1] Desager JP, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme: a reductase inhibitors. Clin Pharmacokinet 1993;31(5):348–71.
[2] Jahangiri A, Jalali MB, Garjani A, et al. Evaluation of physicochemical properties and *in vivo* efficiency of atorvastatin calcium/ezetimibe solid dispersions. Eur J Pharm Sci 2016;82(72):21–30.
[3] Yin YM, Cui FE, Kim JS, et al. Preparation, characterization and *in vitro* intestinal absorption of a dry emulsion formulation containing atorvastatin calcium. Drug Deliv 2009;16(1):30–6.
[4] Shete G, Puri V, Kumar L, Bansal AK. Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. AAPS PharmSciTech 2010;11(2):598–609.
[5] Palanisamy M, James A, Khanam J. Atorvastatin ecyclodextrin systems: Physiochemical and biopharmaceutical evaluation. J Drug Deliv Sci Technol 2016;31:41–52.
[6] Choudhary A, Rana A, Aggarwal G, Kumar V, Zakir F. Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability. Acta Pharm Sci B 2012;2(4):421–8.
[7] Jinno J, Kamada N, Miyake M, et al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Control Release 2006;111(1):56–64.
[8] Li WF, Qing S, Zhi WB, Yao H, Fu CL, Niu XF. The pharmacokinetics and anti-inflammatory effects of chelerythrinr solid dispersion *in vivo*. J Drug Deliv Sci Technol 2017;40:51–8.
[9] Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm 2004;272(1):1–10.
[10] Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50(1):47–60.
[11] Jaywant NP, Rahul TS, Avinash BG. Development of amorphous dispersions of artemether with hydrophilic polymers via spray drying: physicochemical and in silico studies. Asian J Pharm Sci 2016;11(3):385–95.
[12] Pradhan R, Kim SY, Yong CS, Kim JO. Preparation and characterization of spray-dried valsartan-loaded Eudragit® solid dispersion microparticles. Asian J Pharm Sci 2016;11(6):744–50.
[13] Serajuddin ATM. Salt formation to improve drug solubility. Adv Drug Deliv Rev 2007;59(7):603–16.
[14] Engel GL, Farid NA, Faul MM, Richardson LA, Winneroski LL. Salt form selection and characterization of LY333531 mesylate monohydrate. Int J Pharm 2000;198(2):239–47.
[15] Kumar N, Chaurasia S, Patel RR, Khan G, Kumar V, Mishra B. Atorvastatin calcium encapsulated eudragit nanoparticles with enhanced oral bioavailability, safety and efficacy profile. Pharm Dev Technol 2017;22(2):156–67.
[16] Sawicki E, Schellens JHM, Beijnen JH. Pharmaceutical development of an amorphous solid dispersion formulation of elacridar hydrochloride for proof-of-concept clinical studies. Drug Dev Ind Pharm 2017;43(4):584–94.
[17] Sawicki E, Beijnen JH, Schellens JHM, Nuijen B. Pharmaceutical development of an oral tablet formulation containing a spray dried amorphous solid dispersion of docetaxel or paclitaxel. Int J Pharm 2016;511(2):765–73.
[18] Choi JS. Enhanced stability and solubility of pH-dependent drug, telmisartan achieved by solid dispersion. J Drug Deliv Sci Technol 2017;37:194–203.
[19] Chen YC, Ho HO, Chiou JD, Sheu MT. Physical and dissolution characterization of cilostazol solid dispersions prepared by hot melt granulation (HMG) and thermal adhesion granulation (TAG) methods. Int J Pharm 2014;473(1–2):458–68.
[20] Shuai S, Yue S, Huang QT, Wang W, Yang JY, Lan K. Preparation, characterization and *in vitro*/vivo evaluation of tectorigenin solid dispersion with improved dissolution and bioavailability. Eur J Drug Metab Pharmacokinet 2016;41(4):413–22.
[21] Jahangiri A, Jalali MB, Garjani A. Pharmacological and histological examination of atorvastatin-PVP K30 solid dispersions. Powder Technol. 2015;286:538–45.
[22] Riehm JJ, Wang L, Ghadge G, et al. Poloxamer 188 decreases membrane toxicity of mutant SOD1 and ameliorates pathology observed in SOD1 mouse model for ALS. Neurobiol Dis 2018;115:115.
[23] Ban E, Park M, Jeong S, et al. Poloxamer-based thermoreversible gel for topical delivery of emodin: influence of P407 and P188 on solubility of emodin and its application in cellular activity screening. Molecules 2017;22(2):246.
[24] Ha ES, Baek I, Cho W, Hwang SJ, Kim MS. Preparation and evaluation of solid dispersion of atorvastatin calcium with Soluplus® by spray drying technique. Chem Pharm Bull 2014;62(6):545–51 (Tokyo).
[25] Shamsuddin FM, Ansari SH, Ali J. Atorvastatin solid dispersion for bioavailability enhancement. J Adv Pharm Technol Res 2016;7(1):22–6.
[26] Hu LD, Gu DL, Hu QF. Investigation of solid dispersion of atorvastatin calcium inpolyethylene Glycol 6000 and polyvinylpyrrolidone. Trop J Pharm Res 2014;13(6): 835–842.
[27] Ahmed IS, Hosary RE, Shalaby S. PD-PK evaluation of freeze-dried atorvastatin calcium-loaded poly-caprolactone nanoparticles. Int J Pharm 2016;504(1–2):70–9.
[28] Lu TS, Sun YH, Ding DW, Zhang Q, Fan R. Study on enhanced dissolution of azilsartan-loaded solid dispersion, prepared by combining wet milling and spray-drying technologies. AAPS PharmSciTech 2017;18(2):473–80.
[29] Ghanavati R, Taheri A, Homayouni A. Anomalous dissolution behavior of celecoxib in PVP/Isomalt solid dispersions prepared using spray drier. Mater Sci Eng C Mater Biol Appl 2017;72:501–11.
[30] Li ZB, Tao WH, Zhang D, et al. The studies of PLGA nanoparticles loading atorvastatin calcium for oral

administration *in vitro* and *in vivo*. Asian J Pharm Sci 2017;12(3):285–91.
[31] Machado JC, Lange AD, Todeschini V. Development and validation of a discriminative dissolution method for atorvastatin calcium tablets using *in vivo* data by LC and UV methods. AAPS PharmSciTech 2014;15(1):189–97.
[32] Shingel K, Selyanin M, Filion MC. Solid dispersion of drugs in hyaluronan matrix: the role off the biopolymer in modulating drug activity *in vivo*. J Drug Deliv Sci Technol 2017;39:140–6.
[33] Drooge DJ, Hinrichs WLJ, Frijlink HW. Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. J Control Release 2004;97(3):441–52.
[34] Langham ZA, Booth J, Hughes LP, Wren SAC. Mechanistic insights into the dissolution of spray-dried amorphous solid dispersions. J Pharm Sci 2012;101(8):2798–810.
[35] Prabhu P, Patravale V. Dissolution enhancement of atorvastatin calcium by co-grinding technique. Drug Deliv Transl Res 2016;6(4):380–91.
[36] Skorda D, Kontoyannis CG. Identification and quantitative determination of atorvastatin calcium polymorph in tablets using FT-Raman spectroscopy. Talanta 2008;74(4):1066–70.
[37] Maurya D, Belgamwar V, Tekade A. Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium. J Pharm Pharmacol 2010;62(11):1599–606.
[38] Mahmoud MO, Aboud HM, Hassan AH, et al. Transdermal delivery of atorvastatin calcium from novel nanovesicular systems using polyethylene glycol fatty acid esters: ameliorated effect without liver toxicity in poloxamer 407-induced hyperlipidemic rats. J Control Release 2017;254:10–22.
[39] Sun S, Wang R, Fan J, Zhang GQ, Zhang H. Effects of Danshen tablets on pharmacokinetics of atorvastatin calcium in rats and its potential mechanism. Pharm Biol 2018;56(1):104–8.