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ORIGINAL ARTICLE

In vitro and in vivo evaluation of fenofibrate solid dispersion prepared by hot-melt extrusion

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Abstract

Objective: This article aimed to develop fenofibrate solid dispersion with high bioavailability using hot-melt extrusion and compare the difference of Eudragit® E100 and polyvinylpyrrolidone-vinyl acetate copolymer S630 (PVP-VA) in dissolution. *Methods:* Solid dispersion with carrier of Eudragit E100 or PVP-VA was prepared by hot-melt extrusion and then characterized by differential scanning calorimetry (DSC), X-ray diffraction, in vitro dissolution test, and in vivo bioavailability study. *Results:* Fenofibrate exited as noncrystal state in these two kinds of solid dispersions that can be proved by DSC and X-ray diffraction. Eudragit E100 1:2 solid dispersion has the dissolution of 84% and 65% at 60 minutes in 0.1M HCl and water, respectively. Eudragit E100 1:4 solid dispersion has lower dissolution in 0.1M HCl and higher dissolution in water; the values are 73.6% and 87.3%. PVP-VA 1:2 solid dispersion has the dissolution of 60% and 65% at 60 minutes in 0.1M HCl and water, respectively. PVP-VA 1:4 solid dispersion has higher dissolution in 0.1M HCl and lower dissolution in water; the values are 64% and 53%. The different dissolution of fenofibrate from the two polymers is because of their different solubility and gelling tendency. When Eudragit E100 1:4 solid dispersion was administrated to beagle dogs, its relative bioavailability to micronization Lipanthyl capsule was 177.1%. *Conclusion:* Hot-melt extrusion is an excellent method to improve the dissolution and therefore the bioavailability of fenofibrate.

Key words: *Bioavailability; dissolution test; fenofibrate; hot-melt extrusion; solid dispersion*

Introduction

Fenofibrate, launched in 1975, has a potent effect in reducing elevated concentrations of total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B (apo B), total triglycerides, and triglyceride-rich very low-density lipoprotein[1–3]. Fenofibrate is a prodrug. After absorption, it is rapidly hydrolyzed to its predominant active metabolite, fenofibric acid, and no parent compound is detectable in plasma. Fenofibrate is applied in 86 countries now and has become one of the most commonly used lipid-lowering agents worldwide. However, this drug is practically insoluble in water[4,5] and its main drawback is the low bioavailability of the active metabolite, fenofibric acid, when the prodrug is taken orally on an empty stomach. In contrast, its absorption is substantially increased in the presence of fatty food. So, doctors may suggest patients to administer fenofibrate with meals, but this strategy always leads to the variability of bioavailability with different patients or different days. What is more, fatty food is not suitable for the patient who suffers from hyperlipemia. Fortunately, fenofibrate has a high lipophilicity (log P = 5.24) [6] and the only barrier for its absorption is dissolution rate. In fact, many methods have been tried to improve the dissolution of fenofibrate. Laboratoires Fournier SA (Dijon, France) has developed a micronized fenofibrate capsule and obtained a relatively high bioavailability. Whereas the micronized fenofibrate is unstable in thermodynamics, and the micronized particles will aggregate together during storage. Insoluble Drug Delivery®-Microparticle fenofibrate tablets are a new formulation developed to provide fenofibrate bioavailability independent of food and its fat content. The technology used to develop this formulation involves preparing microparticles of drug and stabilizing them with phospholipid surface-modifying agents that prevent the microparticles from reaggregating. Thus, this approach

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preserves the expanded drug surface area that results from microparticularization. Exposure of the expanded drug surface area to the in vivo dissolution medium upon oral administration thereby increases the bioavailability[7]. The principles of the former two methods are to enhance drug surface area, which is not the best choice for practically insoluble drug such as fenofibrate because the hydrophilic property and wettability are not changed during dissolution process. Solid dispersion technique may be a promising method to solve this problem, which can disperse poorly water-soluble drug into hydrophilic carrier at molecule level and improve the dissolution dramatically by enhancing the dispersity and wettability of the drug. Despite the excellent effect in improving the bioavailability of many low-dissolution drugs, few products were developed on the market because of process, equipment, and pollution problems which cannot be avoided.

Hot-melt extrusion, an industrial process technique based on solid dispersion principle, has been developed in pharmaceutical field in recent years. It has been applied to improve the dissolution of poorly water-soluble drugs[8–12] to produce controlled-release dosage forms[13–20] and to prepare films.[21–25]

The dissolution of poorly water-soluble drugs is always improved dramatically by hot-melt extrusion. Hydrophilic polymer carrier is the first choice to prepare excellent solid dispersions in many cases because this technique came from polymer industry. Eudragit® E100 and polyvinylpyrrolidone-vinylacetatecopolymer S630 (PVP-VA), which have suitable melt and favorable hydrophilic properties, are the two mostly used polymers in this field. As we all know, different polymers have different dissolving characters, which will influence the dissolution of solid dispersions. However, few literatures are concerned about the difference between Eudragit® E100 and PVP-VA.

This article aims to develop fenofibrate solid dispersion with high bioavailability using hot-melt extrusion and compares the difference of Eudragit® E100 and PVP-VA in dissolution.

Materials and methods

Materials

Fenofibrate was purchased from Kaifeng Pharmaceutical Co. Ltd. (Henan, China). Eudragit® E100 was kindly provided by Röhm (Darmstadt, Germany); PVP-VA was obtained from ISP Company (Wayne, NJ, USA); and all other reagents were of high-performance liquid chromatography (HPLC) grade or analytical grade. Lipanthyl® capsule was purchased from Laboratoires Fournier SA.

Methods

Preparation of the physical mixture (PM)

Fenofibrate and carriers were weighted according to Table 1 and then were mixed by hand in a polyethylene bag for 10 minutes to obtain uniform mixtures.

Preparation of the solid dispersion by hot-melt extrusion

Solid dispersions composed of fenofibrate and carriers were prepared by hot-melt extrusion using a co-rotating twin-screw extruder (TE-20 32:1; Coperion Keya Co., Nanjing, China) according to Table 1. The extruder configuration consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. The materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw, and then extruded from the die. The feeding and screw rates were fixed at 48 rpm. From feeder to die, the temperatures were set at 100-120-120-120-120°C and 100-130-130-130-130°C for Eudragit E100 PM and PVP-VA PM, respectively. The extrudates were collected by aluminum plate and cooling at ambient temperature. The dried solid dispersions were milled (FW135 pulverizer; Taisite Co., Tianjin, China) and then sieved through a 150–250-μm cribble for further investigation.

Thermal analysis

The thermal stability of fenofibrate was determined using a thermal gravimetric analyzer (TGA 50; Shimadzu, Kyoto, Japan). Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 mL/min. Samples were analyzed using a heating rate of 5°C/min from 30°C to 300°C. Plots of weight versus temperature were recorded.

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the polymer, drug, PMs, and hot-melt extrudates. The DSC analysis was carried out on a DSC 60 differential scanning calorimeter (Shimadzu, Kyoto, Japan). Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 mL/min. Samples were weighed to 10 ± 5 mg, crimped in hermetic aluminum pans with lids, and analyzed using a heating rate of 5°C/min from 30°C to 300°C. Plots of heat flow versus temperature were recorded.

Table 1. Formulations of fenofibrate physical mixture.

Formulation	1	2	3	4
Fenofibrate (g)	50	50	50	50
Eudragit E100 (g)	100	200		
PVP-VA (g)			100	200

Powder X-ray diffraction analysis

The powder X-ray diffraction profiles were obtained using an X-ray powder diffractometer (type D/Max-2400; Rigaku Instrument, Tokyo, Japan). The samples were exposed to CuKa radiation under 56 kV and 182 mA over the 2-theta range from 3° to 45° at increments of 0.5°/min. The extrudates were ground into a fine powder before analysis.

Dissolution tests

The in vitro drug release from samples was studied using a dissolution tester (ZRS-8G, Tianjing Tianda Equipment Factory, Tianjin, China) according to the dissolution test method 2 as described in the British Pharmacopoeia with a paddle rotation speed of 75 rpm. Two kinds of dissolution mediums, i.e. distilled water containing 0.36% SDS and 0.1 M HCl solution containing 0.36% SDS, were utilized to investigate the dissolution behavior. The dissolution mediums were maintained at 37 ± 0.5°C throughout the test. Samples equivalent to 200 mg fenofibrate were added to the dissolution cups and 5 mL test fluid was withdrawn at 10, 20, 30, 45, and 60 minutes. Samples floated at the surface of dissolution medium and suspend into the bulk solution after they were wetted. Samples of the dissolution medium were passed through a 0.45-μm millipore filter, and then fresh medium was used to replace sample volume. The concentration of drug in the filtrate was analyzed by a UV–Visible spectrophotometer (752 model; Shanghai Spectrum Equipment Co., Ltd., Shanghai, China) at 289 nm.

Bioavailability study

Solid dispersion from formulation 2 was filled into a capsule and selected for bioavailability study, and the protocol of animal study was approved by the Ethics Committee of Shenyang. Six beagle dogs were divided into two groups, and a single-dose, randomized crossover study was applied with a wash-out period of 7 days. The mean weight of the dogs was 13–15 kg. After fasting overnight, dogs in group 1 received a 200-mg dose of solid dispersion capsule and group 2 received a 200-mg dose of marked capsule Lipanthy® with 200 mL water. On each dosing day, blood samples were taken pre-dose and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, 60.0 and 72.0 hours post-dose. Four hours post-dose they were provided with standard food. Plasma was separated from samples by centrifugation (8000 × *g* for 10 minutes) and stored at −20°C.

The internal standard solution (flurbiprofen) was added to the protein precipitation agent composed of 5% 1 M HCl and 95% acetonitrile. Plasma sample (0.2 mL) was placed in a 1.5-mL centrifuge tube and mixed with 0.4 mL of the former solution by vortexing. After centrifuging, 50 μL of the solution was injected into the HPLC system (Hitachi D-7000, Hitachi, Ltd., Tokyo, Japan). Chromatography was performed on a HiQ Sil™ C_{18} column (5 μm, 250 × 4.6 mm) using a mobile phase of acetonitrile –0.3% acetic acid (65:35, v/v). The chromatographic analyses were performed at the ambient temperature at a flow rate of 1.0 mL/min and the wavelength was 287 nm.

The data was processed by Topfit 2.0 software and the relative bioavailability was calculated with the following equation:

$$F = \frac{\mathrm{AUC_{test}}}{\mathrm{AUC_{reference}}} \times 100\%.$$

Results and discussion

Miscibility between fenofibrate and carriers

The solubility parameter has been used to evaluate the miscibility between drugs and ingredients. Greenhalgh et al. [26] demonstrated that compounds with $\Delta\delta_t < 7\ \mathrm{MPa}^{1/2}$ were likely to be miscible whereas compounds with $\Delta\delta_t > 10\ \mathrm{MPa}^{1/2}$ were likely to be immiscible. The solubility parameter of fenofibrate, Eudragit E100, and PVP-VA are 20.95, 20.55, and 22.94 $\mathrm{MPa}^{1/2}$, respectively, which were calculated based on Hoftyzer/Van Krevelen method. It can be speculated that the two polymers have good miscibility with fenofibrate.

Thermal analysis

Fenofibrate is a crystal compound with a melting point of 78°C (Figure 1). Below 180°C, it is thermally stable and no weight loss can be seen. Eudragit E100 is an amorphous compound with a T_g of 55°C (Figure 2)

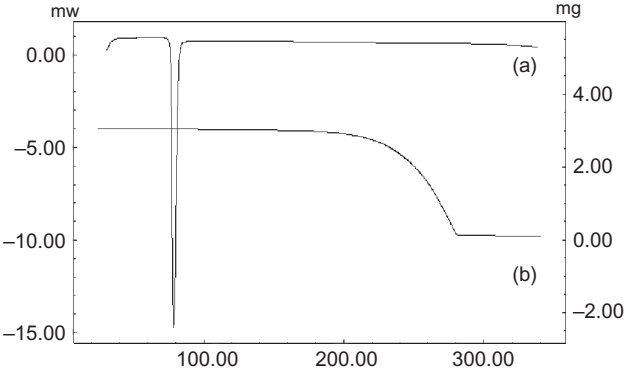

Figure 1. Thermal analysis of fenofibrate powder: (a) DSC and (b) TGA.

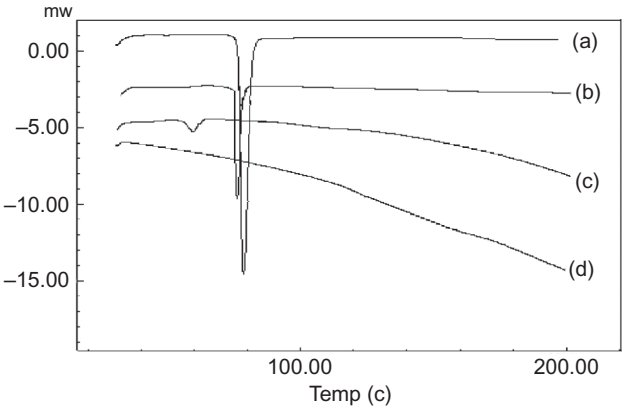

Figure 2. DSC analysis of fenofibrate–Eudragit E100 system: (a) fenofibrate, (b) 1:2 physical mixture, (c) Eudragit E100, (d) 1:2 extrudate.

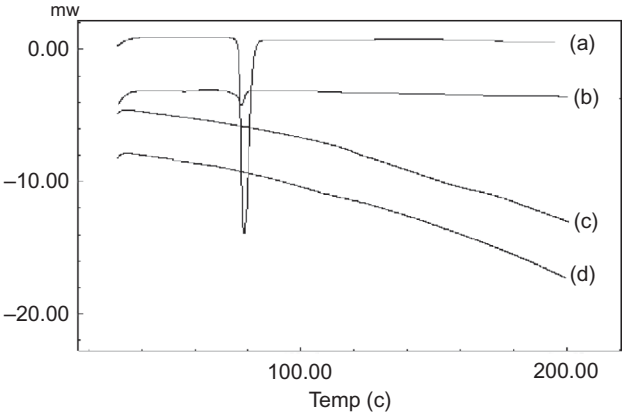

Figure 3. DSC analysis of fenofibrate-PVP-VA system: (a) fenofibrate, (b) 1:2 physical mixture, (c) PVP-VA, (d) 1:2 extrudate.

When it was mixed with fenofibrate, the endothermal peak of fenofibrate was weakened. After hot-melt extrusion, no endothermal peak can be seen from DSC, indicating the formation of solid dispersion. As an amorphous compound, PVP-VA has no endothermal peak (Figure 3). Also, the melting peak of fenofibrate was weakened in PVP-VA PM and disappeared in extrudate.

Powder X-ray diffraction

The X-ray diffraction patterns of fenofibrate, Eudragit E100, PVP-VA, PMs, and extrudates are presented in Figures 4 and 5. As a crystal compound, fenofibrate showed a series of peaks (Figure 4a) at 11.86°, 14.38°, 16.61°, 20.79°, 22.15°, 24.62°, 26.17°, and 36.72°. Both Eudragit E100 and PVP-VA exhibited amorphous characteristics in Figures 4 and 5 and no peak can be seen. The diffraction patterns of Eudragit E100 PM and PVP-VA

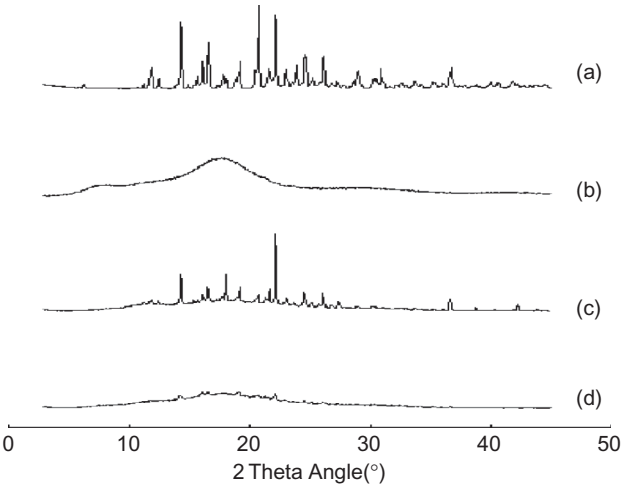

Figure 4. Powder X-ray diffraction of fenofibrate–Eudragit E100 system: (a) fenofibrate, (b) Eudragit E100, (c) 1:2 physical mixture, (d) 1:2 extrudate.

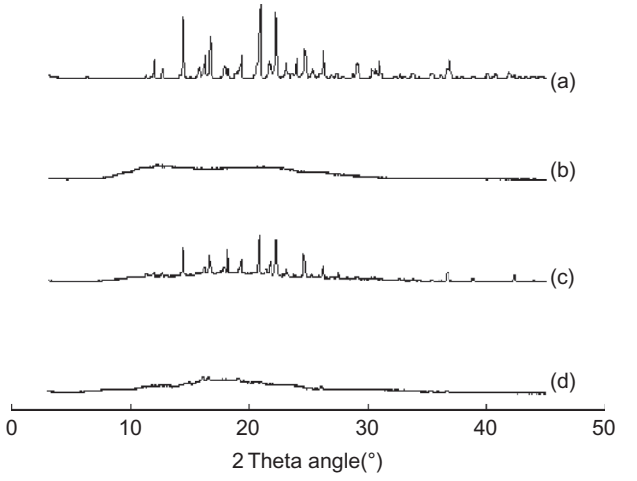

Figure 5. Powder X-ray diffraction of fenofibrate–PVP-VA system: (a) fenofibrate, (b) PVP-VA, (c) 1:2 physical mixture, (d) 1:2 extrudate.

PM were similar to that of the pure drug, suggesting the simple mixing of drugs and carriers. But to the extrudates, very weak drug peaks can be seen. As powder X-ray diffraction is a sensitive technique for crystals, it can be concluded that most of fenofibrate is dispersed in an amorphous or molecular state in Eudragit E100 and PVP-VA while little existed in microcrystal state.

Dissolution test

Fenofibrate is a poorly water-soluble drug with the dissolution of 32.9% and 31.7% at 60 minutes in distilled water containing 0.36% SDS and 0.1M HCl solution containing 0.36% SDS, respectively. Solid dispersions prepared by hot-melt extrusion have improved the dissolution of fenofibrate, which can be seen from

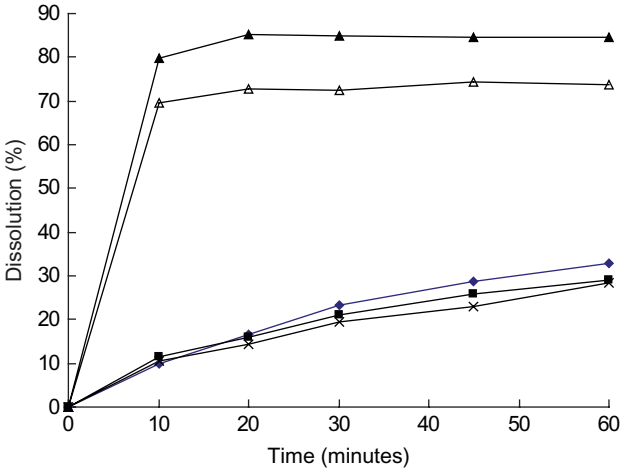

Figure 6. Dissolution profiles of fenofibrate–Eudragit E100 system in 0.1 M HCl (containing 0.36% SDS). (◆) Fenofibrate, (■) Formulation 1 PM, (▲) Formulation 1 extrudate, (×) Formulation 2 PM, (△) Formulation 2 extrudate.

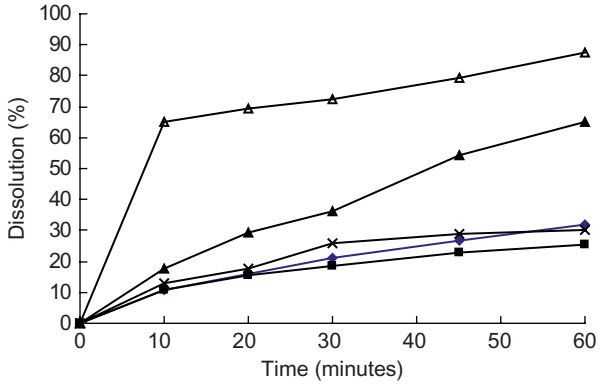

Figure 7. Dissolution profiles of fenofibrate–Eudragit E100 system in water (containing 0.36% SDS). (◆) Fenofibrate, (■) Formulation 1 PM, (▲) Formulation 1 extrudate, (×) Formulation 2 PM, (△) Formulation 2 extrudate.

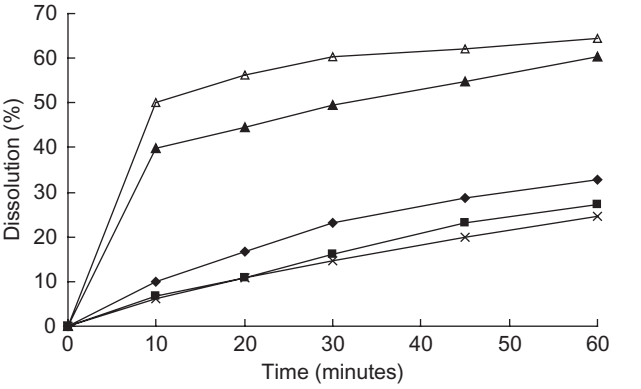

Figure 8. Dissolution profiles of fenofibrate–PVP-VA system in 0.1 M HCl (containing 0.36% SDS). (◆) Fenofibrate, (■) Formulation 3 PM, (▲) Formulation 3 extrudate, (×) Formulation 4 PM, (△) Formulation 4 extrudate.

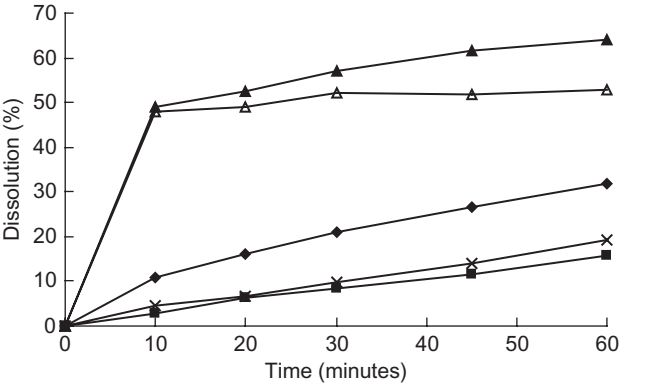

Figure 9. Dissolution profiles of fenofibrate–PVP-VA system in water (containing 0.36% SDS). (◆) Fenofibrate, (■) Formulation 3 PM, (▲) Formulation 3 extrudate, (×) Formulation 4 PM, (△) Formulation 4 extrudate.

Figures 6–9. As a common phenomenon, PM can enhance the dissolution of drug slightly, solid dispersion can improve the dissolution greatly, and the degree will increase with the rising of hydrophilic carrier's percentage, but things are very different in this research. At 60 minutes, Eudragit E100 extrudate from formulation 1 (drug to carrier ratio is 1:2) can dissolve 84.4% drug in 0.1 M HCl while the dissolution decreased to 73.6% when formulation 2 (drug to carrier ratio is 1:4) was used. When dissolution medium changed to water, things dramatically altered, and Eudragit E100 extrudate from formulation 2 has a higher dissolution than formulation 1. This phenomenon may be because of the solubility property of Eudragit E100, which can dissolve quickly in acid condition while slowly in neutral medium. When extrudate powder was placed in 0.1 M HCl, the medium dissolved the surface of powder immediately and penetrated into the powder. Then, some powder absorbed the medium and the polymer chains began to unfold, but the space was limited, leading to the winding between polymer chains, so the pasted clumping was formed. Drug encapsulated into this clumping has little chance to contact the medium. A question then appeared, that is, why the extrudate has higher dissolution than pure drug powder as the pasted clumping prevented the entering of medium and delayed the dissolving process. The following explanation may be utilized. There are two factors determining the dissolve speed: one is the pasted clumping that plays a negative role and the other is the solid dispersion effect that comes from the hydrophilic Eudragit E100 and plays a positive role. The dissolution rate depends on the balance of the two effects. The results displayed that the positive effect plays a greater role in extrudates, so that their

dissolution rates are higher than pure drug. With the increase of Eudragit E100, the negative effect offsets the enhancement partly and results in the decreasing of dissolution. As to the PM, the positive factor is the wetting effect of Eudragit E100, but this effect is too weak to balance the negative effect, so PM has a low dissolution compared with pure drug. Eudragit E100 dissolved slowly in water, and most extrudate powders had dispersed into water before their polymer chains winded with each other, so less pasted clumping was formed and the negative effect decreased greatly. As a result, 1:4 extrudate dissolved more drug than 1:2 extrudate and the dissolution of 1:4 PM is a little higher than pure drug when the medium was changed into water.

Compared with Eudragit E100, Fenofibrate–PVP-VA system has relatively low dissolution in the two dissolution mediums, indicating that the suitable carrier is Eudragit E100. After dissolution, the opposite results appeared. Fenofibrate dissolved more than formulation 3 extrudate in 0.1M HCl while little in water. As a new adjuvant, no literature has reported that the dissolution of PVP-VA exhibits pH dependency. So, equal amounts of PVP-VA were placed into the two mediums in beaker with stirring. Pasted clumping was formed in both the beakers because of the hydrophilic property of PVP-VA, but the clumping is smaller in beaker containing 0.1M HCl, which suggested that this polymer has a relatively slower dissolution rate in it. Then, it is easy to understand the dissolution results by the same consideration. PVP-VA tends to form gels in solution, and the breakdown of these hydrogels is influenced by the ionic strength of the media. The media of 0.1M HCl has stronger ionic strength than water, and the formation of hydrogel was weakened.

Bioavailability study

The plasma concentration versus time curves and pharmacokinetic parameters of solid dispersion capsule and Lipantyl capsule were shown in Figure 10 and Table 2. Obviously, solid dispersion capsule has a higher plasma concentration. After calculating, the bioavailability is 177.05%.

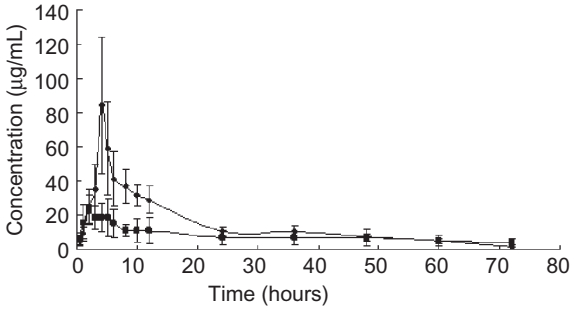

Figure 10. Mean fenofibrate plasma profiles from single-dose (200 mg), randomized, crossover bioavailability study comparing two fenofibrate capsules ($n = 6$). (◆) self-made capsule, (■) Lipanthyl® capsule.

Table 2. Pharmacokinetic parameters of fenofibrate in different dosage forms ($n = 6$).

Sample	C_{max} (μg/mL)	t_{max} (hours)	AUC_{0-72} (μg h/mL)	$AUC_{0-\infty}$ (μg h/mL)
Self-made capsule	84	4	1034	1061
Lipanthyl® capsule	23	2	584	868

As a lipophilic drug, the bioavailability and therapeutic effects of fenofibrate are related to their dissolution. There are some principles to improve the dissolution. According to Noyes–Whitney formulation, two ways can be utilized to get high dissolution. One is increasing the solid surface area or decreasing the particle diameter, the other is enhancing the solubility. For a crystal drug, it must absorb energy to overcome the lattice energy during its dissolution, if it can be turned into noncrystal state by some method, the former process is not needed and high dissolution can also be obtained. Solid solution, one type of solid dispersion, can complete the former three roles. In solid dispersion prepared by hot-melt extrusion, fenofibrate exists as the molecule state that has the largest total surface area and no lattice energy is needed when it dissolves; meanwhile, the hydrophilic carrier can improve its wettability and then the solubility in this process. Therefore, high dissolution and bioavailability are obtained. The principle of micronization technology is only to increase the surface area of drug by decreasing its particle diameter while the wettability and crystal characteristic are unchanged. This technology may be efficient to some poorly water-soluble drugs but will have little effect on insoluble drugs such as fenofibrate.

Conclusions

Hot-melt extrusion is an excellent technique in preparing fenofibrate solid dispersion and can make most of drugs into noncrystal state in Eudragit E100 and PVP-VA carrier. Eudragit E100 extrudate with higher carrier ratio has a lower dissolution in 0.1M HCl and higher dissolution in water. On the contrary, the dissolution of PVP-VA extrudate increased as the carrier ratio increased in 0.1M HCl while decreased in water. Solid dispersion from Eudragit E100 has higher dissolutions than PVP-VA. The different dissolution of fenofibrate from the two polymers is because of their different solubility and gelling tendency. Compared with micronization technology, hot-melt extrusion can improve the bioavailability of fenofibrate greatly.

Declaration of interest

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

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