Improving the Solubility and Bioavailability of Pemaflbrate via a New Polymorph Form II

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ABSTRACT: Pemaflbrate is a new generation of anti-hyperlipidemia drugs. However, its poor solubility in water (0.410 mg/mL at 25 °C) has limited its oral bioavailability. In this study, we aimed to improve the solubility and consequently the oral bioavailability of pemaflbrate via a new polymorph. A new polymorph Form II was successfully obtained by controlling the crystallization temperature and characterized by multiple analysis methods. The thermodynamic properties of Form I and Form II are almost the same, the melting points of crystal Form I [differential scanning calorimetry (DSC) onset: 97.5 °C, melting entropy: −76 J/g] and crystal Form II (DSC onset: 96.6 °C, melting entropy: −80 J/g) are very close, and the crystallinity of both is very high. In pure water, Form II is about 1.9 times that of Form I in terms of the intrinsic dissolution rate (IDR) and powder solubility. In medium, the IDR characterization was performed in a pH 6.8 buffer. The solubility of this Form II in 0.1 M HCl (pH 1.0) and phosphate buffers (pH 6.8) was investigated, and the results showed that the solubility of Form II was 2.1 and 2.0 times that of Form I, respectively. The crystal structure of Form II shows that the hydrophilic carboxyl groups of the compound are arranged outside the unit cell, which may be the reason for the increased solubility. We also studied the pharmacokinetics of beagle dogs. The mean AUC0−24h of Form II is about 2.6 times that of Form I, indicating that the solubility and bioavailability of pemaflbrate can indeed be improved by forming the new polymorph Form II. It may become an ideal solid form of active pharmaceutically ingredient suitable for pharmaceutical preparations, and it can be further studied in the later period.

INTRODUCTION

In recent years, the research on polymorphs has become increasingly fierce, especially in the pharmaceutical industry.1−3 In the pharmaceutical field, a drug polymorph means that the same drug is affected by crystallization conditions during the crystallization process, resulting in different internal molecular arrangement structures, leading to the diversity of drug crystallinity. To the best of our knowledge, there are polymorphic, amorphous, salt-forming, and cocrystal methods for changing the properties, especially solubility of pharmaceutical active ingredients.4−10 Although amorphous drugs can improve certain solubility, their stability is generally problematic. Although salt formation can greatly improve the solubility of drugs, there are certain requirements for the degree of ionization. Although the cocystal can improve the solubility,11−25 it will introduce other ligands besides the active ingredient of the drug and requires intermolecular forces between the ligand and the drug molecule. Polymorphs can change the solubility, bioavailability, and solid stability of the drug. It does not require ionizable groups or the introduction of other ligands. A peroxisome proliferator-activated receptor (PPAR) is known as a member of the nuclear receptor family, and it is known that there are currently three sub types of ruthenium and osmium.26−30 Activated PPAR α can treat hyperlipidemia,31−34 activation of PPAR γ causes obesity,
The poor solubility in water (0.410 mg/mL at 25 °C) has limited its oral bioavailability. This paper reports a new type of anhydrous type Form II, which has higher solubility than the reported crystal Form I. The thermodynamic properties of Form I and Form II are almost the same, the melting points of crystal Form I [differential scanning calorimetry (DSC) onset: 97.5 °C, melting entropy: −76 J/g] and crystal Form II (DSC onset: 96.6 °C, melting entropy: −80 J/g) are very close, and the crystallinity of both is very high. The appearance of this new crystal form can provide a new choice for formulation research.

RESULTS AND DISCUSSION

Crystal Structure. Single-crystal X-ray analysis of new Form II reveals that the structure of new Form II belongs to the monoclinic, P21 space group. The pemafibrate molecule contains one hydrogen bond donor groups (the carboxylic acid) and one acceptor groups (the benzoxazol aromatic nitrogen). The hydrogen bond between the carboxylic acid and the benzoxazol aromatic nitrogen linked molecules together to be a 1-D line (Figure 1). Besides the classical hydrogen bonds, the C−H···O interactions really exist, the van der Waals’ forces between the benzene CH and the methoxy linked the 1-D line to be a 2-D supermolecular layer (Figure 2). There are many π−π stacking interactions existing in the crystal. The π−π
stacking interactions also exist between two benzene rings of pemafibrate from different 2-D layers [3.704(4) Å, 0.000(4)°], which connected these 2-D layers to be a 3-D supramolecular structure (Figure 3). In the crystal Form II, the hydrophilic carboxyl groups of the compound are arranged outside the unit cell, which can increase the contact area between carboxyl groups and water molecules. The carboxyl groups can form hydrogen bonds with water molecules to increase the solubility of molecules, which may have a great effect on improving the solubility of the compound.

**Powder X-ray Diffraction and Thermal Analyses.** Powder X-ray diffraction (PXRD) was used to check the crystalline phase purity of new Form II. The result shows that all the peaks displayed in the measured pattern of new Form II closely match those in the simulated pattern generated from single-crystal diffraction data and completely different from the PXRD pattern of the reported Form I (Figure 4), demonstrating the formation of pure crystalline phase of the new form. The DSC and thermogravimetric analysis (TGA) curves of new Form II are shown in Figures 5 and 6. From these figures, it can be found that new Form II melts at 96 °C and then the new form starts to decompose at the temperature of 220 °C. From Figure 5, we can see that the thermodynamic properties of Form I and Form II are almost the same, the melting points of crystal Form I and crystal Form II are very close.

**Powder Dissolution and IDR Studies.** The powder solubility of the drug substance has a great impact on the design of the formulation and the bioavailability of the drug. This is an important parameter that must be considered in drug development. The powder solubility curve of new Form II and the reported Form I in pH 1.0 hydrochloric acid solution and pH 6.8 phosphate-buffered saline (PBS) are shown in Figure 7. It can be seen from the curve that the solubility and dissolution rate of new Form II are much larger than that of the reported Form I, and it can be seen that the solubility can indeed be improved after becoming a new polymorph. The maximum solubility of new Form II in pH 1.0 hydrochloric acid solution and pH 6.8 PBS is 2.2 times and 2.0 times as large as those of Form I. It can be found from the curve that Form II reaches the maximum solubility of pemafibrate quickly, then reaches a plateau, and is always higher than the solubility of Form I. This solubility curve is very suitable for the pharmaceutical industry.

As far as we know, the intrinsic dissolution rate (IDR) of a drug has a great correlation with the absorption kinetics of the drug in the body. In order to obtain the data of the IDR of the drug, Form II and Form I were tested in pH 6.8 PBS. Several sampling tests were carried out within an hour. It can also be found from the curve (Figure 8) that the linear correlation of Form II ($R^2 = 0.992$) and Form I ($R^2 = 0.996$) are very good. It can be seen from the curve that the IDR of Form II is much greater than that of Form I. The above experiment results show that the new polymorph Form II can be used as a potential drug crystal for improving solubility and solubility rate in pemafibrate formulations.

**Pharmacokinetics in Beagle Dogs Plasma.** Generally speaking, the increase in the powder solubility and IDR of the drug will help to improve the bioavailability of the drug in vivo. It can be seen from the experimental results of the powder solubility and IDR of Form II and Form I that the solubility and IDR of pemafibrate drugs have been greatly improved after the formation of the new polymorph Form II. In order to verify
whether this increase is helpful for the increase in the bioavailability of pemafibrate in vivo, we designed and conducted a beagle pharmacokinetics experiments. The experiments show that the beagle group taking Form II and the beagle group taking Form I have almost the same $T_{\text{max}}$, and the AUC$_{0-24h}$ and $C_{\text{max}}$ of the beagle taking Form II are more than 2.6 times that of the beagle taking Form I (Table 1). From mean plasma concentrations versus time profiles (Figure 9), it can be known that between 0 and 1 h, the blood drug concentration of beagle dogs taking Form II is very high, which is very helpful for the treatment of diseases, and between 1 and 24 h, the blood drug concentration of beagle dogs taking Form II has decreased a lot, but it is still much higher than that of beagle dogs taking Form I. It can be seen from these experimental results that after the formation of new polymorph Form II, the powder solubility, intrinsic dissolution, and bioavailability in vivo are greatly improved. These results have greatly encouraged the continued development of pemafibrate drugs.

**Stability Test.** The new form and the reported crystal form were subjected to stability tests under conditions of high temperature, high humidity, and light. The results showed that for the new form and the reported crystal form, the same degree of degradation occurs under illumination, and both forms are stable under high temperature, high humidity, and light conditions. Both crystal forms have not changed after a 30-days stability test. The results are shown in Table 2. Through other water suspension experiments, we also found that the above two crystal forms did not change after being suspended in an aqueous solution at 37 °C for 12 h, and both forms were quite stable in water.

**Dynamic Vapor Sorption.** Although pemafibrate forms a new polymorph Form II, the increase in solubility, IDR, and bioavailability is very interesting, will this increase greatly
improve the hygroscopicity of active pharmaceutical ingredient (API) solids and affect their storage and preparation processes?

Therefore, we conducted dynamic vapor sorption (DVS) tests on Form II and Form I to obtain their moisture absorption data. It can be seen from Figure 10 that after forming the new polymorph, the moisture absorption of Form II in the

Table 2. Stability Data for Form I and Form II

| crystal form | test condition | 0 days | 30 days |
|--------------|----------------|--------|---------|
| Form II      | 60 °C PXRD/Form II chemistry purity: 99.65% | PXRD/Form II purity: 99.19% | 92.5% RH PXRD/Form II purity: 99.32% | 92.5% RH PXRD/Form II purity: 99.75% |
| Form I       | 60 °C PXRD/Form I chemistry purity: 99.72% | PXRD/Form I purity: 99.35% | 92.5% RH PXRD/Form I purity: 99.38% | 92.5% RH PXRD/Form I purity: 99.69% |

Table 1. Mean Pharmacokinetics Parameters of Form I and Form II in Male Beagle Dogs

| parameter     | Form I         | Form II        |
|---------------|----------------|----------------|
| AUC_{0-24h} (h-ng/mL) | 360            | 926            |
| C_{max} (ng/mL)      | 52             | 110            |
| T_{max} (h)        | 1.12           | 1.25           |

Figure 9. Mean plasma concentrations versus time profiles of pemaflibrate following oral administration of Form I (red square) and Form II (black circle) in male beagle dogs. Each point represents the mean ± SD (n = 3).

Figure 10. DVS isotherm plots for Form II and Form I at 25 °C.
humidity range of 0–90% is about 2 times higher than that of Form I. Although the hygroscopicity has been greatly improved, its actual value is still very low (<0.2%). In the pharmaceutical industry, this value indicates that it has no hygroscopicity. So, Form II and Form I still show non-hygroscopicity after forming a new polymorph. This property indicates that the new polymorph Form II is very suitable for use as a pharmaceutical preparation.

## CONCLUSIONS

For pemafibrate, a poorly soluble drug, we carried out a crystal engineering design on it, hoping to obtain a solid with improved solubility and bioavailability. After conducting the experiment, we successfully obtained a new polymorph Form II. For this new polymorph, we performed element analysis, thermal analysis, and PXRD detection. Its single-crystal structure shows that there are many intermolecular hydrogen bonding forces in the new polymorph molecule, so that new Form II molecule can exist stably. Not only that, the powder solubility, IDR, and in vivo pharmacokinetics data of Form II have been greatly improved compared with Form I. Meanwhile, the hygroscopicity experiment after forming the new polymorph shows that it has almost no hygroscopicity, which is very beneficial for the storage of API and the production and preparation process of the formulation. In short, the acquisition of the new polymorph is of great significance for the subsequent development of the drug pemafibrate. Not only that, these findings also provide a good reference for the development of other innovative drugs.

## EXPERIMENTAL SECTION

**Materials and General Methods.** Pemafibrate (>99%) was obtained from Sichuan Kelun Pharmaceutical Research Institute Co., Ltd. Methanol and acetonitrile of high-performance liquid chromatography (HPLC) grade were purchased from Merck. All the other reagents were of analytical grade and commercially available without further purification. Elemental analyses were characterized by an PerkinElmer 2400 II elemental analyzer. TGA was recorded on a TGA (Mettler Toledo) instrument with a heating rate of 10 °C/min. DSC was recorded on a DSC1 (Mettler Toledo) instrument with a heating rate of 10 °C/min. PXRD patterns were obtained on a PANalytical Xpert3 powder diffractometer with Cu Kα radiation (45 kV, 40 mA).

**Preparation of New Form II.** A sample of 5.0 g of pemafibrate was weighed and heated to 70 °C in a mixed solvent of 30 mL of cyclohexane and 15 mL of ethyl acetate to dissolve and clarify, the temperature was lowered to 45 °C, reslurried for 24 h, filtered, and dried to collect a solid. Anal. Calcd for C28H30N2O6: C, 68.49; H, 6.11; N, 5.71%. Found: C, 68.53; H, 6.14; N, 5.63%.

**Preparation of the Reported Form I.** A sample of 5.0 g of pemafibrate was weighed and heated to 60 °C in a mixed solvent of 45 mL of ethyl acetate and 20 mL of n-heptane to dissolve and clarify, reduced to 25 °C, crystallized for 2 h, and 70 mL of n-heptane was added to stir and crystallize for 2 h, filtered, and dried to collect a solid. Anal. Calcd for C28H30N2O6: C, 68.49; H, 6.11; N, 5.71%. Found: C, 68.56; H, 6.06; N, 5.55%.

**Single-Crystal X-ray Diffraction.** Single-crystal X-ray diffraction data for Form II was collected on a Xcalibur Eos diffractometer system with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal was kept at 293.15 K during data collection. Using Olex2, the structure was solved with the Superflip14–16 structure solution program using charge flipping and refined with the ShelXL refinement package using least squares minimization. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were set in calculated positions and refined by a riding mode, with a common thermal parameter. The crystallographic data and experimental details for the structure analysis are summarized in Table 3, and the hydrogen bonding distances and angles are given in Table 4.

| Table 3. Experimental Data for New Form II |
|-------------------------------------------|
| **compounds** | Form II |
| **empirical formula** | C28H30N2O6 |
| **formula weight** | 490.54 |
| **temperature/K** | 293.15 |
| **crystal system** | Monoclinic |
| **space group** | P21 |
| **a/Å** | 11.6007(8) |
| **b/Å** | 5.3802(3) |
| **c/Å** | 20.9518(16) |
| **α/deg** | 90 |
| **β/deg** | 105.418(8) |
| **γ/deg** | 90 |
| **volume/Å³** | 1260.63(16) |
| **Z** | 2 |
| **ρ(calcd)(g/cm³)** | 1.292 |
| **F(000)** | 520.0 |
| **index ranges** | −14 ≤ h ≤ 13, −6 ≤ k ≤ 6, −26 ≤ l ≤ 25 |
| **independent reflections** | 4664 [Rw = 0.0195, Rsme = 0.0421] |
| **goodness-of-fit on F²** | 1.052 |
| **final R indices [I ≥ 2σ (I)]** | R₁ = 0.0633, wR₂ = 0.1350 |
| **final R indices [all data]** | R₁ = 0.0927, wR₂ = 0.1534 |
| **largest diff. peak/hole/e Å⁻³** | 0.60/-0.34 |
| **flack parameter** | −0.09(4) |

| Table 4. Hydrogen Bond Distances and Angles for New Form II |
|-----------------------------------------------|
| **D–H···A** | **d(D–A)** (Å) | **∠(DHA)** (deg) | **symmetry codes** |
| O(4)–H(4I)···N(1) | 1.857(3) | 165.1 | x − 1, y, z |

**Powder Dissolution Experiments.** Pemafibrate new Form II and reported Form I were ground to obtain a fine powder, sieving with multiple screens, and the powder with size in the range of 58–115 μm was collected for the powder solubility test. 100 mg new Form II powder and 100 mg reported Form I powder were thrown into the solution of hydrochloric acid medium (50 mL, 0.1 M, pH 1.0) and PBS (50 mL, 0.02 M, pH 8.0) to ensure that the solids can be completely dissolved. The obtained solution was filtered, diluted, and placed in the HPLC column (Agilent 1260) for detection with a wavelength of 254 nm. The analytical column was XBridge C18 (4.6 × 150 mm, 3.5 μm). The column temperature was 30 °C, injection volume was 20 μL, and the injection concentration was 0.2 mg/mL with dipropylamine hydrogen phosphate buffer solution (20 mM, pH 10.5) (elucent A) and acetonitrile (elucent B) at a flow rate of 1.0 mL/min. The gradient elution program started with 20% B, 0% A, 2 min, ramped to 70% B in 5 min, held for 5 min, and then ramped to 100% B in 0.5 min, and held for 5 min.
keeps it for 3 min, increases to 40% within 13 min, increases to 80% within 3 min, keeps it for 3 min, then reduces to 25% within 3 min and keeps it for 3 min.

**Pharmacokinetics in Beagle Dogs Plasma.** The male beagle dogs used in the experiment were provided by the animal research center of Sichuan Kelun Pharmaceutical Research Institute Co., Ltd. All animal experiments were carried out in accordance with institutional guidelines in compliance with regulations formulated by Sichuan Kelun Pharmaceutical Research Institute Co., Ltd. The experimental protocol was approved by the Institutional Animal Care and Use Committee of Sichuan Kelun Pharmaceutical Research Institute Co., Ltd. The pharmacokinetics experiments used six male beagle dogs, all weighing around 15 kg, new Form II and after equilibrium at 25 °C for 1 h. The DVS experiment was performed on a DVS intrinsic instrument (Surface Measurement Systems, UK). The dried sample was placed in a nitrogen environment and after equilibrium at 25 °C for 1 h. The DVS experiment was started. The relative humidity is gradually increased from 0% to 90% with an interval of 10%, and the balance time is 3 min, then reduces to 25% within 3 min and keeps it for 3 min.

**Dynamic Vapor Sorption.** DVS study was performed on a DVS intrinsic instrument (Surface Measurement Systems, U.K.). The dried sample was placed in a nitrogen environment and after equilibrium at 25 °C for 1 h. The DVS experiment was started. The relative humidity is gradually increased from 0% to 90% within 15 kg, new Form II and reported Form I were administered orally to the beagle dogs at a specification of 1 mg/kg. After oral administration, at the following time intervals: 0.2, 0.5, 0.8, 1.1, 1.5, 3, 8, and 24 h, blood samples were taken. The blood (10 min, 5000 rpm) was centrifuged and stored at −70 °C. The supernatant was taken and mixed with the methanol/water mixture (1:1) and injected for LC−MS/MS analysis (Agilent 6120B).

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**ASSOCIATED CONTENT**

*Supporting Information* The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04005.

Crystallographic data of CCDC 1973432 (CIF).

Datablock CIF checklist (PDF).

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**Notes**

The authors declare no competing financial interest. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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