Drug Development and Industrial Pharmacy, 2009; 35(7): 827–833

informa
healthcare

ORIGINAL ARTICLE

Preparation of fenofibrate nanosuspension and study of its pharmacokinetic behavior in rats

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Abstract

Background: In this study, nanosuspension was prepared to improve the dissolution rate and bioavailability of lipophilic fenofibrate. *Method*: Melt emulsification method combined with high-pressure homogenization was adapted, and mixture of poloxamer188 and PVP K30 were selected as surfactants. This method consumed less energy and was more efficient than traditional homogenization of drug solid particles suspension directly. *Results*: The dissolution rate of fenofibrate nanosuspension was increased obviously, and the product was evaluated by pharmacokinetic characteristic in rats. The $AUC_{0-36\ h}$ and C_{max} of nanosuspensions were increased when compared with the reference formulations. No significant differences were found between the two nanosuspensions A and B, of which the mean particle sizes were 356 and 194 nm, respectively. Therefore, nanosuspensions may be a suitable delivery system to improve the bioavailability of those drugs with poor water solubility.

Key words: *Fenofibrate; high-pressure homogenization; melt emulsification; nanosuspension; pharmacokinetic*

Introduction

An increasing number of newly developed drugs show bioavailability problems because of poor water solubility. At present about 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble[1]. These poorly soluble drugs require innovative formulation approaches to reach a sufficiently high bioavailability after oral administration or make them available in intravenous injection formulations[2]. The solubility and dissolution behavior of a drug is the key determinant to its oral bioavailability[3,4].

The development of dosage forms of poorly water-soluble drugs is always difficult, especially for the drugs that are poorly soluble in both aqueous and organic media. These drugs when administered from the gastrointestinal tract show irregular absorption and low bioavailability. Micronization technique was used to raise the dissolution and bioavailability[5]. However, the effectiveness of this technology is limited. Nowadays, many of the new drugs are very poor soluble that micronization does not lead to a sufficiently bioavailability enhancement.

Nanosuspension may help to overcome these problems[6]. Pharmaceutical nanosuspensions consist of dispersed drug particles in an aqueous vehicle in the presence of some suitable surfactants[7]. It is a colloidal drug delivery system in which the average particle sizes are less than 1 μm. The major advantages of nanosuspension technology are the increase of saturation solubility and consequently the increase in the dissolution rate of the drug[8]. The existing technologies include the so-called 'bottom up' and the 'top down' technologies. The bottom-up technology dissolves the drug in solvent, and then precipitates it by adding the solvent to a nonsolvent[9]. These techniques are low efficiency and not widely used for production. The top-down technologies are disintegration methods[10,11]. Nowadays the productions of drug nanoparticles mainly focus on high-pressure homogenization. This formulation is prepared by passing a drug microparticle suspension under high pressure through a small homogenization gap. The cavitation forces disintegrate the drug particles to nanoparticles[12]. Homogenization is also used as a combination process of some formulations following precipitation or emulsification to reduce the particle

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(Received 18 Aug 2008; accepted 10 Nov 2008)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040802623941

diameter distribution and avoid Ostwald ripening[10,13]. The drug nanaosuspensions can be given to the patients by oral administration or intravenous injection. To be convenient, liquid nanosuspensions can be transferred to solid dosage forms, e.g., tablets or pellets or capsules with granule[14].

In this study, fenofibrate was chosen as model compound that had been extensively used to lower cholesterol levels. Fenofibrate is practically insoluble in water (0.3 μg/mL at 37°C) and has high lipophilicity. Thus, the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract[15,16]. Attempts to increase the oral bioavailability of the drug therefore focus on particle size reduction. The melt emulsification method and high-pressure homogenization were employed to produce fenofibrate nanosuspension[17]. Compared with the traditional homogenization process of solid particles suspension directly, melt emulsification method combined with high-pressure homogenization had less energy consumption and was more efficient. No organic solvents were used in this formulation. We selected the surfactants and optimized the parameters of homogenization procedure (pressure, number of homogenization cycles) to produce stable nanosuspension with small and narrow-distributed sizes. The combination of poloxamer188 and PVP K30 as surfactants yields nanosuspensions with the smallest average particle size. The formulation of nanosuspension enhanced dissolution rate of fenofibrate greatly. The increase of dissolution rate may favorably affect the bioavailability of the drug and then reduce the dosage[18].

Nanosuspension was considered to be profit to the bioavailability promotion of poor water-soluble drugs. To confirm this viewpoint, in this study, the pharmacokinetics of two formulations of fenofibrate nanosuspensions A and B (with the particle size of 356 and 194 nm, respectively) in comparison with two suspensions containing micronized (5–10 μm) drug and coarse drug (120–150 μm) powder following intragastric administration were investigated in rats.

Materials and methods

Materials

Fenofibrate and fenofibric acid were obtained from NhwaPharma Corporation (Xuzhou, Jiangsu, China). Poloxamer188 (Lutrol F68) was given from Nan-Jing Weller (Nanjing, China). Polyvinylpyrrolidone (PVP) K30 and Tween 80 (polysorbate 80) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Sodium dodecyl sulfate (SDS) was from Shanghai lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Polyvinyl alcohol (PVA) was from Xinyi Chemical Co., Ltd. (Guangzhou, Guangdong, China). Sodium carboxymethyl cellulose (CMC-Na) was from Xilong Chemical Co., Ltd. (Guangzhou, Guangdong, China). Sodium deoxycholate was from Shanghai Kefeng Chemical Reagent Co., Ltd. (Shanghai, China).

Preparation of fenofibrate nanosuspension

About 0.5 g fenofibrate was added to 100 mL aqueous solution of 3–6% (w/v) surfactants. The suspension was heated above the melting point of fenofibrate (approximately 82°C) and emulsionized with Ultra Turrax T25 (IKA, Breisgau-Hochschwarzwald, Germany) at 10,000 rpm for 5 minutes to give an emulsion. It was transferred into a high-pressure homogenizer and firstly homogenized at 300 and 500 bar for five cycles, then the pressure was raised to 800 bar and homogenized for 10 cycles. Before homogenization, the homogenizer should be heated with hot water, and during this process, the sample holder of the high-pressure homogenizer was wrapped with a heating overcoat equipped with temperature controller and the temperature of emulsion was maintained above the melting point of the drug. At last, the nanoemulsion was then cooled in an ice-bath immediately to form nanosuspension.

Lyophilization of nanosuspensions

The nanosuspension was freeze dried immediately after preparation. Twenty milliliter of nanosuspension was placed in 100 mL glass flask, rapidly frozen in −86°C freezer and freeze-dried using a YO-230 freeze drier (Thermo Savant, Waltham, MA, USA) at a vacuum degree of 200 Pa, −30°C for 36 hours to yield dry sample.

Particle size and shape characterization of nanosuspensions

Size and size distribution (polydispersity index, PI) of the particles in fenofibrate nanosuspension following the different homogenization conditions were determined by Zetasizer 3000 (Malvern Instruments, Worcestershire, UK), and the diameters reported were calculated using volume distribution. Zeta potential of nanosuspension system was determined by zeta potential equipment (Brookhaven, NY, USA). Morphological evaluation of nanoparticles was conducted through scanning electron microscopy (SEM) (JSM-5900, JEOL Ltd., Tokyo, Japan) following platinum coating.

Differential scanning calorimetry

Thermal properties of the powder samples were investigated with a differential scanning calorimeter (DSC) (NETZSCH DSC-204, Geretsrieder, Waldkraiburg,

Germany). Accurately weighed samples (5–8 mg) were placed in perforated aluminum-sealed pans. Heat running for each sample has been set from 30°C to 150°C at 10 K/min, with nitrogen as blanket gas.

Dissolution

Dissolution testing of different formulations of fenofibrate samples containing a known amount of fenofibrate (25 mg) was performed using a ZRS-8G dissolution apparatus (paddle method) (Tianda Technology Co., Ltd., Tianjin, China). The rotation speed of the paddles was set to 100 rpm. About 900 mL of 1.0% SDS at 37 ± 0.5°C was used as the dissolution medium. At predetermined time intervals 5 mL samples were withdrawn, filtered through 0.22 μm membrane immediately, and 5 mL blank dissolution medium was added for replenishing of the dissolution medium, respectively. The amount of dissolved drug was determined at 291 nm using a TU-1901 spectrophotometer (Purkinje General, Beijing, China). The mean results and the standard deviation were reported.

Animals and dosing

Male SD rats (weight 220–270 g, Shanghai, China) were used in the test (six rats every group). The animals should be familiar with the environment for a few days before the experiment. Food was withdrawn 12 hours before the beginning of the study. Saline was supplemented to rats freely during the experiment. Two freshly prepared fenofibrate nanosuspensions A and B with the particle diameter of 356 nm (PI = 0.19) and 194 nm (PI = 0.25), respectively, and two suspensions containing micronized (5–10 μm) and course (120–150 μm) drug powder were used. Each group was administered by gavage with one of the formulations. The two formulations with micronized and coarse fenofibrate were uniformly suspended in an aqueous surfactant solution before administration to eliminate relative error corresponding to nanosuspensions. The administration dose was 27 mg/kg body weight. Blood (500 μL) was sampled by capillary tube puncture from the orbital sinus veins at the following predetermine time: 5, 10, 20, and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 22, and 36 hours after administration. Plasma was obtained from whole blood by centrifugation at 625 × *g*, 4°C. The plasma samples were frozen at −20°C until analysis by high-performance liquid chromatography (HPLC).

HPLC analysis

Fenofibrate is metabolized to the main active metabolite fenofibric acid by plasma and tissue esterases. In this study, fenofibric acid was determined using HPLC-UV. Chromatography condition: Pump, UV-detector (DIONEX, Sunnyvale, CA, USA) and a C18 column (5 μm, 4.6 mm × 15 cm, Lichrosorb) (DIKMA Diamonsil, Beijing, China) were used. Mobile phase was composed of methanol and 0.5% phosphoric acid solution (82:28, v/v, pH 3.2). The flow rate was 1.0 mL/min. UV-detection wavelength was 286 nm. About 200 μL acetonitrile was added to 100 μL plasma sample. The mixture was vortexed for 30 seconds. Then the sample was centrifuged at 10,000 × *g* for 15 minutes. About 50 μL clear supernatant was pipetted and injected into the HPLC system. At last the chromatograms were analyzed with Chromeleon Software.

Data analysis

Pharmacokinetic parameters (±SD) were calculated using the pharmacokinetic software 3P97. Statistical analysis comparisons between groups were made using ANOVA by Microsoft Excel and multiple comparisons were performed using SPSS software at the 0.05 level for independent groups.

Results and discussion

In this study, emulsification method that was normally used to produce emulsions was adapted to prepare fenofibrate nanosuspension. Firstly, the drug sample should be heated above its melt point, so the selected drug melt point should be not too high and the drug has good thermostability. After emulsification the hot emulsion was homogenized in high-pressure homogenizer and the drops diminished under the cavitations, then the melted drug was transferred into the solid state. The production was a suspension of drug nanoparticles in a liquid, the so-called nanosuspension. Because the drug was presented as liquid drops following melt emulsification, the homogenization process was much easier for liquid drops than solid particles. In this process, the collision and fusion of droplets should be prevented. The particle size of the nanosuspension was mostly dependent on the size of droplets after high-pressure homogenization. Fast cooling with an ice-bath caused fast solidification and resulted in smaller drug particles compared with cooling slowly to room temperature. This viewpoint was also verified by P. Kocbek et al.[17]. The mean particle size and PI of fenofibrate nanosuspensions were determined by photon correlation spectroscopy (PCS) to qualify the productions. The homogenization conditions had different influence on nanosuspensions size. As presented in Figure 1, when the pressure was 800 bar and the homogenization cycles were 10 times, the mean particle size was below 400 nm. When the pressure achieved 1500 bar, the

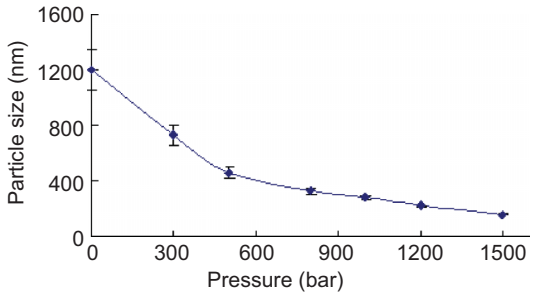

Figure 1. Influence of homogenization pressure on particle size ($n = 5$, means ± SD). The homogenization cycles were 10 times.

nanosuspension with mean diameter less than 200 nm was obtained. We fixed the pressure as 800 bar; the influence of homogenization cycles on the particle size and PI were shown in Figure 2. The cycle number was at least 10–12 when the particle sizes and PI were suitable. A. Hanafy et al.[19] prepared fenofibrate nanosuspension by high-pressure homogenization with 1500 bar for 4 hours and the mean particles size was 400 nm. Because of its simple and high-performance, the melt emulsification method combined with high-pressure homogenization was employed in this study.

Surfactants were one of the most important factors of the stability of fenofibrate nanosuspensions, which should offer sufficient affinity for the droplet surface to stabilize the emulsion system and the subsequent nanosuspension. In preliminary experiments, we selected the surfactants that were most frequently used, such as Poloxamer188, PVP, Tween 80, SDS, CMC-Na, and PVA. To optimize the electrostatic stabilizer in the nanosuspension, we selected an ionic surfactant sodium deoxycholate for the preparation. The size, PI, and zeta potential of nanosuspensions were determined as evaluation index. On the basis of the results, the combination of poloxamer188 and PVP K30 were optimized as surfactants. These two polymers have good surface affinity and could form a substantial mechanical and thermodynamic barrier at the interface. In addition, poloxamer188 and PVP K30 are in solid state at room temperature, so this feature will profit the freeze-dried or spray-dried fenofibrate nanosuspensions. The proportion of poloxamer188 to PVP K30 and the proportion of surfactants to fenofibrate were optimized. The drug and surfactant concentration were fixed (0.5%, 1.5%, w/v) when the influence of the proportion of poloxamer188 to PVP was investigated at the same homogenization condition as described in Section 'Preparation of fenofibrate nanosuspension'. The particle size was small relatively as the proportion extent was 3:1–2:1 (Figure 3). We also investigated the influence of the proportion of surfactant to fenofibrate on particle size when the drug concentration was fixed (0.5%, w/v) (Figure 4). The optimized proportion was 3:1–6:1. If the drug concentration increased greatly, the drug particle number in unit volume increased. The proportion of surfactant to fenofibrate should increase correspondingly to keep the nanosuspension stable.

The mean particle size and PI of fenofibrate nanosuspension produced as described in Section 'Preparation of fenofibrate nanosuspension' were determined using PCS. The average particle size was 356 nm and the PI was 0.19. The zeta potential was −46 mV, which was valid to stabilize

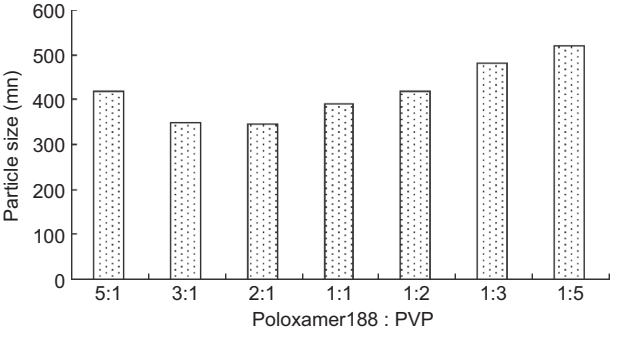

Figure 3. Influence of the proportion of poloxamer188 to PVP on particle size. The drug and surfactant concentration were fixed at 0.5% and 1.5 % (w/v). Each sample was homogenized at 800 bar for 10 cycles.

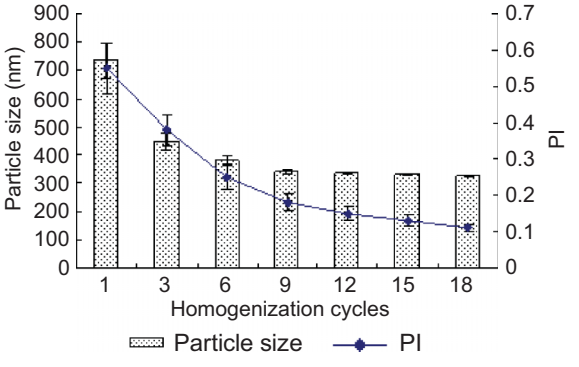

Figure 2. Influence of homogenization cycles on particle size and PI ($n = 5$, means ± SD). The homogenization pressure was 800 bar.

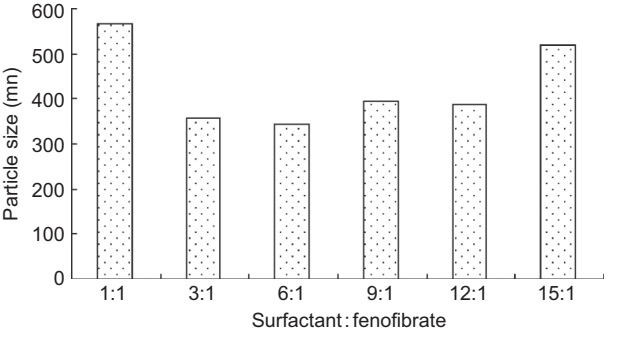

Figure 4. Influence of the proportion of surfactant and fenofibrate on particle size. The drug concentration was fixed at 0.5% (w/v). Each sample was homogenized at 800 bar for 10 cycles.

fenofibrate nanosuspension. The nanoparticles were clearly observed on SEM micrographs of Figure 5.

Because fenofibrate was melted during the production process, the drug crystalline structure may be transferred to amorphous form. This viewpoint was confirmed using DSC. As it was shown on the DSC thermograms of Figure 6, crude fenofibrate powder presented a sharp melting peak at about 77°C, which was absent in fenofibrate nanosuspension freeze-dried powder. It suggested that fenofibrate crystalline in freeze-dried powder might be changed. But the physical mixture of fenofibrate and surfactants demonstrated a significant reduction in the peak at 77°C. Its characteristics were more similar to freeze-dried powder with only some residual solid with the melting characteristics of fenofibrate. This phenomenon indicated that the presence of surfactants might have an influence on the fenofibrate crystalline state during the melting process.

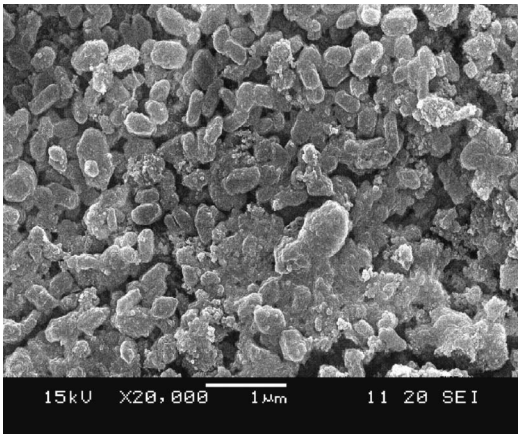

Figure 5. SEM imaging of fenofibrate nanoparticle (×20,000).

Dissolution profiles for fenofibrate coarse suspension, micronized suspension, and nanosuspension (356 nm, PI = 0.19) were shown in Figure 7. Comparison of the profiles obtained from dissolution clearly showed the great dissolution rate enhancement of the nanosuspension systems. For nanosuspension, about 74.1% of the drug was dissolved within 5 minutes when micronized suspension was only 6.5% and coarse suspension was 2.3%. Two hours later, 90.62% of the drug dissolved for nanosuspension when 34.9% for coarse suspension and 70.7% for micronized suspension. Surfactants were shown to only slightly enhance the dissolution of fenofibrate as confirmed by stirring the physical mixture suspension for 8 hours with a magnetic stirrer. The decrease in particle size accompanied by a surface area increasing mainly yielded the increase of dissolution rate of the drug.

Average plasma concentration–time curves of fenofibric acid following intragastric administration were shown in Figure 8. The plasma concentration–time profiles can be fitted by classical compartment model 1, and the pharmacokinetic parameters were calculated, which are presented in Table 1. On the basis of the comparison of the $AUC_{0\text{–}36\ h}$ values, the micronized suspension showed higher bioavailability than the coarse suspension and significantly lower bioavailability than nanosuspensions ($P<0.01$). In terms of C_{max}, the maximum concentration of the coarse suspension was significantly lower than the others ($P<0.01$). Compared to micronized suspension, the maximum concentrations of nanosuspensions were about twofold ($P<0.01$) as summarized in Table 1. With respect to T_{max}, the average parameter of either nanosuspension A or B was lower than 2 hours whereas the micronized

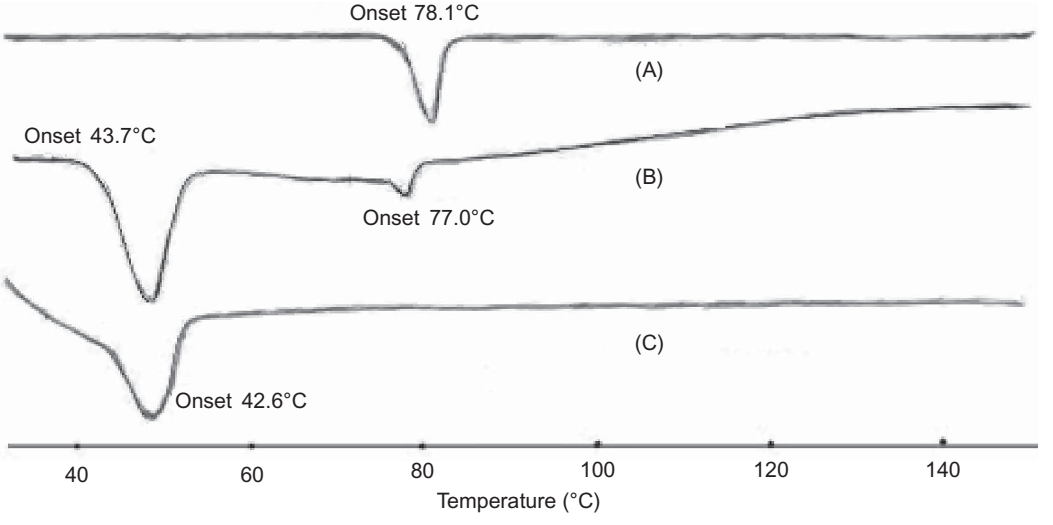

Figure 6. Differential scanning capacity thermography. Heat running for each sample was from 30°C to 150°C at 10 K/min in nitrogen environment. (A) Coarse fenofibrate powder. (B) Physical mixture of fenofibrate and surfactant (fenofibrate: poloxamer 188:PVP=1:2:1, w/w/w). (C) Fenofibrate nanosuspension freeze-dried powder.

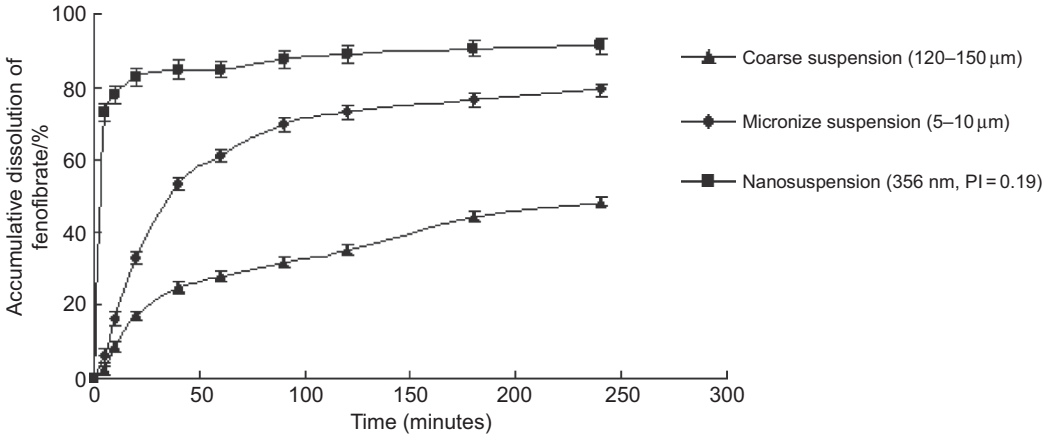

Figure 7. Dissolution profile of different fenofibrate suspension in dissolution media. (n = 5, means ± SD). Each samples contained a known amount of fenofibrate (25 mg). Paddle method was adopted and the rotation speed was 100 rpm. 900 mL of 1.0% SDS at 37±0.5°C was used as the dissolution medium.

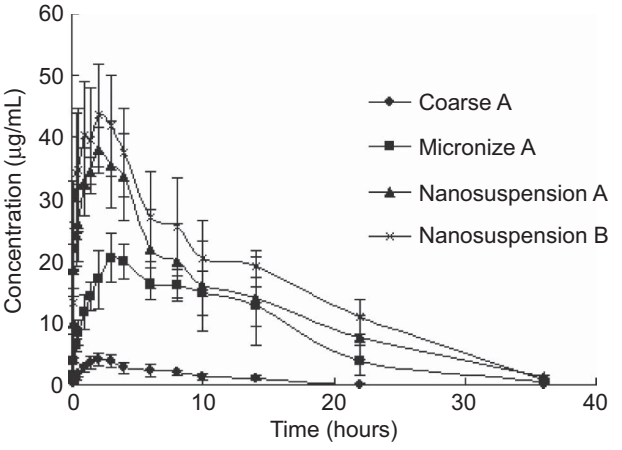

Figure 8. Average plasma concentration–time profiles of fenofibric acid following oral administration of 27 mg/kg in rats. Four different fenofibric samples were tested: coarse suspension (120–150 μm), micronized suspension (5–10 μm), nanosuspension A (356 nm, PI = 0.19) and nanosuspension B (194 nm, PI = 0.25) (means ± SD, n = 6).

suspension was 3.77 ± 0.64 hours (P < 0.01) and coarse suspension was 2.41 ± 0.17 hours. The large C_{max} and short T_{max} of nanosuspension indicated more rapid absorption of the drug from the colloidal drug delivery systems. The mean residence times (MRT) extended from 6.71 ± 0.73 hours of the coarse suspension to about 10 hours of the nanosuspensions. But there was no statistically significant difference of the MRT between nanosized and micronized fenofibrate suspensions (P < 0.05). To evaluate whether the smaller nanoparticles had better absorption as particle size decreased below 1 μm, two nanosuspensions A and B with particle diameter of 356 nm (PI = 0.19) and 194 nm (PI = 0.25), respectively, were compared. There were no statistically significant differences in all pharmacokinetic parameters between nanosuspensions A and B (P < 0.05).

The nanosuspension formulation provided higher exposure to fenofibrate, which might be explained by the feature of absorption process. It was thought nanosuspension had general adhesiveness to the intestinal wall. The adhesiveness of nanoparticles in intestine would raise the passive absorption[20]. Furthermore, the nanoparticles will be transported to the lower gastrointestinal part and accumulate there[21]. Cooperating with the good lipophilicity of fenofibrate and the remarkably increased dissolution rate of nanosuspension, the drug could be absorbed easily in the gastrointestinal tract.

Conclusions

In this study, melt emulsification combined with high-pressure homogenization was employed to prepare fenofibrate nanosuspension and approved to be

Table 1. Pharmacokinetic parameters of different fenofibrate formulations in rats (administration dose 27 mg/kg, means ± SD, n= 6) AUC (hμg/mL), T_{peak} (hours), C_{max} (μg/mL).

Formulation	Coarse	Micronize	Nanosuspension A	Nanosuspension B
$AUC_{0\text{–}36\,h}$	34.42 ± 10.38**	274.68 ± 38.11**	465.13 ± 112.18	585.75 ± 99.63
T_{max}	2.41 ± 0.17	3.77 ± 0.64**	1.83 ± 0.63	1.64 ± 0.64
C_{max}	3.55 ± 1.01**	20.49 ± 2.32**	37.42 ± 4.10	44.47 ± 11.19
$MRT_{0\text{–}36\,h}$	6.71 ± 0.73*	10.49 ± 0.54	9.24 ± 1.78	10.52 ± 1.59

*p<0.05, **p<0.01 versus nanosuspension A. Pharmacokinetic parameters (±SD) were calculated using the pharmacokinetic software 3P97. Statistical analysis and multiple comparisons among groups were performed using SPSS software at the 0.05 level.

a simple and high-performance method. Furthermore, because of the less energy consumption, this method was quite suitable for large-scale manufacture. It has been shown that formulation of fenofibrate as nanosuspension had great success with regard to dissolution rate enhancement. The pharmacokinetic properties of fenofibrate with different particle size were studied in rats to evaluate the exposure to the drug. *AUC* and C_{max} of nanosuspensions improved obviously compared with the coarse and micronize suspensions, indicating greatly increased bioavailability. No significant statistical differences were found in all pharmacokinetic parameters between the two nanosuspensions. The particle size reduction to the nanometer size range seemed to have less influence on bioavailability. This result was the similar to the conclusion of A. Hanafy et al.[19]

In summary, nanosuspension was an effective drug delivery system for drugs with poor water solubility. The method developed in this study was suitable for the nanosuspension preparation of the poor water-soluble drugs with corresponding low melt point and good thermostability.

Acknowledgments

The authors thank the Natural Science Foundation of Jiangsu province (BK2006177) for the financial support of this work.

Declaration of interest: The authors report no conflicts of interest.

References

1. Liversidge EM. (2002). Nanocrystals: Resolving pharmaceutical formulation issues associated with poorly water-soluble compounds. In: Marty JJ, ed. Particles, Marcel Dekker, Orlando.
2. Möschwitzer J, Achleitner G, Pomper H, Müller RH. (2004). Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. Eur J Pharm Biopharm, 58:615–9.
3. Liversidge GG, Conzentino P. (1995). Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm, 125:309–13.
4. Jinno JI, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, et al. (2006). Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Control Release, 111:56–64.
5. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, et al. (2002). Biopharmaceutics classification system: The scientific basis for biowaiver extensions. Pharm Res, 19:921–5.
6. Patravale VB, Date AA, Kulkarni RM. (2004). Nanosuspensions: A promising drug delivery strategy. J Pharm Pharmacol, 56:827–40.
7. Müller RH, Jacobs C, Kayser O. (2001). Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the Future. Adv Drug Deliv Rev, 47:3–19.
8. Langguth P, Hanafy A, Frenzel D, Grenier P, Nhamias A, Ohlig T, et al. (2005). Nanosuspension formulations for low-soluble drugs: Pharmacokinetic evaluation using spironolactone as model compound. Drug Dev Ind Pharm, 31:319–29.
9. Thies J, Müller BW. (1998). Size controlled production of biodegradable microparticles with supercritical gases. Eur J Pharm Biopharm, 45:67–74.
10. Keck CM, Müller RH. (2006). Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization. Eur J Pharm Biopharm, 62:3–16.
11. Liversidge GG, Cundy KC. (1995). Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailabilty of nanocrystalline danazol in beagel dogs. Int J Pharm, 125:91–7.
12. Krause KP, Müller RH. (2001). Production and characterisation of highly concentrated nanosuspensions by high pressure homogenization. Int J Pharm, 214:21–4.
13. Lindfors L, Skantze P, Skantze U, Rasmusson M, Zackrisson A, Olsson U. (2006). Amorphous drug nanosuspensions. 1. Inhibition of Ostwald ripening. Langmuir, 22:906–10.
14. Möschwitzer J, Müller RH. (2006). Spray coated pellets as carrier system for mucoadhesive drug nanocrystals. Eur J Pharm Biopharm, 62:282–7.
15. Sheu MT, Yeh CM, Sokoloski TD. (1994). Characterization and dissolution of fenofibrate solid dispersion systems. Int J Pharm, 103:137–46.
16. Palmeiri GF, Antonini I, Martelli S. (1996). Characterization and dissolution studies of PEG4000/fenofibrate solid dispersions. STP Pharm Sci, 6:188–94.
17. Kocbek P, Baumgartner S, Krist J. (2006). Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. Int J Pharm, 312:179–86.
18. Granero GE, Ramachandran C, Amidon GL. (2005). Dissolution and solubility behavior of fenofibrate in sodium lauryl sulfate solutions. Drug Dev Ind Pharm, 31:917–22.
19. Hanafy A, Spahn-Langguth H, Vergnault G, Grenier P, Tubic Grozdanis M, Lenhardt T, et al. (2007). Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Adv Drug Deliv Rev, 59:419–26.
20. She ZY, Ke X, Ping QN, Xu BH, Chen LL. (2007). Preparation of breviscapine nanosuspension and its pharmacokinetic behavior in rats. Chin Nat Med, 5:50–5.
21. Kayser O. (2001). A new approach for targeting to Cryptosporidium parium using mucoadhesive nanosuspensions: Research and applications. Int J Pharm, 214:83–5.