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Preparation of ultrafine fenofibrate powder by solidification process from emulsion

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ABSTRACT

The solidification process from emulsion, which consisted of emulsifier, water and molten drug as oil phase without use of any organic solvent, was firstly employed to prepare ultrafine fenofibrate (FF) powder. The effects of stirring speed and volume ratios of hot emulsion to cold water on the particle size and morphology were discussed as well as the impacts of different emulsifiers on emulsion. The produced ultrafine powder was characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, specific surface area analysis and a dissolution test. XRD patterns and FT-IR spectra showed that the ultrafine FF was crystalline powder with the structure and the components similar to those of bulk drug. The product had a mean particle size of about 3 μm with a narrow distribution from 1 μm to 5 μm. The specific surface area reached up to 6.23 m^2/g, which was about 25 folds as large as that of bulk FF. In the dissolution tests, about 96.1% of ultrafine FF was dissolved after 120 min, while there was only 38.1% of bulk drug dissolved, proving that the dissolution property of ultrafine FF was significantly improved when compared to commercial drug.

1. Introduction

Fenofibrate (FF) is a potent lipid modulator agent which can be rapidly hydrolyzed to fenofibric acid by esterase after absorption (Rath et al., 2005). It exhibits a melting point reported to be in the range of 79–82 °C (Henry et al., 2003). FF is a benzophenone which contains two substantial hydrophobic groups including para-chlorophenyl and para-isopropyl-oxy-carbonyl isopropoxy-phenyl. This results in its high hydrophobicity (experimental Log P = 5.3), poor solubility and low dissolution rate in the gastrointestinal tract, which limits its effective absorption and bioavailability after oral administration (Grenler et al., 2005; Pace et al., 2004).

The poor dissolution characteristics of water-insoluble drugs, which lead to a poor and/or varying bioavailability after oral administration, are a major challenge for pharmaceutical scientists (Biradar et al., 2006; Friedrich et al., 2006). In the pharmaceutical industry, the most common way to increase the dissolution rate of drugs is to reduce particle size and increase surface area of drug powder by milling, precipitation and high pressure homogenization (Rasenack et al., 2004). However, milling technologies such as wet milling can cause the contamination of products because of the abrasion between the grinding beads and a broad size distribution with only a negligible fraction of the population below 1 μm (Keck and Müller, 2006). One limitation of precipitation is that it is very difficult to choose an appropriate solvent miscible with anti-solvent because many drugs are insoluble simultaneously in aqueous and organic solvents (Müller et al., 2001). Another challenge for precipitation process lies in the difficult control of the growth of drug particles. The major disadvantage of high pressure homogenization is that the crystal structure of drugs varies in some cases due to the high pressure, which may result in instability and pose quality control problems (Kharb et al., 2006).

Usually, emulsions, especially microemulsions, are always developed as different drug delivery systems in the pharmaceutical industry to enhance the overall concentration of poorly water-soluble and -insoluble drugs, due to the high solubility of the active pharmaceutical ingredients (APIs) in the dispersed oil phase (Chen et al., 2006; Djordjevic et al., 2004; Kan et al., 1999; Lawrence and Rees, 2000; Rhee et al., 2001; Tamilvanan and Benita, 2004). However, only a few powders were produced from emulsions. A new crystal form of artificial sweetener aspartame was obtained by cooling hot water/isooctane/AOT (sodium diisooctyl sulfosuccinate) microemulsions containing solubilized aspartame (Füredi-Milhofer et al., 1999) and the drug-loaded powder was prepared from emulsion formulation by spray-freezing into liquid process (Rogers et al., 2003). All of these emulsions mentioned in the literatures at least consist of drugs, oils, emulsifiers and water. In this study, we presented a novel pathway for preparing ultrafine

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drug powder from emulsions in the absence of organic solvents and oils. The model drug, FF with low melting point (79–82 °C), melted in hot water (>95 °C) and self-emulsified with the help of suitable emulsifier. The obtained hot emulsion only including drug, emulsifier and water was rapidly mixed with cold water (<4 °C). Immediately, the ultrafine particles were formed by the solidification of drug droplets with the temperature descent. The similar process can be found in the literatures for the production of solid lipid nanoparticles by cooling the lipid phase (Blasi et al., 2007; Hu et al., 2004; Mehnert and Mäder, 2001). The major advantage of this method is that it is a simple, economical and environment-friendly process, which may be developed to produce other ultrafine powders and suspensions of poorly water-soluble drugs with low melting point (<100 °C), such as gemfibrozil, ibuprofen, ketoprofen, and so on.

2. Materials and methods

2.1. Materials

FF, corresponding to the nomenclature isopropyl 2-(4-(4-chlorobenzoyl) phenoxy)-2-mehtyl-propionate (Curtet et al., 1990), was purchased from Zhejiang Excel Pharmaceutical Co., Ltd. (Taizhou, China). Sodium lauryl sulfate (SLS), Tween 80, polyvinylpyrrilidone (PVP) and polyethylene glycol (PEG) were commercially obtained from Chemical Reagent Co. (Beijing, China) while poloxamer 407 (F-127) was provided by Nanjing Well Chemical Co. (Nanjing, China). De-ionized water used was purified by Hitech-K flow Water Purification System (Hitech. Instruments Co. Ltd., Shanghai, China).

2.2. Methods

2.2.1. Preparation of ultrafine FF powder

2.5 g of bulk FF and 0.25 g of emulsifier were added to 10 ml of de-ionized water under mild stirring using a magnetic stirrer, and the mixture was heated by a thermostatic water bath to the temperature higher than 95 °C. After a while, FF melted and self-emulsified to form O/W emulsion. Subsequently, the hot emulsion was quickly poured into 100 ml of cold water (~2 °C) under vigorous agitation. The drug droplets were re-solidified with the temperature decrease and the suspension was obtained. After agitating for 30 min, the suspension was filtered. The resulting wet cake was washed with de-ionized water and re-dispersed into water for spray-freeze drying to obtain ultrafine FF powder. The suspension were atomized and sprayed into liquid nitrogen at the pressure of 0.6 MPa and a flow rate of 10 ml/min through a 1 mm inner diameter (i.d.) stainless nozzle using a Longer Model BT-100M peristaltic pump (Baoding Longer Precision Pump Co. Ltd., Baoding, China). The cryogenic suspension was then poured into a non-insulated beaker to allow the nitrogen to evaporate. Once the nitrogen had evaporated, the frozen powder was immediately vacuum freeze-dried by a Model LT-105 lyophilizer (Martin Christ Gefriertrocknungsanlagen GmbH, Osterode, Germany).

2.2.2. Scanning electron microscopy (SEM)

SEM photographs were taken by JSM-6360LV Scanning Electron Microscope (JEOL, Japan) to study the morphology and size of FF particles. The dried drug powder was fixed on aluminum stubs using double-sided adhesive tape and coated with Au at 3 mA for 6 min through a sputter-coater (KYKY SBC-12, Beijing, China) under an Ar atmosphere. A scanning electron microscope with a secondary electron detector was used to obtain digital images of the samples at an accelerating voltage of 10 kV.

2.2.3. X-ray diffraction (XRD) studies

X-ray diffraction analysis was performed to detect any change in the physical characteristics and crystallinity of the ultrafine FF powder by use of XRD-6000 (SHIMADZU, Japan). The measuring unit consists of a rotating anode in transmission technique and a specification that Cu $K_{\alpha 1}$ radiation is generated at 30 mA and 40 kV. Sample powder was carefully grounded and placed in an aluminum sample holder. The scanning started from 10° to 50° at a speed of 5° min^{-1}. The step size was 0.05° with a count time of 0.6 s per step.

2.2.4. Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectra were recorded with a Nicolet 8700 (Thermo Electron, America) spectrometer in the range of 400–4000 cm^{-1} using a resolution of 2 cm^{-1} and 32 scans. Samples were diluted with 1% of KBr mixing powder and pressed to obtain self-supporting disks.

2.2.5. BET surface area

The specific surface areas of commercial bulk FF and ultrafine FF were measured using N_2 adsorption method. In this method, the calculation was implemented by Surface Area Analyzer ASAP 2010-M (Micromeritics Instrument Corporation, America) based on the BET equation. Before analyzing, an amount of powder (~200 mg) was loaded into a sample cell and degassed for at least 4 h.

2.2.6. HPLC analyses

The drug content was determined by HPLC system, which consists of a Waters 2996 Photodiode Array Detector and a Waters 2695 Separations Module (Waters Corporation, Miford, MA, USA). The chromatographic separation was performed using a Waters

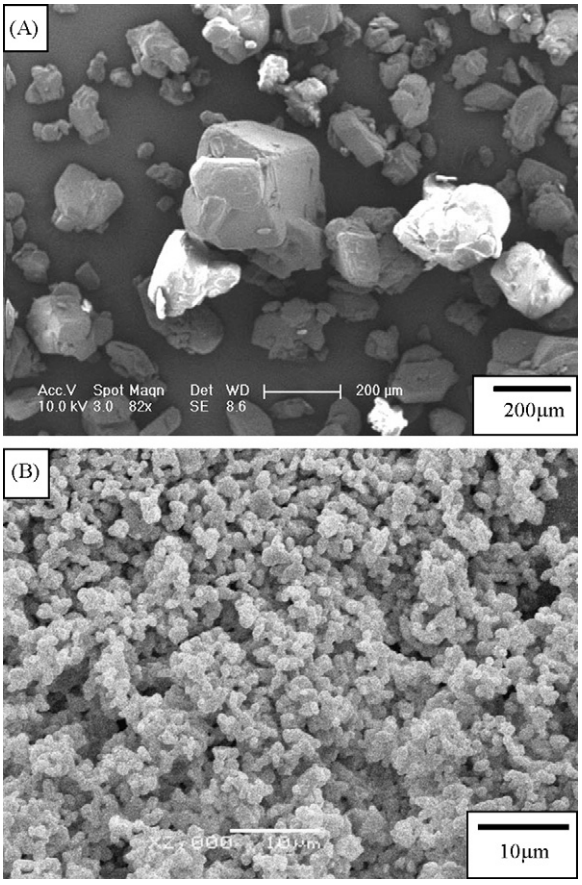

Fig. 1. SEM images of (A) bulk fenofibrate; (B) particles obtained from emulsion containing F-127.

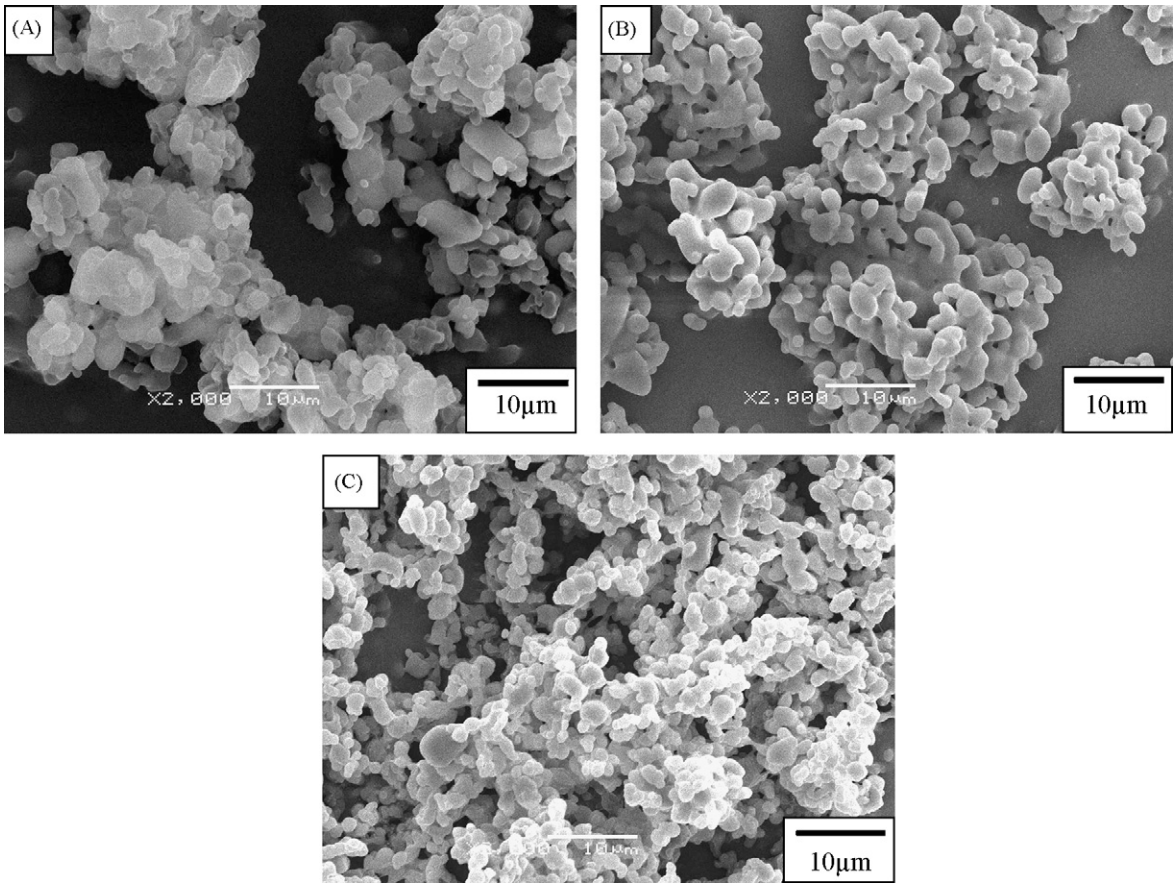

Fig. 2. SEM images of (A) particles solidified without agitation; (B) particles solidified at a speed of 2000 rpm; (C) particles solidified at a speed of 10,000 rpm.

Sunfire™ C18, reverse-phase column (150 mm × 4.6 mm i.d., 5 μm particle size) protected by a guard column (10 mm × 4.6 mm i.d.) which was packed with the same Sunfire™ C18 material. Separation was carried out using a mobile phase consisting of acrylonitrile–water (7:3, v/v) at a flow rate of 1 ml/min and UV detection at 286 nm. The mobile phase was adjusted to pH 2.5 utilizing concentrated phosphoric acid and filtered through 0.45 μm nylon filter prior to use. The column was maintained at 30 °C and was equilibrated for 30 min with the analytical mobile phase before injection.

2.2.7. Dissolution testing

The dissolution characteristics of the drug powder were examined by paddle method (Chinese Pharmacopeia 2005, Type 2) using a dissolution tester (Type D-800, Tianjin, China). Paddle speed and bath temperature were set at 75 rpm and 37.0 ± 0.5 °C, respectively. Approximately 50 mg of powder was weighed and placed into the dissolution media consisting of 900 ml de-ionized water and 0.0225 mol SLS (Stamm and Seth, 2000). Samples (5 ml) were withdrawn at specific intervals and immediately filtered through a 0.45 μm filter (Φ13/0.45). The samples were appropriately diluted prior to analysis of dissolved drug concentration by UV-2501 spectrophotometer (SHIMADZU, Japan) at a wavelength of 286 nm. Calibration curve of absorbance versus concentration was constructed according to the solution of FF in dissolution medium, ranging in concentration from 0.005 mg/ml to 0.012 mg/ml. Absorbance versus concentration plot was linear over the concentration range and was used to determine the concentration of drug dissolved in the dissolution experiments. Each sample was analyzed in triplicate.

3. Results and discussion

3.1. Effect of emulsifier on emulsion and particle size and morphology

In the emulsion system, the emulsifiers were employed for the stabilization of the boundary surface of multiple oil droplets and outer water (FeczkÓ et al., 2008). For the sake of the formation of stable O/W emulsions, the emulsifiers with the HLB (hydrophile–lipophile balance) value >8 are required (Xu, 2000). In our experiments, four kinds of emulsifiers (Tween 80, PVP, PEG and F-127) with the HLB values in the range of 15–22 were evaluated. However, only F-127 could help to form the stable O/W emulsion. Fig. 1 shows SEM images of bulk FF and the particles solidified from the emulsion containing F-127. Bulk fenofibrate powder had an irregular morphology and a mean particle size of about 200 μm with a wide particle size distribution (PSD) from 100 μm to 300 μm (Fig. 1A). The particles solidified from the emulsion including F-127 were spherical with the size of 1–3 μm (Fig. 1B). The possible reason is that F-127 is amphiphilic non-ionic block polymer of hydrophobic propylene oxide and hydrophilic ethylene oxide comprising a central poly-(oxypropylene) (PPO) molecule (Urbán-Morlán et al., 2008). It is capable of forming a mono- or multi-layer coating film around the dispersed liquid droplets to form a mechanical barrier, which can reduce the interfacial tension and enhance the droplet–droplet repulsion to prevent the droplet coalescence and increase the physical stability of emulsion (Tamilvanan, 2004). Furthermore, F-127 was also expected to be adsorbed on the newly formed solid surface to prevent the growth and the aggregation of the particles (Terayama et al., 2004).

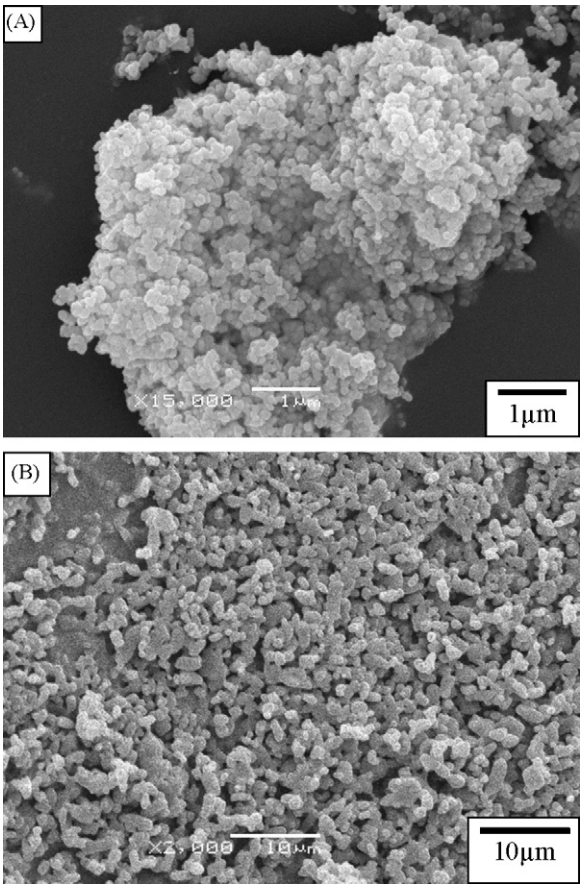

Fig. 3. SEM images of (A) particles obtained from the system with $R_{E/W}$ = 1/100; (B) particles obtained from the system with $R_{E/W}$ = 1/10.

3.2. Influence of stirring speed on particle morphology and size

Fig. 2 demonstrated the effect of stirring speed in the solidification process on the particle size and morphology. The particles solidified without agitation aggregated badly and had an irregular morphology (Fig. 2A) while those obtained under agitation had a spherical shape with the size less than 5 μm (Fig. 2B and C). In addition, compared to those obtained at a stirring speed of 2000 rpm (Fig. 2B), the aggregations were not found in the particles formed at 10,000 rpm (Fig. 2C), indicating that the increase of stirring speed was of advantage to the formation of ultrafine particles and prevention of particle agglomeration. This could be attributed to the fact that the intensification of the micromixing between hot emulsion and cold water was enhanced with the increase of stirring speed (Wang et al., 2007), which reduced the heat-transfer resistance and improved the solidification of droplets before their coalescence.

3.3. Impact of volume ratio on particle morphology and size

Fig. 3 exhibited SEM photographs of particles in the slurry obtained at the different volume ratios of hot emulsion to cold water ($R_{E/W}$). As shown in Fig. 3A, the as-prepared particles had regular spherical morphology with the size of less than 500 nm at $R_{E/W}$ 1/100. The particle size became larger and the morphology tended to more irregular when $R_{E/W}$ was increased to 1/10 (Fig. 3B). It might be explained from the view of heat-transfer. In the process, the drug particles were generated by the solidification of drug droplets resulted from the temperature decrease after mixing, suggesting that the heat-transfer was more important than mass-transfer in the formation of particles. The increase of $R_{E/W}$ might lead to the decrement of heat-transfer rate and accelerate the coalescence of drug droplets before they solidified completely.

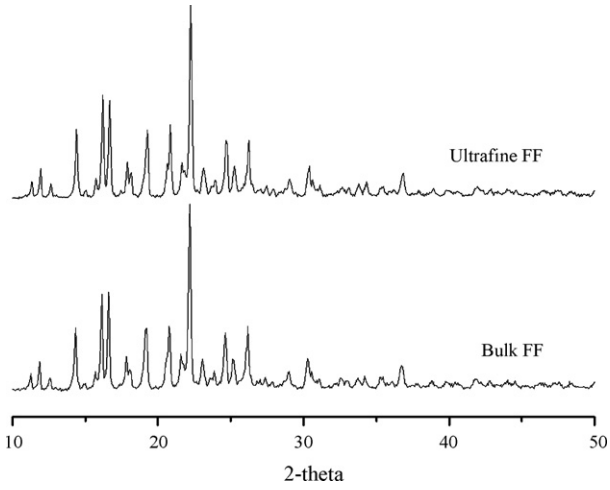

Fig. 4. XRD patterns of bulk fenofibrate and ultrafine fenofibrate.

3.4. Powder X-ray diffraction studies

The patterns of X-ray powder diffraction, which was performed to determine the physical state of commercial bulk FF and ultrafine FF, were displayed in Fig. 4. The sharply crystalline peaks were found in the diffraction patterns of the as-prepared FF powder as well as those of bulk drug, demonstrating that the samples are crystalline. Obviously, the peak positions of the different samples were almost the same, indicating that the solidification process from emulsion had no effect on the physical characteristics of FF.

3.5. FT-IR spectroscopy

Typical FT-IR spectra of bulk fenofibrate and ultrafine fenofibrate in the range of 400–4000 cm^{-1} were compared carefully and it could be seen that the spectrum of ultrafine fenofibrate showed no obvious difference from that of bulk drug in the whole area of the FF absorption bands. This well demonstrated that the addition of F-127 and the employment of solidification process from emulsion did not change the physical characteristics of FF, which had been confirmed by XRD patterns (Fig. 4).

3.6. Drug content analyses

About 5 wt% (based on the weight of FF) F-127 was used to prepare emulsion. Some F-127 might be remained in the ultrafine powder. Therefore, the drug contents were examined by HPLC system. The results showed that drug content for ultrafine FF was 99.7% (99.7 ± 0.12%), which proved that most of F-127 had been removed by washing the cake with de-ionized water for several times.

3.7. Dissolution test

The dissolution profiles of bulk product and the as-prepared FF in 0.025 mol/L SLS aqueous solution were depicted in Fig. 5. At 37 °C, the dissolution rate of ultrafine FF was increased to 31.1% after 5 min, while only 14.7% of bulk FF dissolved in the same time. After 120 min, about 96.1% of ultrafine FF was dissolved, but there was only 38.1% of bulk drug dissolved. The increase of the dissolution rate of ultrafine FF could be mainly attributed to the obvious

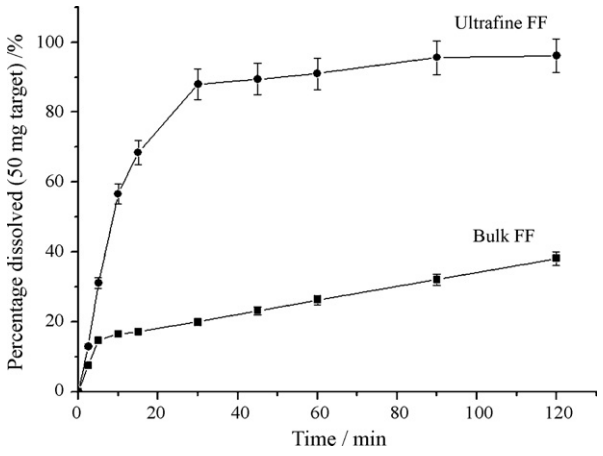

Fig. 5. Dissolution profiles of bulk fenofibrate and ultrafine fenofibrate.

reduction of the particle size (from about 200 μm for bulk FF to around 3 μm for ultrafine FF) and the great increase of BET surface area (from 0.25 m^2/g for bulk drug to 6.23 m^2/g for ultrafine FF). According to Nernst–Noyes–Whitney equation, which described the dissolution rate of drug in a diffusion-controlled process, an increase in the surface area could result in an increase of dissolution rate (Drooge et al., 2004; Mosharraf and NyatrÖm, 1995; Müller and Peters, 1998).

4. Conclusions

In this study, ultrafine FF powder was successfully prepared by solidification from O/W emulsion system containing F-127 as emulsifier, water and molten drug as oil phase. The obtained particles had a spherical shape and a PSD from 1 μm to 5 μm. XRD patterns and FT-IR spectra indicated that there was no change in crystal structure of ultrafine FF powder. In the dissolution test, about 96.1% of ultrafine FF was dissolved after 120 min, while there was only 38.1% of bulk drug dissolved. The as-prepared powder demonstrated a great improvement in dissolution rate owing to a decreased particle size from ~200 μm to ~3 μm and a corresponding increased specific surface area from 0.25 m^2/g to 6.23 m^2/g. Therefore, the solidification process from emulsion would be a feasible and potentially effective pathway for the micronization of drugs with a low melting point.

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