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Micronization of gemfibrozil by reactive precipitation process

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ABSTRACT

Ultrafine gemfibrozil (GEM) was prepared by reactive precipitation process in which methyl cellulose (MC) was employed to inhibit the growth and the agglomeration of particles. The impact of NaOH concentrations on bulk GEM consumption was explored. The effects of H_2SO_4 concentrations and the drying methods on the particle size and morphology were also discussed. The produced ultrafine powders were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, specific surface area analysis and dissolution test. XRD patterns and FT-IR spectra showed that the as-obtained ultrafine GEM was a crystalline powder with the structure and components similar to those of bulk GEM. The ultrafine GEM had a mean particle size of about 1.25 μm with a narrow distribution from 0.6 to 3 μm. The specific surface area reached up to 11.01 m^2/g, which was about 6 times as large as that of bulk GEM. In the dissolution tests, about 91.2% of ultrafine GEM was dissolved after 120 min, while there was only 23.6% of bulk GEM dissolved, proving that the dissolution property of ultrafine GEM was significantly enhanced when compared to commercial GEM owing to a decreased particle size and an increased specific surface area.

1. Introduction

Water insolubility of drug has always been a key obstacle in pharmaceutical formulation, affecting formulation stability and drug bioavailability (Kipp, 2004). Presently, about 40% of drugs in the development pipelines and approximately 60% of drugs coming directly from synthesis exhibit high lipophilicity and lack of aqueous solubility, i.e., their equilibrium solubility in water is below 10 μg/mL (Keck and Müller, 2006; Kharb et al., 2006; Kuentz et al., 2006; Oda et al., 2004), which make the bioavailability of water-insoluble drugs after oral or parenteral administration insufficient and far below the therapeutic level (Müller and Peters, 1998; Muhrer et al., 2006). For class II drugs and class IV drugs, according to the biopharmaceutics classification system (Löbenberg and Amidon, 2000), the limiting factor for in vivo performance of the drugs, following oral administration, is their resistance to being wetted and dissolved into the fluid in the gastrointestinal tract (Rasenack et al., 2003, 2004). Enhancing the dissolution rate to increase the rate and the extent of the absorption of poorly water-soluble drugs is thus important for optimizing bioavailability (Kocbek et al., 2006).

According to the Noyes–Whitney equation, the dissolution rate of drugs could be increased by reducing the size at the micro- or nano-scale to increase the surface area of drug particles (Drooge et al., 2004; Mosharraf and NyatrÖm, 1995; Müller and Peters, 1998). The conventional approaches to produce ultrafine drug particles can be divided into top-down and bottom-up technologies (Gupta and Kompella, 2006; Keck and Müller, 2006; Rabinow, 2004). In case of top-down technologies including jet-milling, pearl/ball milling and high pressure homogenization, the bulk drugs with the size of several hundred microns are comminuted into micro- or nano-sized range by the use of mechanical force (Rasenack et al., 2004). However, milling technologies such as wet milling can cause contamination of products because of the abrasion between the grinding beads, leading to a broad size distribution with only a negligible fraction of the population below 1 μm (Kharb et al., 2006; Keck and Müller, 2006). 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). In the case of bottom-up technologies such as precipitation, spray-freezing into liquid, supercritical fluid (SCF) technology and so on, the ultrafine particles can be built from the molecular state. These technologies

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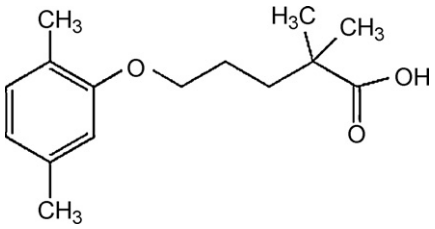


Fig. 1. Chemical structure of GEM.

have been employed to prepare several drugs in micro- or nano-scale, such as cephradine (Zhong et al., 2005), cefuroxime axetil (CFA) (Zhang et al., 2006), danazol (Rogers et al., 2002), ibuprofen (Rasenack et al., 2004), etc.

Reactive precipitation is one of the liquid precipitation processes, which is commonly used to prepare micro- or nano-sized acidic or basic drug particles. These ultrafine particles can be formed by adjusting pH values of the liquid. In a typical reactive precipitation process, the bulk drug firstly reacts with an acid or alkali in aqueous solution. Subsequently, the as-prepared solution is quickly poured into the basic or acidic solvent and the drug particles are generated by metathetical reaction. The primary particles in the slurry usually have a tendency to agglomerate because of their hydrophobicity and the increase of system energy (Javadzadeh et al., 2007; Rasenack et al., 2004). In order to decrease the system energy and hinder the growth and the agglomeration of particles, different hydrophilic polymers such as hydroxyl propyl methyl cellulose (HPMC) and methyl cellulose (MC) are used to modify the surface of particles and lower the interfacial intension. The polymers are expected to be adsorbed on the surface of the particles and form a protective layer acting as steric hindrance (Terayama et al., 2004).

Gemfibrozil (GEM), corresponding to the nomenclature 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid and the chemical structure as shown in Fig. 1, is a widely used lipid-regulating agent, which is generically classified as a fibric acid derivative (Ammazzalorso et al., 2005; Martinac et al., 2002). As a nonhygroscopic lipophilic drug, GEM has a very poor solubility and a low dissolution rate in the gastrointestinal tract, which limits its effective absorption and bioavailability after oral administration (Ghebre-Sellassie and Fawzi, 1994).

The objective of this study was to prepare ultrafine GEM powder by reactive precipitation process to enhance the dissolution rate of drug. In this procedure, MC was added as a hydrophilic polymer to enhance the wettability of hydrophobic drug and prevent the generated particles from growing and agglomerating. The process parameters were investigated and the ultrafine GEM particles were characterized in detail.

2. Materials and methods

2.1. Materials

Bulk GEM was purchased from Zhejiang Excel Pharmaceutical Co., Ltd. (Zhejiang, China). Hydrochloric acid (37 wt.%), sulfuric acid (98 wt.%), nitric acid (65 wt.%), phosphoric acid (85 wt.%), sodium hydroxide (NaOH), potassium dihydrogen phosphate (KH_2PO_4) and glacial acetic acid were analytical grade and obtained commercially from Chemical Reagent Co. (Beijing, China). MC was gained from Niansha Chemical Co. (Kunshan, China) and used as received. Methanol was HPLC grade and provided by FisherChemical (New Jersey, USA). Deionized water was purified by Hitech-K Flow Water Purification System (Hitech Instruments Co. Ltd., Shanghai, China).

2.2. Methods

2.2.1. Experimental principle

There is a carboxyl group in the structure of GEM (as shown in Fig. 1), which makes it possible for the drug to form a kind of soluble salt (marked as GEM-R) in the neutralization reaction process. Then the as-formed solution, in which GEM-R dissociates into GEM^- and R^+, is poured into the acidic solution. Immediately, particles precipitate due to metathetical reaction. The experimental reactive process is described in Scheme 1, in which the effects of the concentrations of basic and acidic solutions will be investigated.

2.2.2. Reactive precipitation process

3 g of raw GEM and 0.15 g of MC were added to 100 mL of 0.15 mol/L NaOH aqueous solution under vigorous agitation, and water-soluble GEM-Na was thus generated by neutralization reaction. The temperature of the as-prepared GEM-Na solution and 100 mL of acidic solution was decreased to $5 \pm 1\,^{\circ}C$ using a thermostatic water bath. Subsequently, two solutions were quickly mixed under vigorous agitation and thermally controlled between 4–8 °C. Instantaneously, GEM particles precipitated from the mixed liquid and a milk-like suspension was formed. After agitating for 30 min, the suspension was filtered and the wet cake was washed with deionized water until pH value of the filtrate reached 7 and then redispersed into deionized water for spray-freeze drying or dried in an oven at 40 °C for at least 3 h to obtain the ultrafine drug powder.

2.2.3. Scanning electron microscopy (SEM)

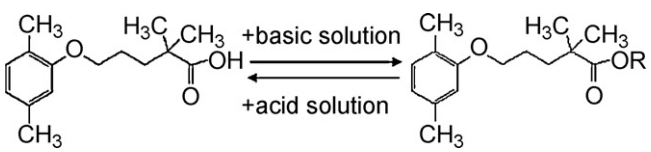
SEM photographs were taken by JSM-6360LV scanning electron microscope (JEOL, Japan) to study the morphology and size of the GEM particles. The dried drug powder was fixed on aluminium stubs using double-sided adhesive tape and coated with Au at 2 mA for 3 min through a sputter-coater (KYKY SBC-12, Beijing, 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. The particle size and distribution were determined by Image-Pro Plus software (release 5.0, MediaCybernetics, USA) via the obtained SEM photomicrographs.

2.2.4. X-ray diffraction studies (XRD)

X-ray diffraction analysis was performed to detect any change in the physical characteristics and crystallinity of the ultrafine GEM powder by use of a model XRD-6000 diffractometer (Shimadzu Inc., Japan). The measuring unit consisted of a rotating anode in transmission technique with a specification that Cu $K_{\alpha 1}$ radiation was generated at 30 mA and 40 kV. Sample powder was carefully grounded and placed in an aluminum sample holder. The scanning speed was 5°/min from 5° to 50° with a step size of 0.05°.

2.2.5. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra of samples were recorded with a Nicolet model 8700 spectrometer (Nicolet thermo electron instrument corporation, USA) 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.



Scheme 1. Experimental reactive process (R represents monovalent cations).

2.2.6. Specific surface area

The specific surface areas of commercial bulk GEM and ultrafine GEM powder were measured using N_2 adsorption method. In this method, the calculation was implemented by Surface Area Analyzer ASAP 2010-M (Micromeritics Instrument Corporation, USA) 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.

2.2.7. Contact angle measurement

Compact discs of sample powders were prepared at a 40 MPa compression force using a laboratory powder press (model 769YP-15A, Tianjin, China). A droplet of purified water was placed onto the surface of the compact disc and observed through a low-power microscope. The contact angle was determined by measuring the tangent of the droplet on the surface with a Contact Angle System OCA20 (Dataphysics, Germany).

2.2.8. HPLC instrumentation and conditions

The alliance HPLC system consists of a Waters 2996 Photodiode Array Detector and a Waters 2695 Separations Module including an autosampling system, column oven, integrated solvent and sample management configuration (Waters Corporation, Miford, MA, USA). A Waters' Empower 2 Chromatography Data Software was used to record and evaluate the data collected during and following chromatographic analysis. The chromatographic separation was performed using a Waters 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.) packed with the same Sunfire™ C18 material. Separation was carried out using a mobile phase consisting of methanol–water–glacial acetic acid (75:24:1, v/v) at a flow rate of 1 mL/min and UV detection at 276 nm. The mobile phase was filtered through 0.45 μm nylon filter prior to use. The column was maintained at 30 °C and equilibrated for 30 min with the analytical mobile phase before injection.

2.2.9. Dissolution testing

The dissolution properties of the drug powder were examined by paddle method (USP30-NF25, Type 2) using a dissolution tester (Type D-800, Tianjin, China). Paddle speed and bath temperature were set at 50 rpm and 37.0 ± 0.5 °C, respectively. 200 mg of powder was weighed and put into 900 mL of the dissolution media, which was 0.2 mol/L phosphate buffer (pH 7.5) prepared by dissolving 98.1 g of KH_2PO_4 in 500 mL of deionized water, adding 23.58 g of NaOH, diluting with deionized water to about 800 mL, mixing well, adjusting with 1 mol/L NaOH aqueous solution to a pH of 7.5, and diluting with deionized water to 900 mL. The samples (2 mL) were withdrawn at specific intervals and immediately filtered through a 0.45 μm filter (Ø 13/0.45). The GEM concentrations of samples were measured by HPLC system and calculated according to the calibration curves which were constructed by plotting peak areas of GEM versus GEM concentrations and were linear over the concentration range of 0.5–50 μg/mL (R^2 = 0.9999). Each sample was analyzed in triplicate.

3. Results and discussion

3.1. Effect of NaOH concentration on GEM consumption

In reactive precipitation process, GEM-Na was firstly formed by the reaction of GEM with NaOH in aqueous solution. The GEM consumption increased to the maximum at the point of 0.15 mol/L and then declined with the increment of NaOH concentration, as presented in Fig. 2. According to the calculation, the mole ratio of consumed GEM to NaOH was about 1:1 when NaOH concentration was 0.15 mol/L. Thus, it could be concluded that the deficiency of NaOH resulted in low consumption of GEM when NaOH concentration < 0.15 mol/L. However, as NaOH concentration was higher than 0.15 mol/L, the content of water in the solution decreased with the increase of NaOH concentration, thereby causing the decline of the corresponding GEM consumption. Therefore, 0.15 mol/L NaOH solution was chosen to prepare the GEM-Na solution.

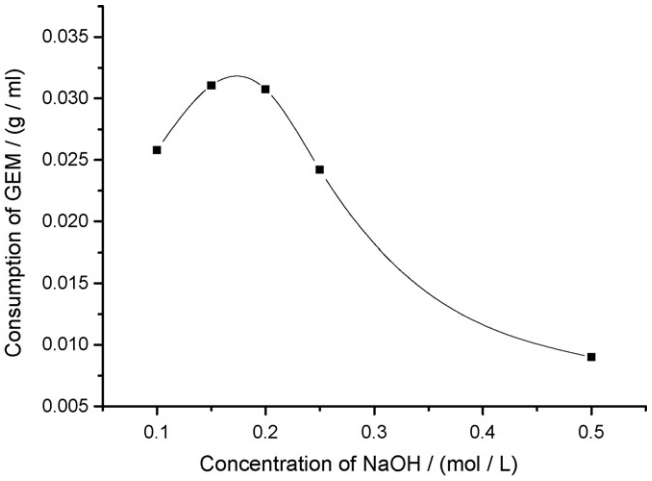


Fig. 2. Consumption of GEM in different NaOH solutions.

3.2. Selection of reactive system

SEM images of bulk GEM and the ultrafine particles obtained from different systems were given in Fig. 3. The bulk GEM had an irregular shape and a mean particle size of about 110 μm with a wide particle size distribution (PSD) from 40 to 300 μm. The particles precipitated from NaOH–HCl, NaOH–HNO_3 and NaOH–H_2SO_4 systems exhibited similar spherical morphology with the mean sizes of 2.38, 2.28 and 1.88 μm, respectively, while those from NaOH–H_3PO_4 system were irregular flakes with a size larger than 10 μm. The variations in the particle size and morphology of particles from different systems could be explained as follows.

According to the classical nucleation theory, the radius (r) of newly formed particles is affected by the supersaturation ratio (S) which is given by Eq. (1) (Dirksen and Ring, 1991).

$$S = \frac{C}{C_{eq}} \tag{1}$$

where C and C_{eq} are the solute concentration and the equilibrium solubility of the solute at the temperature and pressure of the system, respectively. Eq. (1) shows that S is obviously influenced by C and C_{eq}. The relationship between r and S can be explained by Eq. (2) (Horn and Rieger, 2001).

$$lnS = \frac{2\sigma\nu}{kT} \cdot \frac{1}{r} \tag{2}$$

where σ stands for the effective surface tension, ν for the molecular volume, T for the temperature of the system and k for the Boltzmann constant. Eq. (2) indicates that the radius of particles decreases reciprocally with the supersaturation ratio.

As a weakly acidic drug, the equilibrium model of GEM in aqueous solution can be described in Scheme 2. Where GEM_{solid} represents solid-state drug molecules, GEM stands for dissolved and unionized drug molecules, GEM^- is ionized drug, K_{sp} is solubility product constant of GEM_{solid} and K_a is dissociation constant. Thus, Eq. (1) can be transformed into Eq. (3) to describe the super-

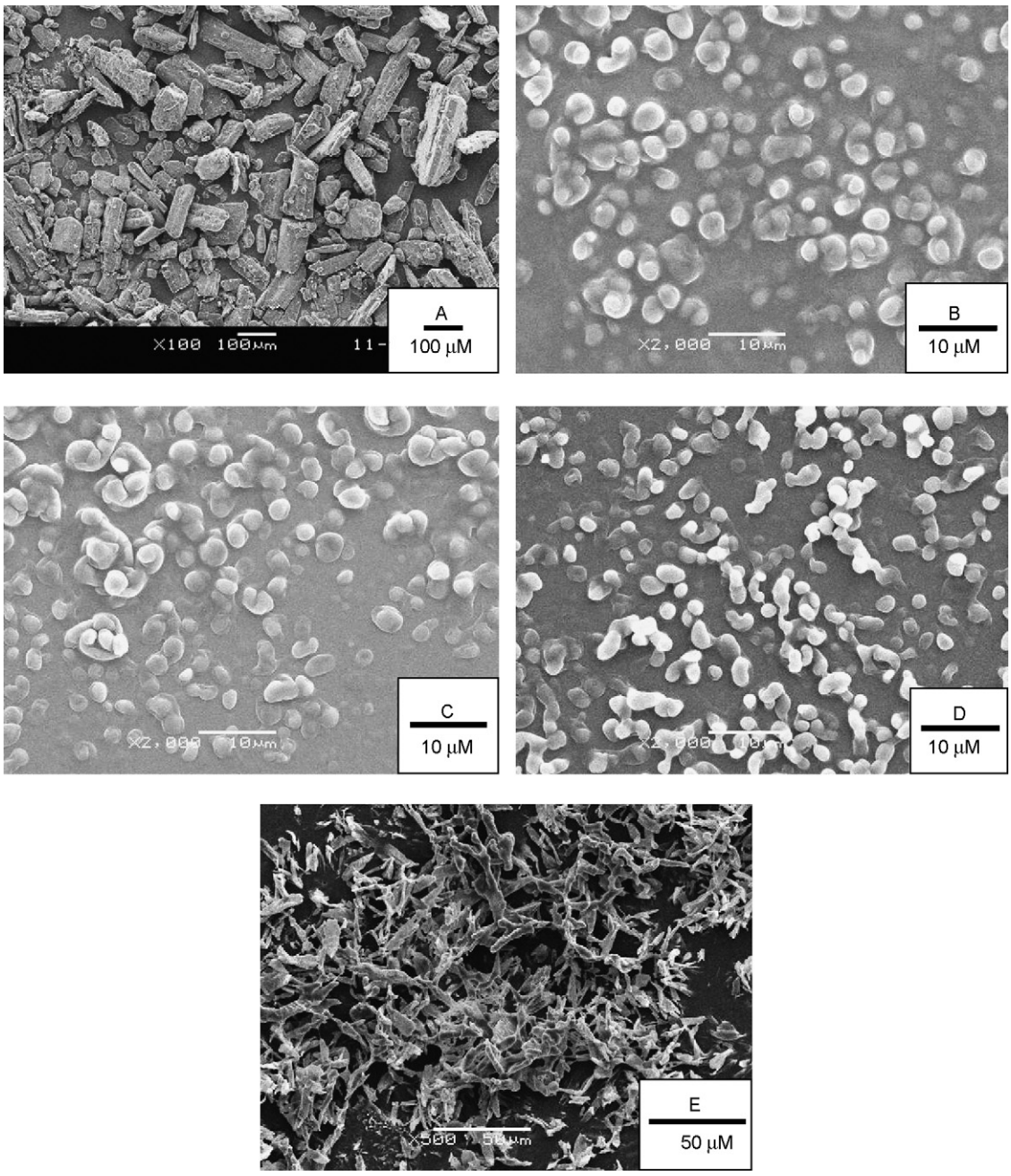


Fig. 3. SEM images of (A) bulk GEM and particles precipitated from (B) NaOH–HCl system; (C) NaOH–HNO_3 system; (D) NaOH–H_2SO_4 system; (E) NaOH–H_3PO_4 system.

saturation ratio of GEM in aqueous solution.

$$S = \frac{C_{\text{total}}}{(C_{\text{total}})_{\text{eq}}} = \frac{C_{\text{GEM}} + C_{\text{GEM}^-}}{(C_{\text{GEM}})_{\text{eq}} + (C_{\text{GEM}^-})_{\text{eq}}} \quad (3)$$

where C_{total} is the total concentration consisting of C_{GEM} and C_{GEM^-}; C_{GEM} and C_{GEM^-} are the concentrations of unionized and ionized GEM in basic solution, respectively; $(C_{\text{total}})_{\text{eq}}$ is the total equilibrium concentration including $(C_{\text{GEM}})_{\text{eq}}$ and $(C_{\text{GEM}^-})_{\text{eq}}$; $(C_{\text{GEM}})_{\text{eq}}$ and $(C_{\text{GEM}^-})_{\text{eq}}$ stand for the equilibrium concentrations of unionized and ionized GEM in the mixture after precipitation, respectively. It is obvious that the value of C_{total} in basic solution is a constant for all systems. $(C_{\text{GEM}})_{\text{eq}}$ is the intrinsic solubility of GEM in aqueous solution and maintains constant in different systems. According to Eq. (3), it can thus be found that the supersaturation ratio is affected by $[H^+]$ concentration since it is associated with the ionization process having impact on $(C_{\text{GEM}^-})_{\text{eq}}$. The effect of $[H^+]$ concentration can be demonstrated by the following Eq. (4).

$$K_a = \frac{(C_{\text{GEM}^-})_{\text{eq}}[H^+]}{(C_{\text{GEM}})_{\text{eq}}} \quad (4)$$

Eq. (4) suggests that the equilibrium solubility of the ionized drug, rather than the unionized drug, is the component influenced by the pH effect and increased reciprocally with $[H^+]$ concentration.

$$\text{GEM}_{\text{solid}} \overset{K_{sp}}{\rightleftharpoons} \text{GEM} \overset{K_a}{\rightleftharpoons} H^+ + \text{GEM}^-$$

Scheme 2. Equilibrium model of GEM in aqueous solution.

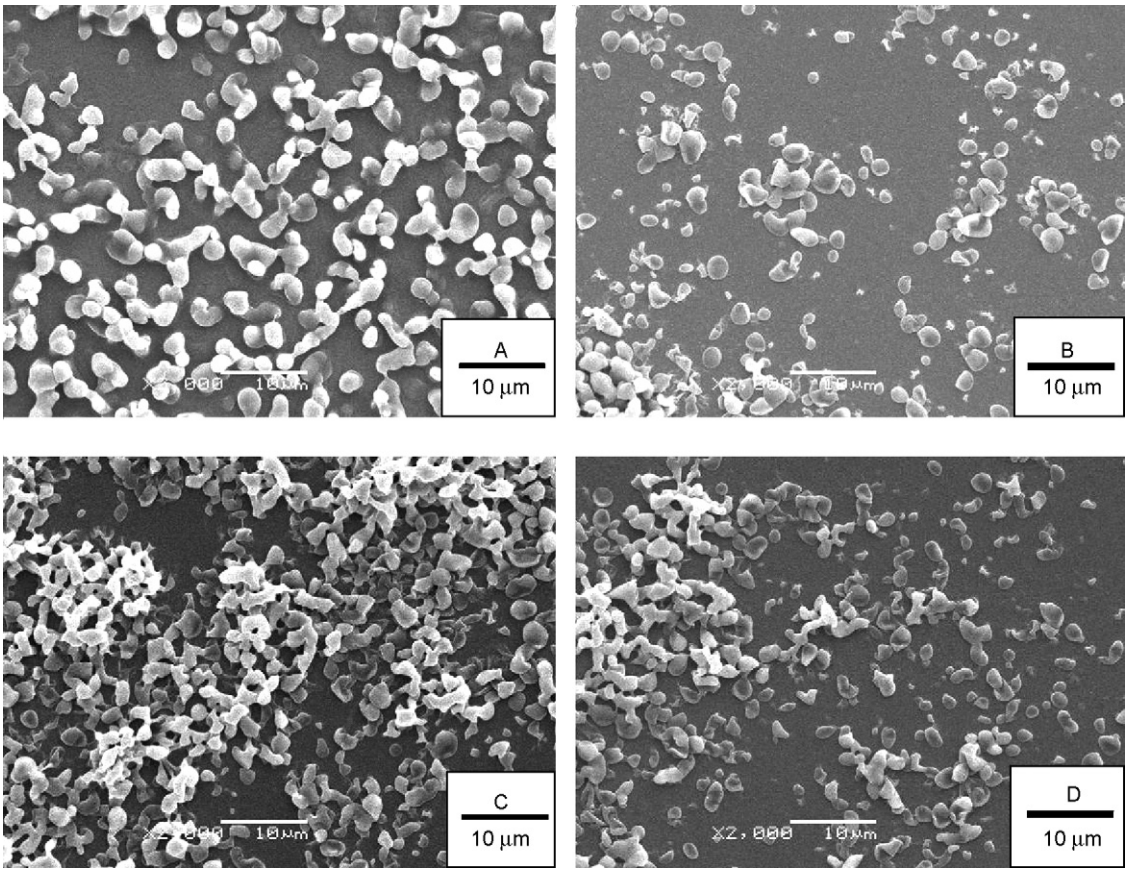


Fig. 4. SEM images of particles precipitated from NaOH–H_2SO_4 system with different initial H_2SO_4 concentrations: (A) 0.075 mol/L; (B) 0.1125 mol/L; (C) 0.225 mol/L; (D) 0.300 mol/L.

Compared to the other systems, NaOH–H_3PO_4 system has the lowest $[H^+]$ concentration. According to Eq. (4), the decrease of $[H^+]$ concentration results in the increase of $(C_{GEM^-})_{eq}$ by promoting the ionization of GEM. Based on Eq. (3), the augment of $(C_{GEM^-})_{eq}$ leads to the increment of $(C_{total})_{eq}$ and the decrease of S, which could accelerate the growth of particles (Wang et al., 2007). Therefore, the particles obtained from NaOH–H_3PO_4 system are larger than those from NaOH–HCl, NaOH–HNO_3 and NaOH–H_2SO_4 systems.

3.3. Effect of H_2SO_4 concentration

The effects of H_2SO_4 concentrations were explored and demonstrated in Fig. 4. The morphology of particles precipitated under various H_2SO_4 concentrations exhibited spherical shape and good dispersibility. The mean sizes of particles under four H_2SO_4 concentrations were 2.04 μm (for 0.075 mol/L), 1.85 μm (for 0.1125 mol/L), and 1.70 μm (for 0.225 and 0.300 mol/L), respectively, suggesting that the particle size was slightly reduced with the increase of

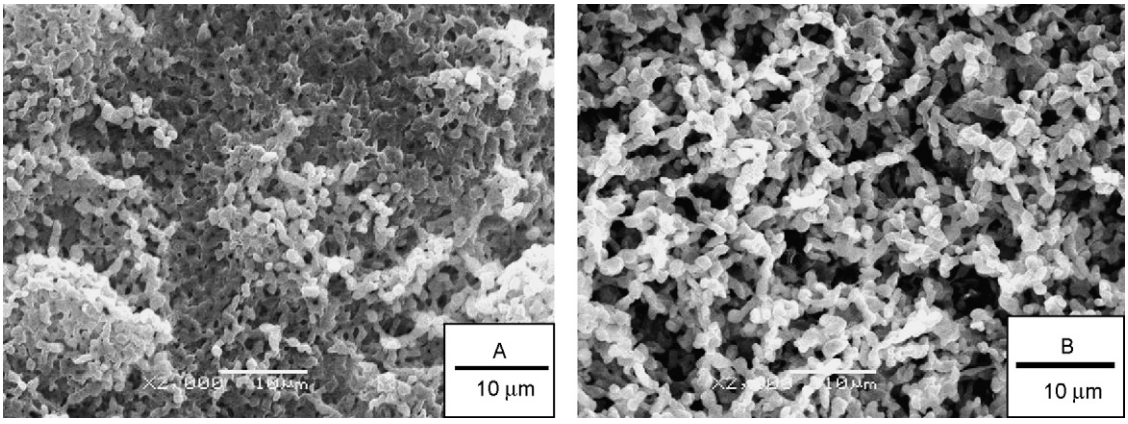


Fig. 5. SEM images of powders obtained from: (A) normal oven drying; (B) spray-freeze drying.

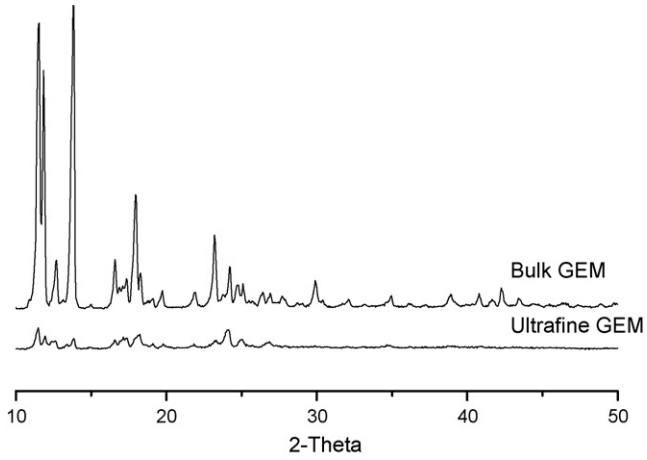


Fig. 6. XRD patterns of bulk GEM and ultrafine GEM.

H_2SO_4 concentration since the ionization of GEM was restrained by $[H^+]$ concentration.

3.4. Effect of drying methods

The spray-freeze drying process is a cryogenic atomization technology in which either a solution or slurry containing an active pharmaceutical ingredient (API) and pharmaceutical excipient(s) is atomized directly into a compressed liquid such as liquid nitrogen (Rogers et al., 2002). The advantage of spray-freeze drying is that the solution or slurry can be frozen at the ultra-rapid rate and the solvent or water sublimes slowly at low temperature, which can prevent the crystalline growth and the powder aggregation. Fig. 5A and B gave SEM images of the powders obtained from oven drying and spray-freeze drying. The cake dried in the oven at 40 °C was fractured into aggregates and could not be completely pulverized, although the size and morphology of the primary particles were kept similar to those of particles in slurry (Fig. 5A). However, when the as-obtained wet cake was re-dispersed into the appropriate deionized water and then dried by spray-freeze drying, the spherical particles with a mean size of 1.25 μm and a narrow PSD ranging from 0.6 to 3 μm could be generated, as shown in Fig. 5B.

3.5. Powder X-ray diffraction studies

X-ray powder diffraction was performed to determine the physical state of commercial bulk GEM and ultrafine GEM. The corresponding patterns were displayed in Fig. 6. The crystalline peaks were found in the diffraction patterns of the as-prepared GEM as well as those of bulk drug, demonstrating that the samples were crystalline. Obviously, different samples had almost the same peak positions, clearly indicating that the reactive precipitation process had no effect on the physical characteristics of GEM. In addition, it could also be seen that the peaks of ultrafine GEM had lower intensities than those of bulk GEM, suggesting lower crystallinity and smaller particle size in the former case. Usually, the pharmaceuticals with lower crystallinity and smaller size have higher dissolution rate and bioavailability (Zhong et al., 2005; Sarkari et al., 2002). Therefore, the loss in crystallinity and the reduction of particle size of ultrafine GEM are expected to enhance its dissolution rate and biovailability.

3.6. FT-IR spectroscopy

Typical FT-IR spectra of bulk GEM and ultrafine GEM in the range of 400–4000 cm^{-1} were compared in Fig. 7. The spectrum of ultrafine GEM showed no obvious difference from that of bulk GEM in the whole area of GEM absorption bands. This well demonstrated that the addition of MC and the employment of reactive precipitation process did not change the physical characteristics of GEM, which were confirmed by XRD patterns (Fig. 6).

3.7. Drug content analyses

In the reactive precipitation, about 5 wt.% (based on the weight of GEM) MC was used in basic solution to inhibit the growth and the agglomeration of particles. Some MC might remain in the ultrafine powder. Therefore, the drug contents were examined by HPLC system. The result showed that drug content of ultrafine GEM was 99.5% (99.5 ± 0.34%), which proved that most of MC had been removed by washing the cake multiple times with deionized water.

3.8. Wettability

The wettability of ultrafine GEM and bulk GEM was evaluated by measuring the contact angle at the purified water/compact of powder. The contact angles of ultrafine GEM and bulk GEM were 65° and 61°, respectively, indicating that the wettability of GEM was not evidently affected by the reduction of particle size.

3.9. Dissolution test

The dissolution profiles of bulk product and the as-prepared GEM powder in 0.2 mol/L phosphate buffer solution (pH 7.5) were depicted in Fig. 8. At 37 °C, the dissolution rate of ultrafine GEM increased to 43.5% after 30 min, while only 8.5% of bulk GEM dissolved. After 120 min, about 91.2% of ultrafine GEM was dissolved, but there was only 23.6% of bulk GEM dissolved. The increase of the dissolution rate of ultrafine GEM could be mainly attributed to the obvious reduction of the particle size (from about 110 μm for bulk GEM to around 1.25 μm for ultrafine GEM) and the great increase of specific surface area (from 1.7816 m^2/g for bulk GEM to 11.0162 m^2/g for ultrafine GEM), which could be explained by the

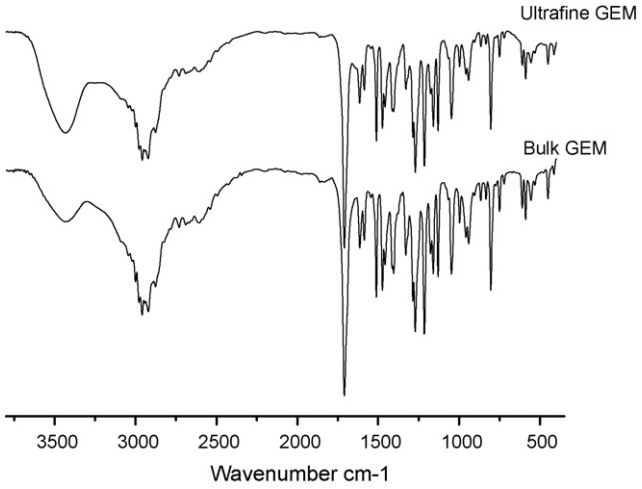


Fig. 7. FT-IR spectra of bulk GEM and ultrafine GEM.

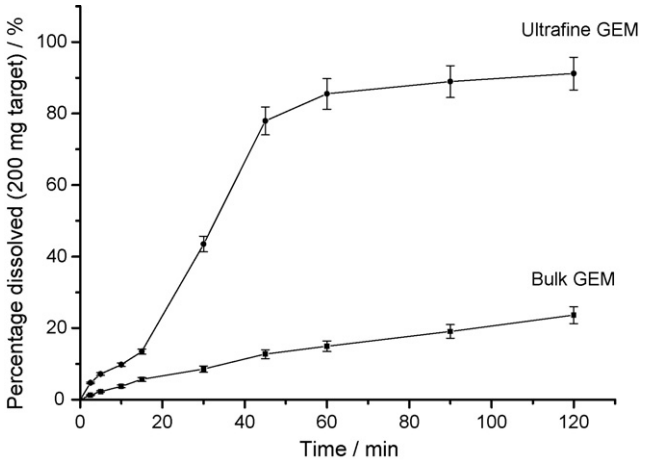


Fig. 8. Dissolution profiles of bulk GEM and ultrafine GEM.

Nernst–Noyes–Whitney equation.

$$\frac{dm}{dt} = \left(\frac{DA}{h}\right)(C_s - C) \quad (5)$$

where dm/dt is the rate of dissolution, D represents the diffusion coefficient, A indicates the surface area, h stands for the diffusion layer thickness, C_s and C are the saturation concentration and the bulk concentration, respectively.

4. Conclusions

In this study, ultrafine gemfibrozil was prepared using reactive precipitation process in which MC was employed as a hydrophilic polymer to inhibit the growth and the agglomeration of particles. In the process, NaOH aqueous solution (0.15 mol/L) was utilized to prepare GEM-Na solution. According to the particle size, H_2SO_4–NaOH system was the most appropriate one to prepare ultrafine GEM among four systems. The obtained ultrafine GEM particles were spherical and had a mean size of 1.25 μm with a narrow PSD from 0.6 to 3 μm. XRD patterns and FT-IR spectra indicated that there was no change in composition and crystal structure of ultrafine GEM powder. In the dissolution test, about 91.2% of ultrafine GEM was dissolved after 120 min, while there was only 23.6% of bulk GEM dissolved. The as-prepared GEM demonstrated a dramatic improvement in dissolution rate owing to a decreased particle size from ~110 to ~1.25 μm and an increase of specific surface area from 1.7816 to 11.0162 m^2/g. Therefore, reactive precipitation process is a feasible and potentially effective pathway to prepare ultrafine drug powder.

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