International Journal of Pharmaceutics 404 (2011) 198–204

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Continuous and scalable process for water-redispersible nanoformulation of poorly aqueous soluble APIs by antisolvent precipitation and spray-drying

Jun Hu[a,*], Wai Kiong Ng[a], Yuancai Dong[a], Shoucang Shen[a], Reginald B.H. Tan[a,b,**]

[a] Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore
[b] Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 119260, Singapore

ARTICLE INFO

Article history:
Received 2 August 2010
Received in revised form 28 October 2010
Accepted 30 October 2010
Available online 5 November 2010

Keywords:
Antisolvent precipitation
Spray-drying
Fenofibrate
Nanoformulation
Nanocrystal
Poorly water-soluble drug

ABSTRACT

This work investigates the technical feasibility of formulating water-redispersible nanocrystals of a poorly aqueous soluble drug by a continuous and scalable route. By coupling antisolvent precipitation with immediate spray-drying, fenofibrate nanoparticles were precipitated and formulated into a dry powder form containing lactose or mannitol as redispersant, hydroxylpropyl methyl cellulose (HPMC) and sodium dodecyl sulfate (SDS) as stabilizers. Field emission scanning electron microscopy (FESEM) and dynamic laser light scattering (DLLS) showed that nanosized fenofibrate were observed both upon precipitation and after the formulated powder was reconstituted in water. Analyses with powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) showed that the formulated drug remained predominantly in the crystalline state. USP dissolution testing in 0.1 N HCl solution with 0.5% (w/w) Tween-80 showed that the nanocrystals could be readily redispersed upon reconstitution and exhibited significantly a higher dissolution rate with 84.2% drug dissolved in 5 min as compared to the conventional spray-dried formulation (31.7%) and the physical mixture (9.7%) using micronized fenofibrate. The results suggest the potential of combining static mixing and spray drying for large-scale continuous production of pharmaceutical nanoformulations.

1. Introduction

Poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and has led to the development of novel formulation technologies (Kesisoglou et al., 2007). While the strategy of reducing the particle size of an active pharmaceutical ingredient (API) by micronization has already been applied in the pharmaceutical industry for several decades, nanonization either by "top-down" or "bottom-up" approach can further enhance the dissolution rate of the poorly water-soluble drugs and increase oral bioavailability (Jia et al., 2002; Merisko-Liversidge et al., 2003; Rabinow, 2004; Keck and Muller, 2006; Kesisoglou et al., 2007). In comparison to micronized-APIs, drug nanocrystals possess some specific advantages, such as enlarged surface area, enhanced saturation solubility, and increased dissolution rate, which result in an increased and consistent oral bioavailability. Drug nanocrystals have been defined as nanoparticles being composed of 100% drug without any matrix material and with a mean particle size below 1 μm (Keck and Muller, 2006). Currently, industrial-scale production of drug nanocrystals falls mainly into the category of "top-down" approaches, in particular media milling and high pressure homogenization, which basically rely on mechanical attrition to render large crystalline particles into nanoparticles (Van Eerdenbrugh et al., 2008). In contrast, the "bottom-up" approaches, which rely on controlled precipitation/crystallization to form nanoparticles by building particles up from the molecular state, are not widely used for drug nanocrystal production due to difficulties to retain the nanosize after precipitation, subsequent particle growth, solid-state stability, scale-up difficulties, poor drug redispersibility, residual solvent content, and high production costs (Horn and Rieger, 2001; Rasenack and Muller, 2002; Rogers et al., 2004; Matteucci et al., 2006; de Waard et al., 2008a; Dong et al., 2009b). Such methods include supercritical fluid technologies such as rapid expansion of supercritical solution (RESS) and gas antisolvent precipitation (GAS) (Tom and Debenedetti, 1991; Elvassore et al., 2001; Turk et al., 2002; Pathak et al., 2004; Turk and Lietzow, 2004; Shekunov et al., 2006) and spray freezing/evaporation into liquid (Hu et al., 2002, 2004; Rogers et al., 2002; Sarkari et al., 2002). Among them, antisolvent precipitation was reported as a

* Corresponding author. Tel.: +65 67963848; fax: +65 63166183.
** Corresponding author at: Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore. Tel.: +65 67963841; fax: +65 63166183.
E-mail addresses: hu_jun@ices.a-star.edu.sg (J. Hu), reginald_tan@ices.a-star.edu.sg (R.B.H. Tan).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.10.055

simple and cost effective approach with scale-up potential (Horn and Rieger, 2001; Rogers et al., 2004). Examples are the hydrosols developed by Sucker (Novartis, previously Sandoz) and the product Nanomorph by Soliqs/Abbott (previously Knoll/BASF) and other precipitation techniques differing in precipitation details (Keck and Muller, 2006). In comparison to the "top-down" technologies which can only be used in a batch-production process, antisolvent precipitation has the potential to be applied in a continuous manufacturing process, which meets the new trend of changing the manufacturing concept from batch-wise to continuous processing in the pharmaceutical industry (Leuenberger, 2001; Gonnissen et al., 2008). Besides, it may lead to smaller particle size and amorphous drug nanoparticles which are theoretically able to get the highest saturation solubility and dissolution rate, and totally avoid potential metal contamination problems existing in "top-down" technologies (Kesisoglou et al., 2007; Mueller and Keck, 2008).

In principle, nanonization by antisolvent precipitation involves the intensive mixing of an organic solvent containing a poorly water-soluble drug with an antisolvent (such as an aqueous medium), which results in the precipitation of finely dispersed drug nanocrystals. Although the particle formation process sounds straightforward, retaining the nanosize of the fresh precipitates is a key challenge. As smaller particles are more soluble than large ones, material transfer occurs from the fines to the coarse particles driven by a phenomenon called "Ostwald ripening" whereby coarse particles grow at the expense of fine particles re-dissolving (Horn and Rieger, 2001). "Top-down" approaches are not notably affected by this phenomenon, as the drug nanocrystals produced are typically not soluble in the working medium and remain comparatively stable in particle size. Although some surfactants (e.g. sodium dodecyl sulfate, modified gelatins, hydroxypropyl methyl cellulose, poloxamer, etc.) can act as short-term stabilizers to retard the growing process of the nanocrystals, prolonged stabilization can only be achieved by immediate drying (Gassmann et al., 1994). And prior to drying, redispersants need to be added to the nanosuspension to ensure that the dried drug nanocrystals remain unaggregated as individual nanoentities. After conversion to the dry powder form, it is of high importance that upon reconstitution, the drug nanocrystals are released from the formulation as an ultrafine dispersion without aggregates to retain the main advantage of bioavailability enhancement. Otherwise, if aggregation occurs, the bioavailability decreases with increasing proportion of aggregates. To achieve this, the drug needs to remain nanodispersed in solid matrix of the solid dosage form (Keck and Muller, 2006; Kesisoglou et al., 2007). Sugars, such as lactose, mannitol, and sucrose, are commonly used as redispersants in oral formulations, which need to be added to the nanosuspension before spray-drying or freeze-drying to ensure complete redispersion of nanoparticles into their pre-drying state (Abdelwahed et al., 2006; Kesisoglou et al., 2007). The principle is that the dried drug nanocrystals are interdispersed and stabilized in the continuous solid matrix of the sugars to prevent aggregation. Freeze-drying and spray-drying are two commonly used methods to convert nanosuspensions into redispersible dry powders (Abdelwahed et al., 2006; Chaubal and Popescu, 2008). Compared with freeze-drying, spray-drying is reported as more cost-effective and easier to be implemented directly after antisolvent precipitation in continuous production process (Gassmann et al., 1994).

Our previous work has described a continuous and highly effective static mixing process for the production of drug nanocrystals via the antisolvent precipitation approach (Dong et al., 2009a). The use of a static mixer has major scale-up advantages in process development, since it maintains practically the same precipitation conditions in a beaker, and avoids stirring and mixing problems at production-scale (Keck and Muller, 2006). In order to extend this work to formulate the nanocrystals produced into a water-redispersible dry powder form in a continuous process, this work is aimed at stabilizing the nanocrystals stream against particle growth ("Ostwald ripening" effect) and aggregation with the aid of stabilizers and redispersant, followed by immediate spray-drying. As a proof-of-concept at lab-scale, antisolvent precipitation was conducted batch-wise by antisolvent precipitation followed by immediate spray-drying using a mini-spray dryer (within 1 min). This batch precipitation process is used as a proxy for continuous static mixing because the static mixing process would produce a large quantity of nanocrystals and require a spray dryer beyond lab-scale at much higher costs. To ensure that the batch results are equivalent to static mixing, the particle size of nanocrystals from this batch process is analyzed and compared with those by static mixing.

Fenofibrate was chosen as the model API as it is a lipophilic drug with negligible water solubility and belongs to BCS Class II drugs (Munoz et al., 1994). Bioavailability of fenofibrate solely depends on the dissolution rate in the gastrointestinal tract. This drug is used in lipid regulation as it decreases low-density lipoprotein level (LDL) and very-low-density lipoprotein level (VLDL), as well as increases high-density lipoprotein level (HDL). As fenofibrate has a very low glass transition temperature (T_g) of −21.3 °C (de Waard et al., 2008b), there is a high risk of uncontrolled crystallization as a solid dispersion (Drooge et al., 2006). Therefore, this work may be useful to address potential application of nanocrystals. Currently, there are two types of fenofibrate nanocrystal formulation tablets in the market. One is Tricor®, which is developed via Elan's NanoCrystal® media milling technology and being marketed by Abbott. The other is Triglide®, which is developed via SkyPharma's IDD®-P high-pressure homogenization technology and being marketed by SkyPharma (Van Eerdenbrugh et al., 2008). As both products are produced by "top-down" technologies, our work using a "bottom-up" approach may provide an alternative route to prepare fenofibrate nanoformulations.

2. Materials and methods

2.1. Materials

Fenofibrate (micronized), α-lactose monohydrate, mannitol, sodium dodecyl sulfate (SDS), and Tween-80 were purchased from Sigma–Aldrich. Hydroxylpropyl methyl cellulose (HPMC) E3 was obtained from Shin-Etsu Chemical Co., Ltd. Ethanol and hydrochloric acid were supplied by Fisher Scientific. Ethanol was selected as it is a water-miscible organic solvent with low toxicity and boiling point.

2.2. Methods

2.2.1. Antisolvent precipitation of drug nanocrystals by batch and static mixing

The compositions of drug solution and antisolvent containing excipients are given in Table 1. During batch precipitation at room temperature, 1 ml of drug solution (solvent) was rapidly injected using an Eppendorf Pipette into a 50 ml-beaker containing 10 ml of antisolvent at the stirring rate of 1000 rpm (IKA Magnetic Stirrer, Germany) to produce a fine milky suspension.

Table 1
Compositions of drug solution and antisolvent containing excipients.

Solvent/antisolvent	Composition
API in organic solvent	50 mg/ml of fenofibrate in ethanol
Excipients in aqueous medium	Water containing 10 mg/ml lactose or mannitol, 0.5 mg/ml SDS and 0.5 mg/ml HPMC E3

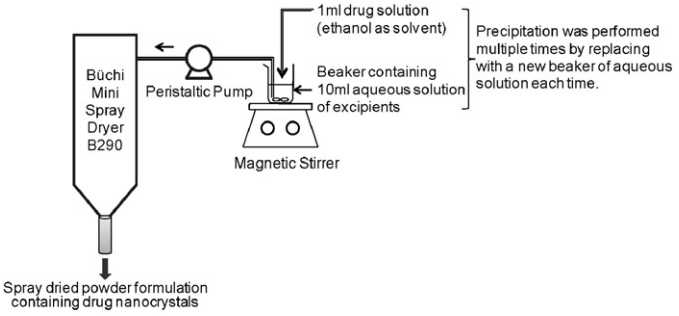

Fig. 1. Process flow of batch precipitation followed by spray-drying.

During static mixing at room temperature, the drug and anti-solvent solutions were pumped into a 6-element SMV DN25 static mixer (Sulzer Chemtech, Switzerland) at flow rates of 50 ml/min and 500 ml/min respectively, with the nozzle diameters of 0.5 and 1.5 mm.

2.2.2. Preparation of drug nanoformulation in powder form by immediate spray-drying

In order to minimize the "Ostwald ripening" effect, the batch precipitation (as a proxy to static mixing) was followed by immediate spray-drying (Büchi Mini Spray-dryer B-290 with inlet loop B-295, Germany) as illustrated in Fig. 1.

Upon precipitation, the fine milky suspension was immediately and continuously fed to the spray dryer via a peristaltic pump and dried within 1 min. The inlet temperature was kept at 150 °C and the feeding rate was 11 ml/min. Shortly before the spray-drying process ends, batch precipitation was repeated followed by spray-drying in the same manner. By repeating the same procedures, approximately 10 g of drug nanoformulation in powder form was produced in 1 h.

2.2.3. Preparation of control samples

To evaluate the performance of the spray-dried nanoformulation, two control samples with a similar composition but containing micronized fenofibrate were prepared as comparison. The first sample is a physical mixture consisting of 1 g of micronized fenofibrate, 2 g of lactose, 0.1 g of HPMC E3 and 0.1 g of SDS, which was mixed using a mortar and pestle. The second sample is prepared by spray-drying a suspension of the physical mixture in 200 ml water with inlet temperature of 150 °C and feeding rate of 10 ml/min while being agitated at 600 rpm. Prior spray-drying, the suspension was ultrasonically dispersed for 10 min.

2.2.4. Particle size measurement

Dynamic laser light scattering technique (Nano-Zetasizer, Malvern, UK) was used to measure the size of the freshly precipitated drug particles and the reconstituted drug particles upon redispersing the spray-dried formulation in water. To reduce the effect of particle interaction, the particle concentration was diluted with deionized water to approximately 0.25 mg/ml for each measurement. The measurements were done in triplicate to determine the *z*-average size. To measure the size of reconstituted drug particles, ~50 mg dry powder containing ~15 mg fenofibrate was added into 10 ml water, and then the resultant suspension was vigorously shaken by hand for 1 min.

2.2.5. Field emission scanning electron microscopy (FESEM)

To prepare freshly precipitated or reconstituted drug particles for analysis, one drop of the suspension obtained by antisolvent precipitation or reconstitution was placed onto a carbon-coated copper grid and then vacuum dried at 35 °C for 1 h. All samples were mounted on aluminum sample studs using double-sided carbon tapes and Au sputtered at 20 mA for 70 s before examination using a Field Emission Scanning Electron Microscope (JEOL JSM-6700F, Japan) at 5 kV.

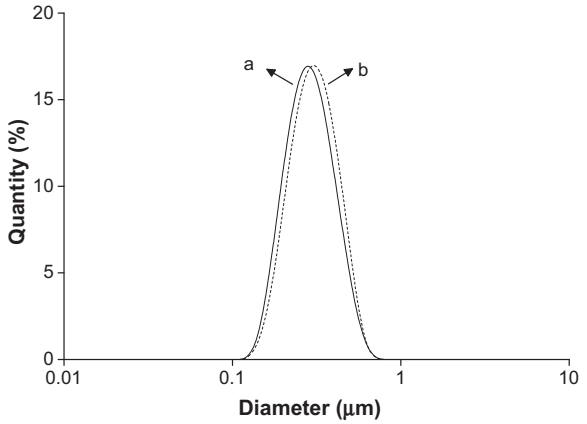

Fig. 2. Size distribution of freshly precipitated particles by (a) batch mixing and (b) static mixing.

2.2.6. Powder X-ray diffraction (PXRD)

The crystallinity of powder samples was analyzed using an X-ray diffractometer (D8-Advance Bruker, Germany). Samples were scanned from 5° to 40° (2θ) with a step size of 0.017° and a time per step of 1 s using Cu Kα radiation.

2.2.7. Differential scanning calorimetry (DSC)

A Diamond DSC Calorimeter (PerkinElmer, USA) was used to determine the degree of crystallinity of the formulated samples. This was defined as the ratio of the melting enthalpy of fenofibrate in the formulated sample to the heat of fusion of as purchased fenofibrate multiplied by the weight fraction of fenofibrate of the formulated sample. Due to the very low glass transition temperature of fenofibrate, it was assumed that as purchased micronized-fenofibrate was completely crystalline. 3–5 mg of powder was filled into a hermetically closed aluminum pan before being heated at 10 °C/min from 40 to 110 °C.

2.2.8. Dissolution test

The dissolution profiles of powder samples were measured in 900 ml of 0.1 N hydrochloric acid solution with 0.5% (w/w) Tween-80 at 37 °C, using a USP dissolution apparatus II (VK 7010

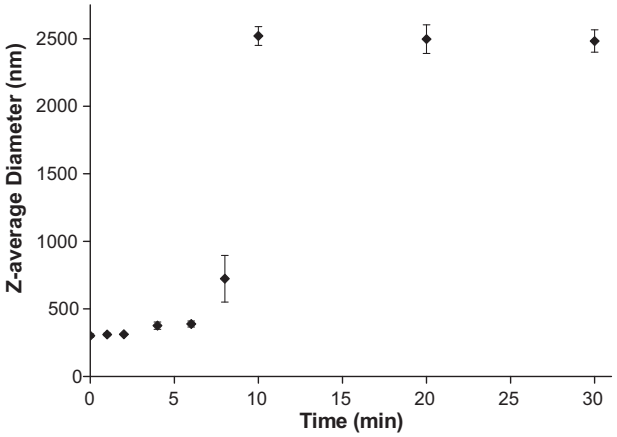

Fig. 3. The effect of ageing time on the size of freshly precipitated drug particles under stirring condition at the rate of 600 rpm.

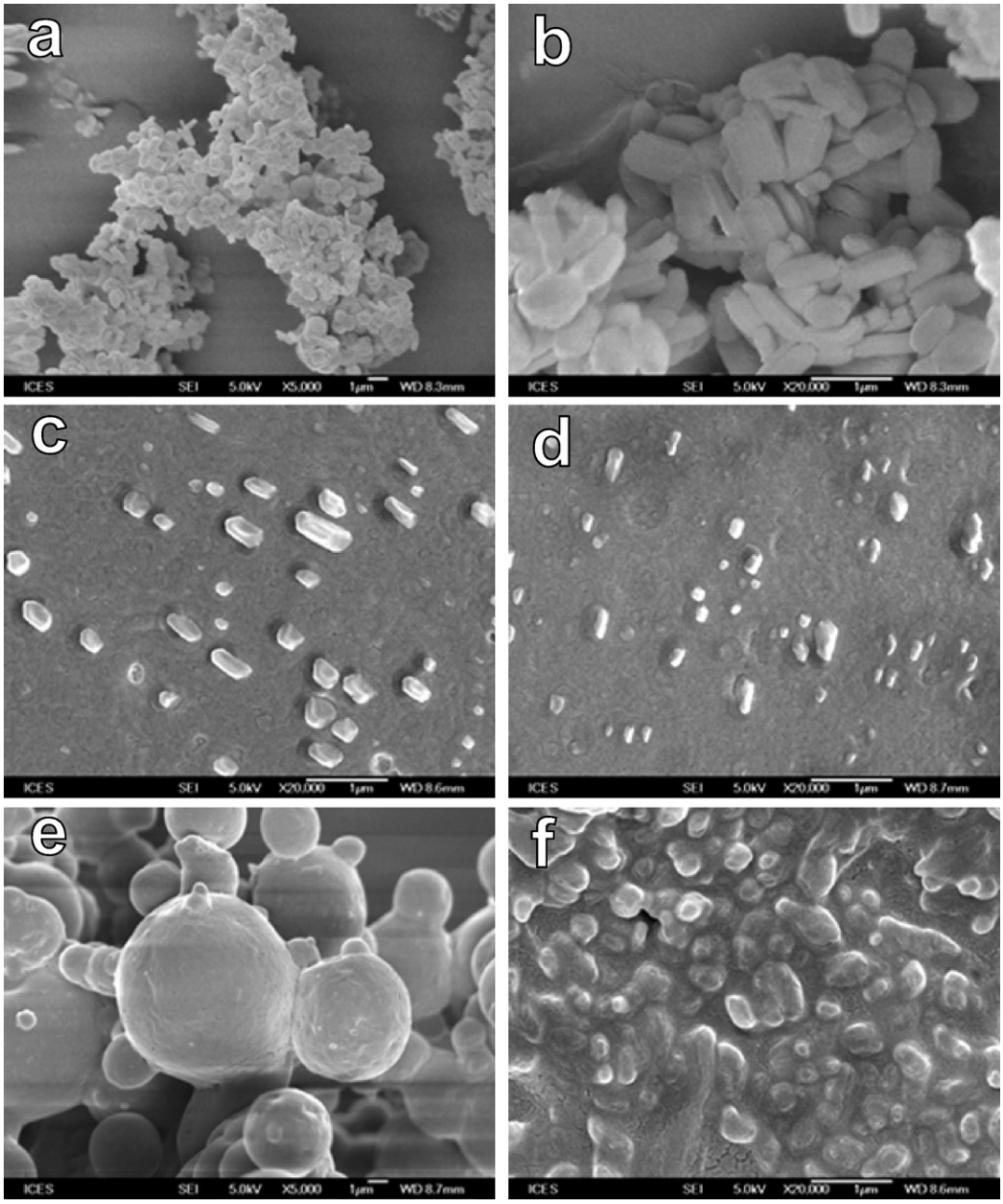

Fig. 4. Scanning electron micrographs of (a) and (b) micronized fenofibrate, (c) and (d) freshly precipitated fenofibrate particles by batch and static mixing respectively, (e) spray-dried nanoformulation, and (f) reconstituted drug particles by redispersing the spray-dried nanoformulation in water.

Dissolution Tester, VARIAN, UK) with the paddle speed set at 100 rpm. Sample was taken by auto sampling system equipped with filter (pore size: 0.22 μm) at interval of 5 min. The concentration of fenofibrate was measured online spectrophotometrically at wavelength of 290 nm. Each powder sample contained 25 mg of fenofibrate.

3. Results and discussion

3.1. Antisolvent precipitation and formulation of fenofibrate nanoparticles

In both the batch and static mixing experiments, rapid mixing of the fenofibrate solution with the antisolvent induces high supersaturation, which results in fast nucleation and a large number of fine particles being precipitated. As shown in Fig. 2, DLLS analysis showed that both methods produced particles that were submicron in size. Sodium dodecyl sulfate (SDS) and hydroxylpropyl methyl cellulose (HPMC) E3, which are present in the antisolvent solution, are found to be effective in retaining the particles within the nanosized range by minimizing particle aggregation and retarding the Ostwald ripening effect. As the *z*-average diameters of these particles by batch and static mixing were quite comparable at 318 ± 19 nm and 328 ± 22 nm respectively, the results also confirmed that batch mixing can be used as a suitable proxy for static mixing to produce nanosized particles in this study.

Although a suspension of nanosized fenofibrate particles has been prepared after precipitation, the presence of ethanol solvent in the suspension increases the solubility of fenofibrate in the aqueous phase and accelerates the process of Ostwald ripening, which may result in the growth of nanoparticles in size and/or change in crystallinity (Liu et al., 2007; Kumar and Prud'homme, 2009).

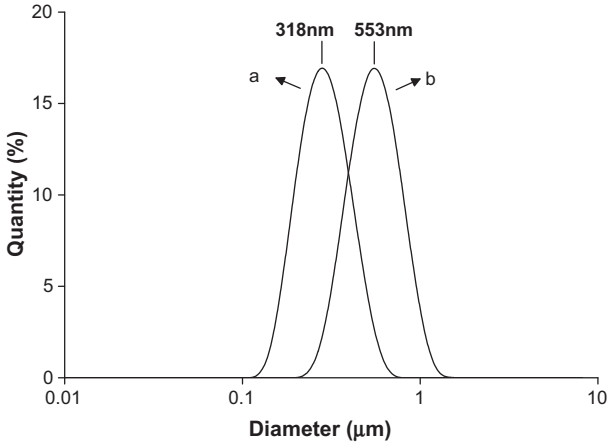

Fig. 5. Size distribution and *z*-average diameter of (a) freshly precipitated particles and (b) reconstituted drug particles by redispersing the spray-dried powder formulation in water.

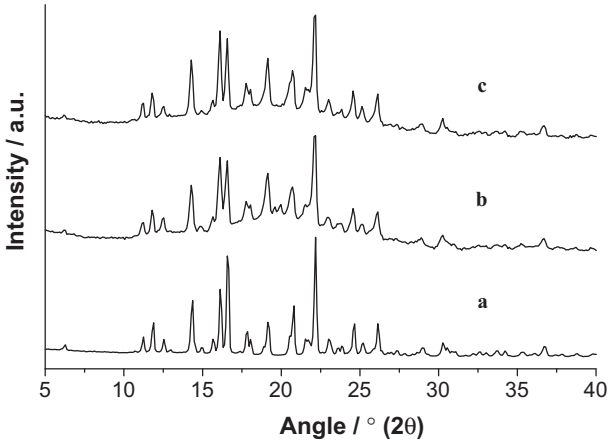

Fig. 6. Powder X-ray diffractograms of (a) micronized fenofibrate, (b) spray-dried formulation containing micronized fenofibrate, and (c) spray-dried nanoformulation.

Fig. 3 shows the size evolution of the freshly precipitated fenofibrate nanoparticles under stirring condition at the rate of 600 rpm. As can been seen, within 2 min after precipitation, the drug particles maintained similar *z*-average diameter as the freshly precipitated particles. At 2 min, particle size started to increase slowly, which reached a sharp rise after 6 min. After 10 min, the mean particle size

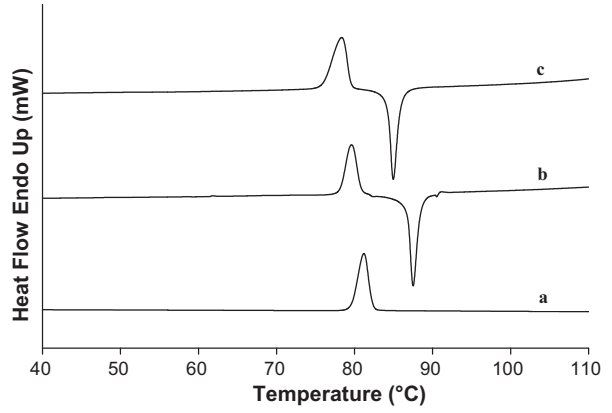

Fig. 7. DSC thermograms of (a) micronized fenofibrate, (b) spray-dried formulation containing micronized fenofibrate, and (c) spray-dried nanoformulation.

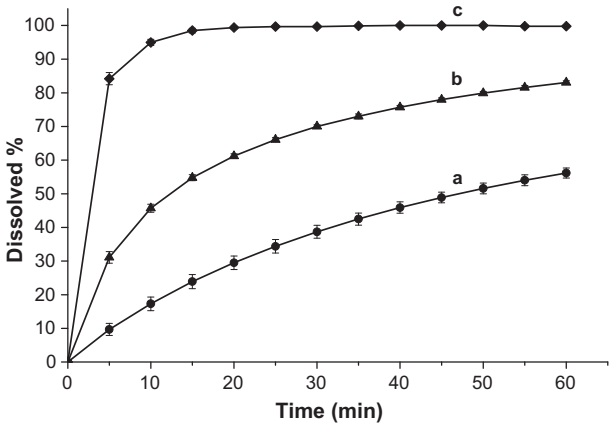

Fig. 8. Dissolution profiles of (a) physical mixture of micronized fenofibrate and excipients, (b) spray-dried physical mixture, and (c) spray-dried nanoformulation ($n = 6$, mean ± SD). Lactose was used as the redispersant in the formulation.

increased to 2.5 μm. The result indicates the necessity of immediate drying to help stabilize the freshly precipitated drug nanoparticles. In this study, immediate spray-drying following antisolvent precipitation is carried out to inhibit particle growth and formulate the suspension into a water-redispersible powder form, which can be used for subsequent tabletting or capsule filling.

3.2. Physicochemical characterization

3.2.1. Morphology

As compared to aggregated clusters of as purchased micronized fenofibrate in Fig. 4a and b, drug nanocrystals freshly precipitated by batch and static mixing are easily distinguishable as individual nanoparticles in Fig. 4c and d. Their geometric dimensions in hundreds of nanometer agreed with the earlier particle size measurements. After spray-drying, a micron-sized spherical matrix-structure of fenofibrate and excipients was observed in Fig. 4e, which is likely due to the presence of redispersant lactose. Upon reconstitution in water, as the redispersant lactose is very soluble as compared to fenofibrate, it dissolves very quickly exposing the fenofibrate nanoparticles in Fig. 4f.

3.2.2. Redispersibility

In Fig. 5, DLLS analysis shows that the *z*-average diameter of the reconstituted drug particles remained in the submicron range and

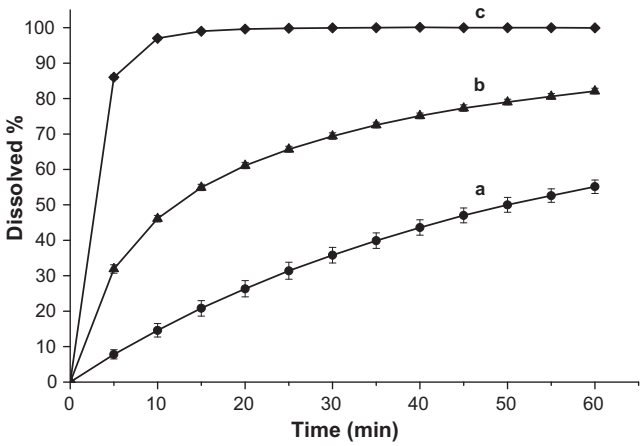

Fig. 9. Dissolution profiles of (a) physical mixture of micronized fenofibrate and excipients, (b) spray-dried physical mixture, and (c) spray-dried nanoformulation ($n = 6$, mean ± SD). Mannitol was used as the redispersant in the formulation.

demonstrates good redispersibility of fenofibrate nanocrystals in the spray-dried nanoformulation.

3.2.3. Powder X-ray diffraction

As shown in Fig. 6, characteristic peaks of fenofibrate are clearly observed in both the nanoformulation and the spray-dried powder sample having the same composition but with micronized fenofibrate. The results suggest that the crystalline form of fenofibrate is present. The low amorphous humps in Fig. 6b and c as compared with the diffractogram (Fig. 6a) of micronized fenofibrate are likely contributed by amorphous lactose after spray-drying.

3.2.4. Differential scanning calorimetry

As shown in Fig. 7, the endothermic peaks at approximately 78–82 °C are resulted from the melting of fenofibrate in the crystalline form in micronized fenofibrate, spray-dried formulation containing micronized fenofibrate and nanoformulation. The subsequent exothermic peaks in Fig. 7b and c are due to the recrystallization of amorphous lactose. Using micronized fenofibrate as the 100% crystalline reference, the degree of crystallinity of the nanoformulation was determined to be approximately 90%. The results suggest that fenofibrate in the nanoformulation is predominantly in the crystalline state, which agree with the PXRD data.

3.2.5. Dissolution

Fig. 8 compares the dissolution profiles of the spray-dried nanoformulation, the physical mixture containing the same composition but micronized fenofibrate and the spray-dried physical mixture. The spray-dried nanoformulation exhibits a much faster dissolution rate (84.2% dissolved within 5 min) than the physical mixture with (31.7%) and without spray-drying (9.7%). The enhancement in dissolution rate of the physical mixture by spray-drying is probably due to the deaggregation of the micronized fenofibrate. As shown in Fig. 4a and b, micronized fenofibrate is composed of largely aggregated particles and aggregation reduces the surface area available for dissolution. After physical mixing with a mortar and pestle, the mechanical stress applied tends to encourage further particle aggregation. By ultrasonic dispersion of the physical mixture prior spray-drying, some of the fenofibrate particles may become deaggregated leading to an increase in surface area and a higher dissolution rate. According to Noyes–Whitney equation, the drug dissolution rate is linearly proportional to the surface area exposed to the dissolution medium (Kesisoglou et al., 2007). As compared with micronized fenofibrate, the spray-dried nanocrystals have a much larger surface area and increased saturation solubility, which would further accelerate the drug dissolution rate (Muller and Peters, 1998; Kesisoglou et al., 2007). In addition, the spray-dried nanoformulation was completely dissolved in approximately 15 min, 17% and 44% drug remained undissolved from the physical mixture with and without spray-drying respectively, even after 60 min. The substitution of lactose with mannitol as redispersant produced similar dissolution results as shown in Fig. 9. The fast release of drug nanocrystals from the matrix provides an advantage for this formulation as compared with the conventional solid dispersion whereby the matrix made of polymer materials provides a sustained release.

4. Conclusions

An experimental study was conducted to develop a continuous and scalable process that can precipitate fenofibrate nanocrystals and formulate them into a water-redispersible powder form.

In this process, fenofibrate was dissolved in ethanol and rapidly mixed with the antisolvent water solution of excipients to prepare a nanosuspension, which was then immediately spray-dried into a powder form to minimize the effect of Ostwald ripening. Sodium dodecyl sulfate (SDS) and hydroxypropyl methyl cellulose (HPMC) as stabilizers and lactose or mannitol as redispersant were added into the antisolvent solution to minimize particle growth and aggregation and to keep the drug as individual nanoentities in the powder composition. Particle size measurements and SEM observations showed that the freshly precipitated fenofibrate was submicron in size and the spray-dried nanoformulation disintegrated into nanosized fenofibrate upon reconstitution in water. According to PXRD and DSC data, the drug remains predominantly in the crystalline state. Dissolution test results showed that the nanoformulation achieved a significantly higher drug dissolution rate at 84.2% within 5 min than the physical mixture with (31.7%) and without (9.7%) spray-drying. The developed process is a direct and fast formulation approach to produce drug nanocrystals in a water-redispersible powder form. The results demonstrate the potential of coupling antisolvent precipitation using static mixing and spray-drying to achieve continuous industrial-scale production of pharmaceutical nanoformulations.

Acknowledgement

This work was supported by project Grant ICES/09-222A02 from A*STAR (Agency for Science, Technology and Research) of Singapore.

References

Abdelwahed, W., Degobert, G., Stainmesse, S., Fessi, H., 2006. Freeze-drying of nanoparticles: formulation, process and storage considerations. Adv. Drug Deliv. Rev. 58, 1688–1713.
Chaubal, M.V., Popescu, C., 2008. Conversion of nanosuspensions into dry powders by spray drying: a case study. Pharm. Res. 25, 2302–2308.
de Waard, H., Hinrichs, W.L., Frijlink, H.W., 2008a. A novel bottom-up process to produce drug nanocrystals: controlled crystallization during freeze-drying. J. Control. Release 128, 179–183.
de Waard, H., Hinrichs, W.L., Visser, M.R., Bologna, C., Frijlink, H.W., 2008b. Unexpected differences in dissolution behavior of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated. Int. J. Pharm. 349, 66–73.
Dong, Y., Ng, W.K., Hu, J., Shen, S., Tan, R.B., 2009a. A continuous and highly effective static mixing process for antisolvent precipitation of nanoparticles of poorly water-soluble drugs. Int. J. Pharm. 386, 256–261.
Dong, Y., Ng, W.K., Shen, S., Kim, S., Tan, R.B., 2009b. Preparation and characterization of spironolactone nanoparticles by antisolvent precipitation. Int. J. Pharm. 375, 84–88.
Drooge, D.J.v., Hinrichs, W.L., Visser, M.R., Frijlink, H.W., 2006. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int. J. Pharm. 310, 220–229.
Elvassore, N., Bertucco, A., Caliceti, P., 2001. Production of insulin-loaded poly(ethylene glycol)/poly(L-lactide) (PEG/PLA) nanoparticles by gas antisolvent techniques. J. Pharm. Sci. 90, 1628–1636.
Gassmann, P., List, M., Schweitzer, A., Sucker, H., 1994. Hydrosols – alternatives for the parenteral application of poorly water-soluble drugs. Eur. J. Pharm. Biopharm. 40, 64–72.
Gonnissen, Y., Goncalves, S.I.V., De Geest, B.G., Remon, J.P., Vervaet, C., 2008. Process design applied to optimise a directly compressible powder produced via a continuous manufacturing process. Eur. J. Pharm. Biopharm. 68, 760–770.
Horn, D., Rieger, J., 2001. Organic nanoparticles in the aqueous phase – theory, experiment, and use. Angew. Chem. Int. Ed. 40, 4331–4361.
Hu, J., Johnston, K.P., Williams 3rd, R.O., 2004. Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. Int. J. Pharm. 271, 145–154.
Hu, J., Rogers, T.L., Brown, J., Young, T., Johnston, K.P., Williams 3rd, R.O., 2002. Improvement of dissolution rates of poorly water soluble APIs using novel spray freezing into liquid technology. Pharm. Res. 19, 1278–1284.
Jia, L., Wong, H., Cerna, C., Weitman, S.D., 2002. Effect of nanonization on absorption of 301029: ex vivo and in vivo pharmacokinetic correlations determined by liquid chromatography/mass spectrometry. Pharm. Res. 19, 1091–1096.
Keck, C.M., Muller, R.H., 2006. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur. J. Pharm. Biopharm. 62, 3–16.
Kesisoglou, F., Panmai, S., Wu, Y., 2007. Nanosizing – oral formulation development and biopharmaceutical evaluation. Adv. Drug Deliv. Rev. 59, 631–644.
Kumar, V., Prud'homme, R.K., 2009. Nanoparticle stability: processing pathways for solvent removal. Chem. Eng. Sci. 64, 1358–1361.
Leuenberger, H., 2001. New trends in the production of pharmaceutical granules: batch versus continuous processing. Eur. J. Pharm. Biopharm. 52, 289–296.

Liu, Y., Kathan, K., Saad, W., Prud'homme, R.K., 2007. Ostwald ripening of beta-carotene nanoparticles. Phys. Rev. Lett. 98.
Matteucci, M.E., Hotze, M.A., Johnston, K.P., Williams, R.O., 2006. Drug nanoparticles by antisolvent precipitation: mixing energy versus surfactant stabilization. Langmuir 22, 8951–8959.
Merisko-Liversidge, E., Liversidge, G.G., Cooper, E.R., 2003. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur. J. Pharm. Sci. 18, 113–120.
Mueller, R.H., Keck, C.M., 2008. Second generation of drug nanocrystals for delivery of poorly soluble drugs: smartCrystal technology. Eur. J. Pharm. Sci. 34, S20–S21.
Muller, R.H., Peters, K., 1998. Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size-reduction technique. Int. J. Pharm. 160, 229–237.
Munoz, A., Guichard, J.P., Reginault, P., 1994. Micronised fenofibrate. Atherosclerosis 110, S45–S48.
Pathak, P., Meziani, M.J., Desai, T., Sun, Y.P., 2004. Nanosizing drug particles in supercritical fluid processing. J. Am. Chem. Soc. 126, 10842–10843.
Rabinow, B.E., 2004. Nanosuspensions in drug delivery. Nat. Rev. Drug Discov. 3, 785–796.
Rasenack, N., Muller, B.W., 2002. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm. Res. 19, 1894–1900.
Rogers, T.L., Gillespie, I.B., Hitt, J.E., Fransen, K.L., Crowl, C.A., Tucker, C.J., Kupperblatt, G.B., Becker, J.N., Wilson, D.L., Todd, C., Broomall, C.F., Evans, J.C., Elder, E.J., 2004. Development and characterization of a scalable controlled precipitation process to enhance the dissolution of poorly water-soluble drugs. Pharm. Res. 21, 2048–2057.
Rogers, T.L., Nelsen, A.C., Hu, J.H., Brown, J.N., Sarkari, M., Young, T.J., Johnston, K.P., Williams, R.O., 2002. A novel particle engineering technology to enhance dissolution of poorly water soluble drugs: spray-freezing into liquid. Eur. J. Pharm. Biopharm. 54, 271–280.
Sarkari, M., Brown, J., Chen, X.X., Swinnea, S., Williams, R.O., Johnston, K.P., 2002. Enhanced drug dissolution using evaporative precipitation into aqueous solution. Int. J. Pharm. 243, 17–31.
Shekunov, B.Y., Chattopadhyay, P., Seitzinger, J., Huff, R., 2006. Nanoparticles of poorly water-soluble drugs prepared by supercritical fluid extraction of emulsions. Pharm. Res. 23, 196–204.
Tom, J.W., Debenedetti, P.G., 1991. Particle formation with supercritical fluids – a review. J. Aerosol Sci. 22, 555–584.
Turk, M., Hils, P., Helfgen, B., Schaber, K., Martin, H.J., Wahl, M.A., 2002. Micronization of pharmaceutical substances by the Rapid Expansion of Supercritical Solutions (RESS): a promising method to improve bioavailability of poorly soluble pharmaceutical agents. J. Supercrit. Fluids 22, 75–84.
Turk, M., Lietzow, R., 2004. Stabilized nanoparticles of phytosterol by rapid expansion from supercritical solution into aqueous solution. AAPS PharmSciTech 5.
Van Eerdenbrugh, B., Van den Mooter, G., Augustijns, P., 2008. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. Int. J. Pharm. 364, 64–75.