Pharmaceutical Research, Vol. 25, No. 9, September 2008 (© 2008)
DOI: 10.1007/s11095-008-9586-3

Research Paper

Production of Ultrafine Sumatriptan Succinate Particles for Pulmonary Delivery

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Received December 14, 2007; accepted March 31, 2008; published online June 26, 2008

Purpose. Drug particle physical properties are critical for the efficiency of a drug delivered to the lung. The purpose of this study was to produce ultrafine sumatriptan succinate particles for inhalation.
Methods. Sumatriptan succinate particles were produced via reactive precipitation without any surfactants. Several low toxic organic solvents such as acetone, isopropanol, and tetrahydrofuran were investigated as the reaction medium. And the dry powder was obtained via spray drying. FT-IR, HPLC, SEM and XRD were exploited to characterize the physicochemical properties of the ultrafine sumatriptan succinate dry powder. The aerosol performance of the powder was evaluated using an Aeroliser®connected to a multi stage liquid impinger operating at 60 l/min.
Results. The mean particle size of the ultrafine sumatriptan succinate particles obtained under optimum conditions was in the range of 630~679 nm and consequently they were in the respirable range. The spray-dried powder whose fine particle fraction was increased up to 50.6±8.2% showed good aerosol performance whereas the vacuum-dried powder was approximate 18.2±3.0%.
Conclusions. Good aerosol performance ultrafine sumatriptan succinate particles could be produced by reactive precipitation without any additives followed by spray drying at the optimum parameters.

KEY WORDS: pulmonary delivery; reactive precipitation; sumatriptan succinate; ultrafine particle.

INTRODUCTION

Sumatriptan succinate which is a selective serotonin 5-HT agonist at the 5-HT_{1B} and 5-HT_{1D} receptors has been used in the treatment of acute migraine episodes and cluster headache (1,2). It is the first of the "triptan" drugs which have had a significant impact on the treatment of acute migraine attacks and it is available in several dosage forms including products for oral, intranasal, subcutaneous and rectally (3,4). However, a substantial proportion of patients suffer severe nausea or vomiting which may make oral and intranasal treatment unsatisfactory during their migraine attack. Subcutaneous and rectally administration are alternatives, but they are unacceptable to some individuals for their inconvenience such as rubefaction, phlebitis and shock (5,6). The pulmonary delivery for sumatriptan succinate may be a viable alternative for self-administration, whereby these limitations could be overcome.

For the pulmonary delivery, the particles require the aerodynamic diameter between 0.5 and 2 μm for good lung deposition and good flow properties to ensure accurate dosing of the drugs (7–9). Aerodynamic diameter could be depicted as follows

$$D_{ae} = D_{eq}\sqrt{\frac{\rho_P}{\rho_0 \chi}}$$

where D_{ae} and D_{eq} are the aerodynamic diameter and the physical diameter; χ is the dynamic shape factor; ρ_P and ρ_0 are particle and unit densities. The aerodynamic diameter can be decreased by decreasing the particle size, decreasing particle density, or increasing the dynamic shape factor. Particle size and its distribution are the most important design variables of a dry powder inhalation (DPI) formulation (10); so decreasing the particle size is our scope in the present study.

Microstructured materials can be prepared by attrition of parent coarse grained materials using the top-down approach from the macroscale to the microscale, or conversely, by assembly of atoms or particles using the bottom-up approach (11, 12). Some of conventional approaches based on the top-down technique including pearl-ball milling, jet-milling and high pressure homogenizers were applied for preparation of micronized particles (13). The major disadvantage of these techniques is that they produce particles with a broad size distribution (0.5–25 μm). In most cases, the process of micronization by milling is connected with a high input of energy which can induce disorder and defects on the surface of the drug particles and as a result changes in the crystallinity. Consequently, changes in the physical stability of the powders may occur. In order to avoid these thermodynamically activated sites, the drug was prepared directly micro-sized without the use of reduction techniques by milling (14,15).

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In contrast to the techniques previously described, liquid precipitation is a typical bottom-up approach including anti-solvent precipitation (a physical method based on the change of the supersaturation causing by mixing the solution and the antisolvent) and reactive precipitation, which are effective ways to prepare micro- or nano-sized drug particles (16–18). In a chemical reaction, the components of the final product are in a "mixture" with atomic scale mixing. In a precipitation process, solutions of two or more reagents are mixed and an insoluble precipitate or a gelatinous precipitate forms. During a reactive precipitation process, high levels of supersaturation are generated. Thus primary nucleation predominates and consequently micro- or nano-scale particles are formed (19). Furthermore, the production of organic pharmaceutical micro- or nano-products using reactive precipitation technique has been recently demonstrated to be feasible for salbutamol sulfate (20).

The aim of this investigation was to prepare ultrafine sumatriptan succinate particles for dry powder inhalation via reactive precipitation without any surfactants. The corresponding physicochemical properties and aerosol performance of the as-prepared sumatriptan succinate powders were characterized by Fourier transform infrared spectrophotometry (FT-IR), high performance of liquid chromatography (HPLC), scanning electronic microscope (SEM), X-ray diffraction (XRD) and Aeroliser® connected to a multiple stage liquid impinger.

MATERIALS AND METHODS

Materials

In this study, sumatriptan base was purchased from Beijing Lianben Pharm_Chemicals Tech. Co. Ltd, China. Succinic acid was supplied by Beijing Chemical Co. Ltd. Tetrahydrofuran (THF), acetone and isopropyl alcohol (IPA) were obtained from Beijing Yili fine chemicals Co. Ltd. being of analytic grade (Beijing, People's Republic of China).

Methods

Particle Preparation

Liquid precipitation was carried out using the reaction method by instantaneously mixing two reagents as follows (Fig. 1).

The precipitation process was performed in a thermostatic water bath to keep a constant temperature. In the first step, 0.30 ± 0.03 g of sumatriptan base was dissolved in 30 ml of the reaction medium such as acetone, isopropyl alcohol and THF respectively. By mixing the two reagents of sumatriptan base (solution) and succinic acid (THF solution, 0.025 g/ml, 10 ml) in a mol ratio of 1:2, the dispersion was formed spontaneously as the drug was reactive precipitated. The resulting dispersion was then filtrated (or centrifugated) and the filtered paste could be dried at 60°C under vacuum condition or re-dispersed in a suitable solvent such as ethyl acetate (about 100 ml) for spray drying.

Spray Drying

Since spray drying was considered as the preferred drying method to produce the dry powder for inhalation (21–23), the sumatriptan succinate filter paste (about 0.4 g) was redispersed in 100 ml of ethyl acetate to form a suspension and spray-dried (LabPlant SD-basic, UK). In this study, spray-drying was not used to form particles as if solutions were to be dried, but to dry the pre-formed particles. Spray drying was performed under such conditions: feed rate 20 ml/min, inlet and outlet temperatures of 120°C and 80°C, respectively. The spray dried powder collected was then transferred into a container and stored over silica gel until further use for characterization and test.

Particle Characterization

Scanning Electron Microscopy (SEM)

Particle morphology was examined by scanning electron microscopy (SEM, JSM6360, Joel, Japan). Samples were fixed on aluminum stubs with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50 mA for 6 mins.

The particle size and its distribution were determined via the obtained SEM images using the Image-Pro Plus software (Release 5.0, MediaCybernetics, USA).

Fourier Transform Infrared Spectroscopy (FT-IR)

Fourier Transform Infrared (FT-IR) spectra of samples were recorded with a Nicolet model 8700 spectrometer (Nicolet Instrument Corporation, USA) in the wavenumber range of 400–4,000 cm^{-1}. Samples were diluted with KBr mixing powder.

HPLC Method

To determine sumatriptan succinate, several analytical methods are proposed, including HPLC with UV/Vis, Mass

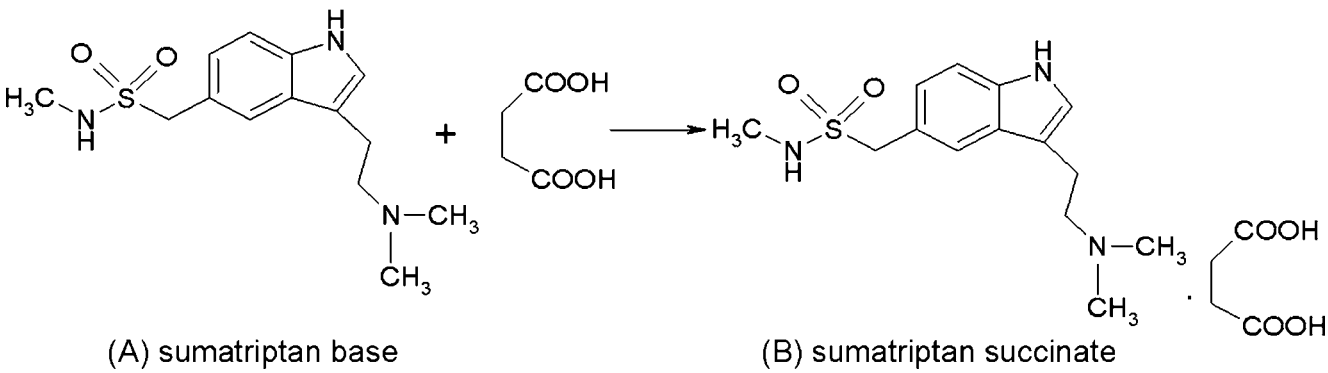

Fig. 1. Reaction formulation.

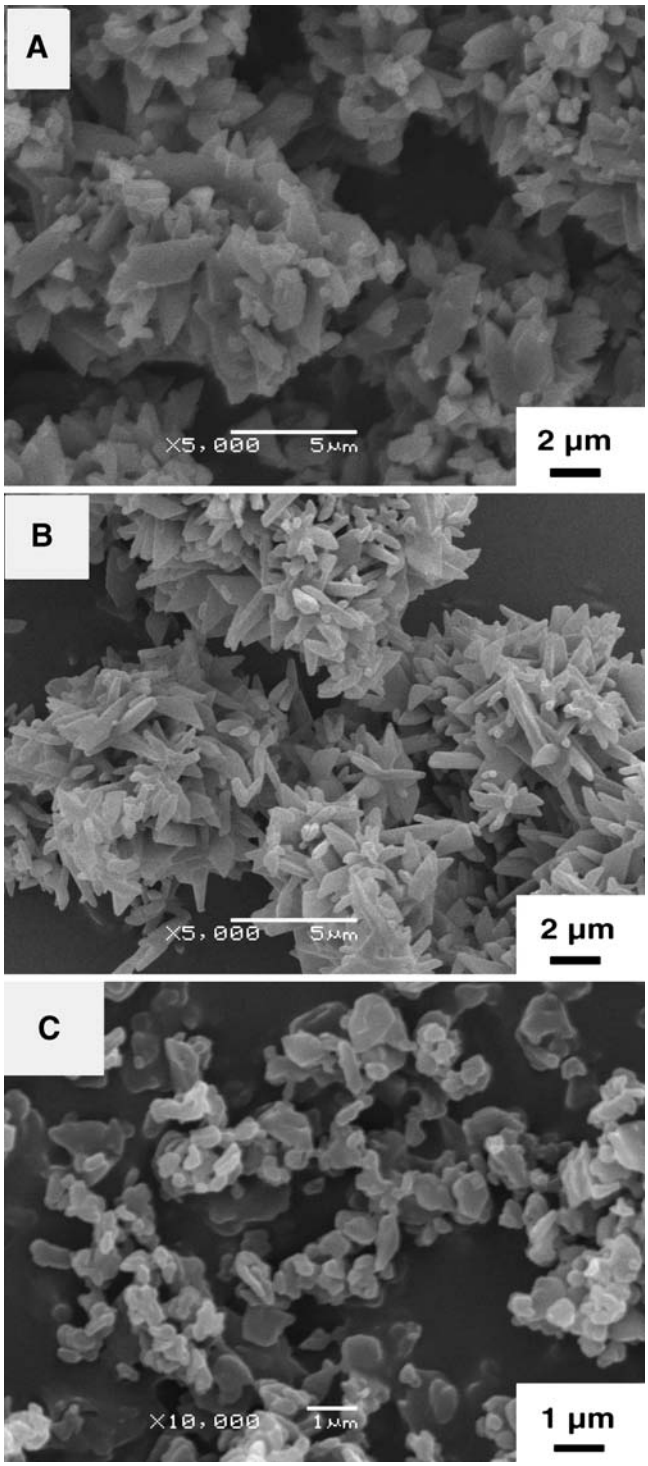

Fig. 2. SEM images of the powder via vacuum-drying under different medium: **A** acetone, **B** IPA, **C** THF.

spectrometry and electrochemical detection. The most recommended are methods that include HPLC (Waters Corporation, Miford, MA, USA) on C18 columns (150 mm×4.6 mm i.d., 5 μm particle size) with detection in UV region.

The mobile phase was a mixture of ammonium phosphate monobasic (0.05 M)–methanol (85:15, *v*/*v*), pH 3.3. The flow rate was set at 1.0 ml/min. Column temperature was 25°C. Peak integration was carried out at 281 nm using computer-controlled software.

X-ray Diffraction

X-ray diffraction analysis was performed using XRD-6000 (Shimadzu Inc., Japan) to detect any change in the physical characteristics and crystallinity. The measuring unit consists of a rotating anode in transmission technique with Cu Kα radiation. The scanning speed was 5° per minute from 8° to 40° with a step size of 0.05°.

Aerodynamic Particle Size Analysis

The aerodynamic particle size of the powder was evaluated by an Aeroliser® (Novartis Pharmaceuticals, Australia) coupled with an USP stainless steel throat to a multi-stage liquid impinger (MSLI, Copley, UK), operating at 60 l/min. The powder (about 10 mg) was filled into a hydroxypropyl methylcellulose capsule (size 3). Five independent experiments were carried out in parallel at the same conditions. The content of sumatriptan succinate deposited at different locations was assayed by UV-Vis spectrophotometry (Shimadzu, UV-250, Japan) at 281 nm. The solution of sumatriptan succinate could be diluted if necessary. A calibration curve of standard sumatriptan succinate (Beijing Lianben Pharm_Chemicals Tech. Co. Ltd, China) in water was constructed linear in the concentration range of 0.01–0.30 mg/ml [concentration (mg/ml)=0.0843×absorbance−0.0003; R^2=0.9999, n=3].

Fine particle fraction is the percentage of particles which are in the respirable range. Fine particle fraction loaded (FPF_{loaded}) is defined as the mass fraction of drug particles smaller than 5 μm in the aerosol cloud (interpolated from the mass of the drug collected from stages 3, 4 and filter) relative to the total mass recovered and the $FPF_{emitted}$ the mass fraction of the drug particles smaller than 5 μm in the aerosol cloud relative to the emitted dose (the drug mass collected from the throat, stages 1–4, and filter).

RESULTS AND DISCUSSION

In the reaction precipitation process, sumatriptan base should be dissolved in a suitable medium in which sumatriptan

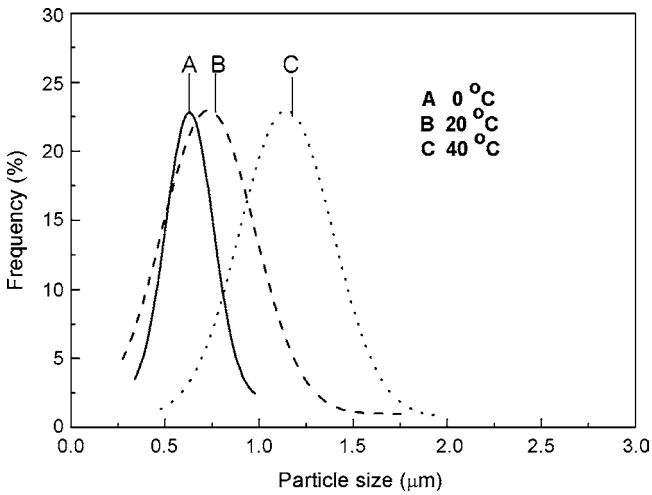

Fig. 3. Effect of temperature on the particle size distribution of the powder via vacuum-drying.

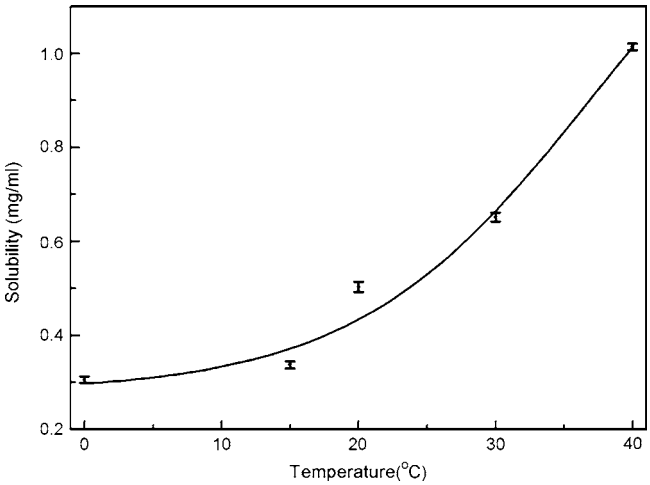

Fig. 4. Effect of temperature on the solubility of sumatriptan succinate in THF.

succinate was practically insoluble. From the point of polarity and solubility, acetone, IPA and THF were investigated herein as the reaction medium, the dielectric constant of which were 20.70, 18.3 and 7.58 respectively.

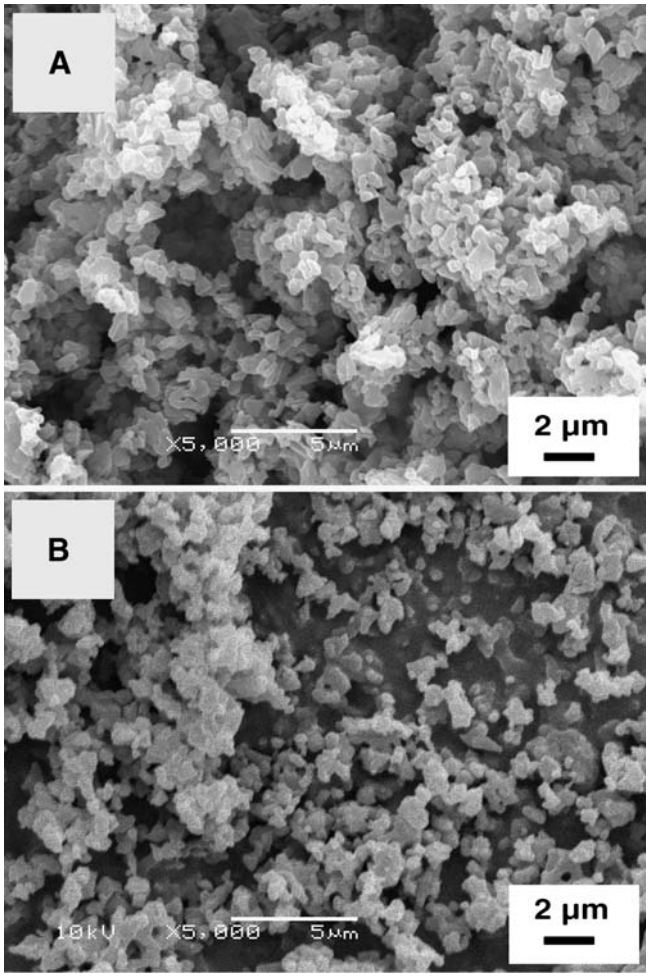

Fig. 5. SEM images of ultrafine sumatriptan succinate particles obtained from THF system under different drying method **A** vacuum drying **B** spray drying.

It was obviously that when the low polarity solvent was chosen as the reaction medium, the obtained particles were relative small (about 679 nm in THF system shown in Fig. 2) and dispersible. On the contrary, badly agglomerate sumatriptan succinate particles were created in polar solvents. Consequently the molecular structure of the solvent could take great effects on particle size and morphology, i.e., the solvents played an important role on the reaction crystallization process. Considering the toxicity and dissolvability of the reactants, not much low polarity solvents were available. THF was thus chosen as the optimal reaction medium for the subsequent experiments to produce powders for further characterization.

Temperature was a crucial parameter in the process. The effect of temperature on the particle length and its distribution were revealed in Fig. 3. It was evident that the size of sumatriptan succinate particles decreased from 1.14 μm to 630 nm in length as the temperature decreased from 30°C to 0°C and the particle size distribution was much tighter when under lower temperature. This indicated the lower the reaction temperature, the smaller the particles.

The following reasons may be responsible for the phenomenon (24). Firstly, the solubility of sumatriptan succinate in THF became lower with the temperature decreased as shown in Fig. 4 (about 0.3 mg/ml at 0°C while 1.0 mg/ml at 40°C) and the THF was a poor solvent for sumatriptan succinate at 0°C which could easily reach a high degree of supersaturation. Secondly, the nucleating process was a process of free energy decrease and heat release, thus, it favored to form the high

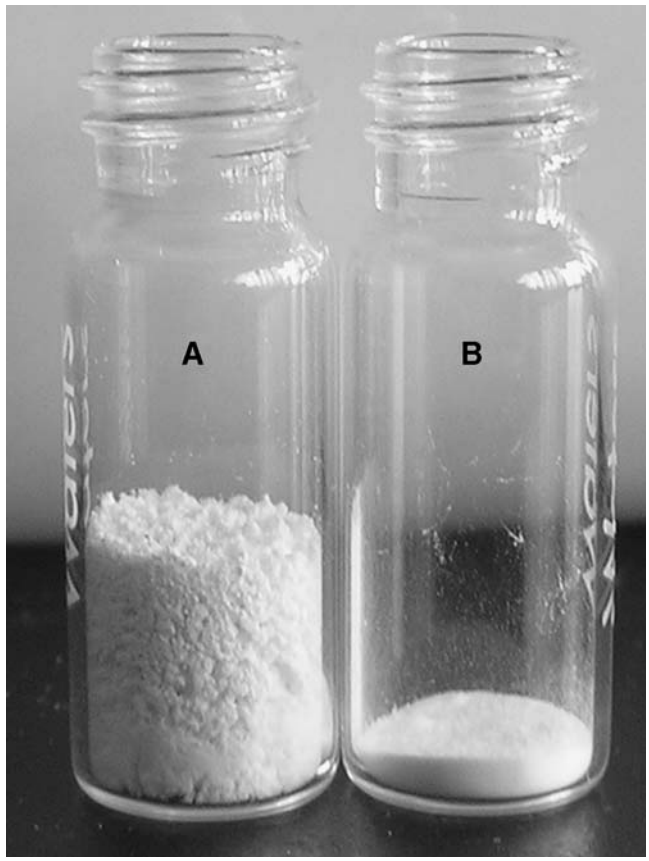

Fig. 6. Comparison in the density between **A** ultrafine, **B** commercial samples.

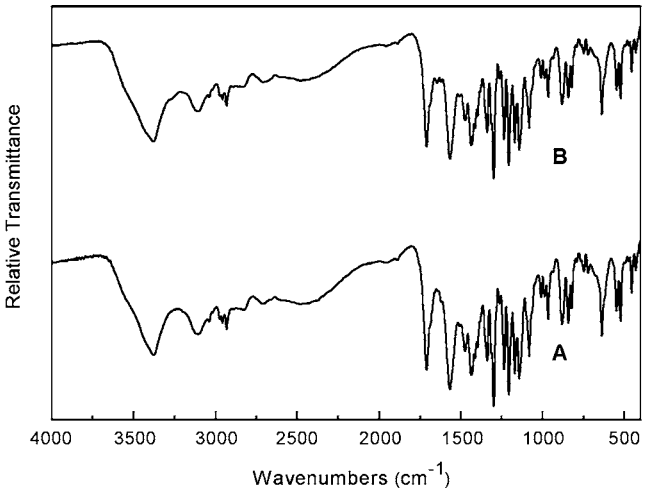

Fig. 7. Fourier transform infrared (FT-IR) spectra of **A** standard and **B** ultrafine sumatriptan succinate obtained under optimum conditions.

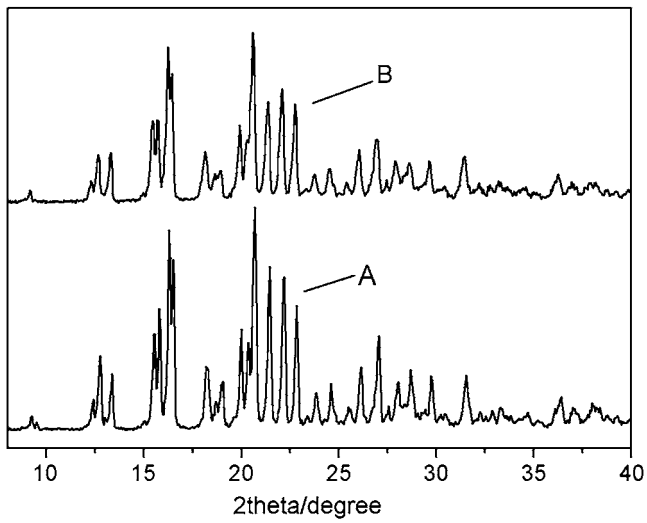

Fig. 9. XRD patterns of **A** standard and **B** ultrafine sumatriptan succinate obtained under optimum conditions.

nucleation rate at low temperature. Thirdly, temperature affected the crystal growth rate (16). The crystal growth rate could be expressed as

$$\frac{dl}{dt} = K_g(C_i - C^*)^b$$

where K_g was the crystal growth rate constant. C_i and C^* are the solute concentration on the crystal surface and saturation concentration, respectively. The value of b was usually in the range of 1–3 and deceased with reductions in temperature. As a result, fine particles were obtained at low temperature which inhibited the crystal growth. In addition, the yield might increase with temperature decrease as the reduction of sumatriptan succinate solubility in THF.

Spray drying was considered to be the proper drying technique to obtain the dry powder for inhalation. In this case, the vacuum dried particles whose size was less than 1 μm were in poor dispersibility and fluidity. A re-disperse method was employed to treat the filter paste turning into suspension for spray drying. The powder via spray drying was in good dispersibility. It was expected that smaller particles tended to escape collection in the cyclone of the spray drier. However, smaller particles will also be accommodated better than particles in small droplets. In addition, the high shear at the nozzle during spray drying could break the agglomeration into small fragments which was confirmed by the SEM images (Fig. 5).

As discussed, it was the aerodynamic diameter that determines lung disposition, irrespective of geometric particle size (to a certain point). The aerodynamic diameter could be decreased by decreasing particle density. The powder of ulrafine and commercial sumatriptan succinate were exhibited in Fig. 6 (A for ultrafine and B for commercial sample). The height in

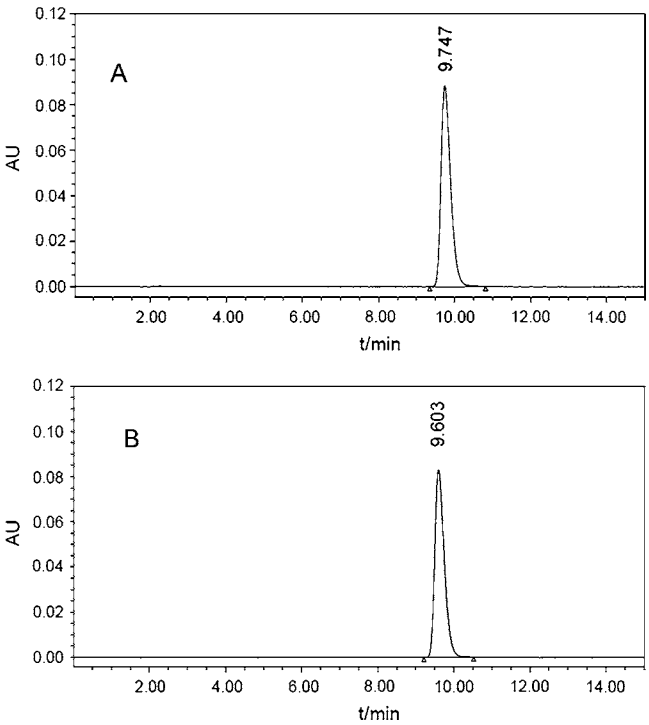

Fig. 8. Chromatograms of **A** standard, **B** ultrafine sumatriptan succinate obtained under optimum conditions.

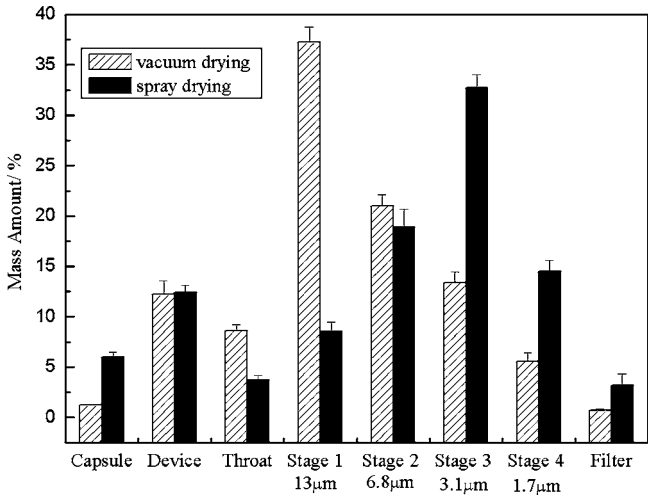

Fig. 10. Comparison between the powder aerosol behavior of sumatriptan succinate via vacuum drying and spray drying samples (n=5 runs, error bars showing standard deviation).

the chart indicated that the ultrafine sample was in low powder density (both of the samples were of 0.07 g but in different height) which merited the aerosol performance of the as-prepared samples.

For sumatriptan succinate prepared through a reaction system, chemical structure of the compound and its crystalline form should be firstly confirmed. FT-IR and HPLC were employed to assay both the as-prepared sample and standard sumatriptan succinate in order to identify its molecular structures.

The FT-IR spectra (Fig. 7) illustrated that the ultrafine sumatriptan succinate powder was well matched with the standard according to the information on vibrations in the powder composition. Reliable identification must, therefore, additionally include a comparison of the retention times of the analyte with the reference compounds. Fig. 8 showed that the two samples (sumatriptan succinate) shared the same retention time at 9.7 min under the same HPLC conditions. Therefore, all the results revealed that the as-prepared product might have the same chemical structure as the standard sample.

The powder was confirmed by XRD to be crystalline and was of the same polymorphic form as the standard sample (Fig. 9). It was observed that the relative intensity of the diffraction peaks in Fig. 9b decreased compared with the corresponding peaks in Fig. 9a, which revealed that the particle size got smaller.

Besides the particle size of a drug, the de-agglomeration behavior in an air stream was important for the pulmonary drug delivery. Generally speaking, the fine particle fraction could be increased by preparing the drug powders according to controlled precipitation technique. These powders were less cohesive and adhesive as their surface were naturally grown and more uniform than the powders prepared by milling which were agglomerated and electrostatically charged, increasing the aerodynamic particle size. The aerosol performance of ultrafine sumatriptan succinate powder increased dramatically after spray drying which was illustrated in Fig. 10.

The *in vitro* deposition profiles showed a high deposition of the dry powder via vacuum drying in the inhaler, throat and stage 1. However, when the filter residue was redispersed and dried via spray drying, the sumatriptan succinate powder was in a deposition mainly on stages 3, 4 and the filter. The vacuum-dried and spray-dried sumatriptan succinate powder showed different FPF_{loaded} values (18.2%±3.0% and 50.6%± 8.2% respectively). Most of the vacuum-dried powder stayed at stage 1, although the particle size is about or even less than 1 μm. The dispersity of sumatriptan succinate powder obtained by vacuum drying was very poor, for the fine particles had a high tendency to agglomerate which made a high deposition in stages 1. So approximately 80% of the powders exhibited the property of the aerodynamic diameter D_{ae}>13 μm. In contrast, the particles obtained via spray drying became uniform and less cohesive, and the aerosol performance of the spray-dried powder was high as confirmed by the results which exhibited the property of the aerodynamic diameter D_{ae}<5 μm.

In conclusion, ultrafine particles of sumatriptan succinate (in the range of 630~679 nm) could be synthesized by reactive precipitation without any additives followed by spray drying at the optimal parameters, and it was detected having the same physicochemical properties as the standard product. Furthermore, it was estimated being propitious to the pulmonary delivery for the FPF value was up to 50.6%± 8.2%. The synthesis process offered a relatively simple method, and revealed that great potential for industry.

ACKNOWLEDGMENTS

This work was partially supported by the NSF of China (through Grant NO. 20325621).

REFERENCES

1. S. S. Colman, M. I. Brod, A. Krishnamurthy, C. R. Rowland, K. J. Jirgens, and B. Gomez-Mantilla. Treatment satisfaction, functional status, and health-related quality of life of migraine patients treated with Almotriptan or Sumatriptan. *Clin. Ther.* **23**:127–145 (2001).
2. F. R. Taylor. Migraine headache: options for acute treatment. *Curr. Neurol. Neurosci. Rep.* **5**:86–92 (2005).
3. N. T. Mathew, and E. W. Loder. Evaluating the triptans. *Am. J. Med.* **Suppl 118**:28S–35S (2005).
4. A. Femenía-Font, C. Balaguer-Fernández, V. Merino, and A. López-Castellano. Combination strategies for enhancing transdermal absorption of sumatriptan through skin. *Int. J. Pharm.* **323**:125–130 (2006).
5. P. Tfelt-Hansen, P. De Vries, and P. R. Saxena. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs*. **60**:1259–1287 (2000).
6. R. J. Majithiya, P. K. Ghosh, M. L. Umrethia, and R. S. R. Murthy. Thermoreversible–mucoadhesive gel for nasal delivery of Sumatriptan. *AAPS PharmSciTech.* **7**:E1–E7 (2006).
7. Y. Kato, K. Muraki, M. Fujitaka, N. Sakura, and K. Ueda. Plasma concentrations of disodium cromoglycate after various inhalation methods in healthy subjects. *Br. J. Clin. Pharmacol.* **48**:154–157 (1999).
8. N. Rasenack, H. Steckel, and B. W. Müller. Preparation of microcrystals by *in situ* micronization. *Powder Technol.* **143144**:291–296 (2004).
9. H. Steckel, N. Rasenack, and B. W. Müller. In-situ-micronization of disodium cromoglycate for pulmonary delivery. *Eur. J. Pharm. Biopharm.* **55**:173–180 (2003).
10. M. J. Telko, and A. J. Hickey. Dry powder inhaler formulation. *Respir. Care*. **50**:1209–1227 (2005).
11. C. C. Koch. Nanostructured materials-processing, properties and potential applications. William Andrew Publishing, Norwich, NY, 2002.
12. A. A. Date, and V. B. Patravale. Current strategies for engineering drug nanoparticles. *Curr. Opin. Colloid. In.* **9**:222–235 (2004).
13. G. Nykamp, U. Carstensen, and B. W. Müller. Jet milling-a new technique for microparticle preparation. *Int. J. Pharm.* **242**:79–86 (2002).
14. M. D. Ticehurst, P. A. Basford, C. I. Dallman, T. M. Lukas, P. V. Marshall, G. Nichols, and D. Smith. Characterisation of the influence of micronisation on the crystallinity and physical stability of revatropate hydrobromide. *Int. J. Pharm.* **193**:247–259 (2000).
15. K. Brodka-Pfeiffer, P. Langguth, P. Graß, and H. Häusler. Influence of mechanical activation on the physical stability of salbutamol sulphate. *Eur. J. Pharm. Biopharm.* **56**:393–400 (2003).
16. J. F. Chen, M. Y. Zhou, L. Shao, Y. Y. Wang, J. Yun, N. Y. K. Chew, and H. K. Chan. Feasibility of preparing nanodrugs by high-gravity reactive precipitation. *Int. J. Pharm.* **269**:267–274 (2004).
17. Z. Wang, J. F. Chen, Y. Le, Z. G. Shen, and J. Yun. Preparation of ultrafine beclomethasone dipropionate drug powder by antisolvent precipitation. *Ind. Eng. Chem. Res.* **46**:4839–4845 (2007).
18. X. S. Li, J. X. Wang, Z. G. Shen, P. Y. Zhang, J. F. Chen, and J. Yun. Preparation of uniform prednisolone microcrystals by a controlled mcroprecipitaition method. *Int. J. Pharm.* **342**:26–32 (2007).
19. J. F. Chen, Y. H. Wang, F. Guo, X. M. Wang, and C. Zheng. Synthesis of nanoparticles with novel technology: high gravity reactive precipitation. *Ind. Eng. Chem. Res.* **39**:948–954 (2000).
20. T. Hu, H. Chiou, H. K. Chan, J. F. Chen, and J. Yun. Preparation of inhalable salbutamol sulphate using reactive high gravity controlled precipitation. *J. Pharm. Sci.* **97**:932–937 (2008).

21. J. Elversson. Spray-dried powders for inhalation—particle formation and formulation concepts. Uppsala University, Sweden, 2005.
22. H. K. Chan, and N. Y. K. Chew. Novel alternative methods for the delivery of the drugs for the treatment of asthma. *Adv. Drug Deliv. Rev.* **55**:793–805 (2003).
23. R. Vehring, and W. R. Foss. David Lechuga-Ballesteros. Particle formation in spray drying. *J. Aerosol Sci.* **38**:728–746 (2007).
24. J. Y. Zhang, Z. G. Shen, J. Zhong, T. T. Hu, J. F. Chen, Z. Q. Ma, and J. Yun. Preparation of amorphous cefuroxime axetil nanoparticles by controlled nanoprecipitation method without surfactants. *Int. J. Pharm.* **323**:153–160 (2006).