Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 269 (2004) 267–274
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Note

Feasibility of preparing nanodrugs by high-gravity reactive precipitation

Jian-Feng Chen [a,*], Min-Yi Zhou [a], Lei Shao [a], Yu-Yong Wang [a], Jimmy Yun [b], Nora Y.K. Chew [c], Hak-Kim Chan [c]

[a] *Research Centre of the Ministry of Education for High Gravity Engineering & Technology, College of Chemical Engineering, Beijing University of Chemical Technology, Beijing 100029, PR China*
[b] *NanoMaterials Technology Pte Ltd., Singapore 139944, Singapore*
[c] *Faculty of Pharmacy, University of Sydney, Sydney, NSW 2006, Australia*

Received 30 June 2003; received in revised form 8 September 2003; accepted 9 September 2003

Abstract

To study the feasibility of producing nanoparticles of organic pharmaceuticals using a novel high-gravity reactive precipitation (HGRP) technique, reactive precipitation of benzoic acid as a model compound was carried out in a rotating packed bed under high gravity. The main factors such as the rotating bed speed, concentration and volume flow rate of the reactants (sodium benzoate and HCl) affecting the particle size of the precipitate were studied. Particle size was measured by transmission electron microscopy. Benzoic acid was precipitated as nanoparticles as fine as 10 nm. The particle size was decreased with increasing rotating bed speed, concentration and volume flow rate of the reactants. The formation of ultrafine particles was due to intensified micro-mixing of reactants in the rotating bed to enhance nucleation while suppressing crystal growth. The results have demonstrated the feasibility to produce nanodrugs by the principle of acid–base precipitating reaction using HGRP.
© 2003 Elsevier B.V. All rights reserved.

Keywords: Nanodrugs; Benzoic acid; High-gravity technology; Rotating packed bed

Nanomaterials have immense potential in the area of pharmaceuticals; it has been estimated that about half of all production will be dependent on nanotechnology, affecting over US$ 180 billion per year in the next 10–15 years (Roco, 2001).

The availability of pharmaceutical particles in the micron and nanometer size range, and with a narrow particle size distribution, provides considerably greater flexibility and convenience in the methods of both formulation and drug delivery. Drug particles as small as a few microns to submicron sizes can be delivered to site-specific areas such as target organs by parenteral injections and the respiratory tract by inhalation aerosols. The production of particles by micronisation is also one of the most widely used approaches for enhancing solubility and dissolution rates of solid pharmaceutical formulations.

Particle size reduction has been carried out mainly by mechanical milling in the past. Milling, however, is of limited efficiency and produces materials in partially amorphous state. Broad particle size distribution, and contamination from mechanical attrition are additional concerns. Because of these limitations, alternative powder production processes are attractive

* Corresponding author. Tel.: +86-10-64446466; fax: +86-10-64434784.
E-mail address: chenjf@mail.buct.edu.cn (J.-F. Chen).

0378-5173/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.09.044

to the pharmaceutical industry. Crystallisation processes assisted by ultrasound based on sonochemistry principles have been developed (Ultrasound, 2002). Techniques using supercritical fluids have also been in their advanced stage of development and commercialisation (York and Hanna, 1996; Bustami et al., 2000; Eiffel Technologies, 2002). In an effort to produce an efficient and cost effective method, a novel precipitation method involving high-gravity micro-mixing (i.e. mixing on the molecular scale) to control nucleation and crystallisation of pure drug particles is utilised (Chen et al., 1995, 1996, 1998, 2000; Guo et al., 2000).

High-gravity technology in the form of a rotating packed bed on the earth has been used to intensify mass transfer and heat transfer by several orders of magnitude in multiphase systems (Fowler, 1989; Chen et al., 2000). The method has successfully been used to produce nanomaterials including $CaCO_3$ (15–40 nm), $Al(OH)_3$ (1–10 nm), and $SrCO_3$ (40 nm), and is currently used for commercial scale production of $CaCO_3$ at 10,000 tonnes per year. These nanomaterials have a narrow particle size distribution, consistent quality, specific crystal shape and morphology at significantly lower production cost than conventional nanomaterial production methods (Chen et al., 1995). Despite the success with inorganic nanomaterials, application of the technique for organic drugs is lacking. In this communication, the applicability of the technique on organic pharmaceutical compounds is explored using benzoic acid as a model.

The experimental set-up for the high-gravity precipitation is shown schematically in Fig. 1. The key component is a rotating packed bed (RPB) (Chen et al., 1996, 2000), with inner and outer diameters of 50 and 150 mm, respectively. The axial width of the rotating bed is 50 mm. The distributor consists of two pipes (10 mm in outer diameter and 1.5 mm in wall thickness), each having a slot (1 mm in width and 48 mm in length) which just covers the axial length of the packing section in the rotator. The rotator is installed inside the fixed casing and rotates at the speed of several hundreds to thousands times per minute. Liquid is introduced into the eye space of the rotator from the inlet pipe and then sprayed by the slotted pipe distributor onto the inside edge of the rotator. The two liquid streams entered the bed mix and react together to yield particles. The mixture flows in the radial direction under centrifugal force, passing the packing and outside

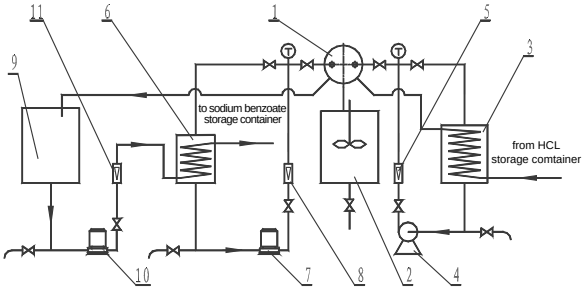


Fig. 1. Schematic diagram of the high-gravity reactive precipitation set-up. (1) RPB, (2) benzoic acid storage container, (3) sodium benzoate storage container, (4) sodium benzoate transportation pump, (5) sodium benzoate flowmeter, (6) HCl storage container, (7) HCl transportation pump, (8) HCl transportation flowmeter, (9) circulation water storage container, (10) circulation water transportation pump, (11) circulation water flowmeter.

space between the rotator and shell, and finally leaves the equipment through the liquid exit for collection.

In this study, the experiment was initiated with the valve at the inlet to the RPB closed. With the recirculating valve opened, the volume flow ratio of HCl (Analytical grade, Beijing Yili Fine Chemical Co., China) and sodium benzoate (Analytical grade, Wuhan Shenshi Fine Chemical Co., China) aqueous solutions at fixed concentrations was adjusted accurately until steady state was reached. After setting the rotating frequency to a known value, the RPB was switched on. As the recirculating valve was closed, the inlet valve to the RPB was opened simultaneously to start precipitation of benzoic acid by reaction between the HCl and sodium benzoate. The HCl/benzoate flow ratio, rotating speed, or the reactant solution concentration ratio was varied at a fixed time interval, and after equilibrium was established samples were taken for particle sizing by transmission electron microscopy (Model H-800, Hitachi, Japan).

1. Effect of rotating speed

As the rotating frequency of the packed bed was increased, the mean particle size decreased rapidly at frequencies below 20 Hz. A steady particle size was reached at higher frequencies (Fig. 2). It is worth to note that after 25 Hz, any further increase in the rotating speed did not affect the particle size as shown in Fig. 3.

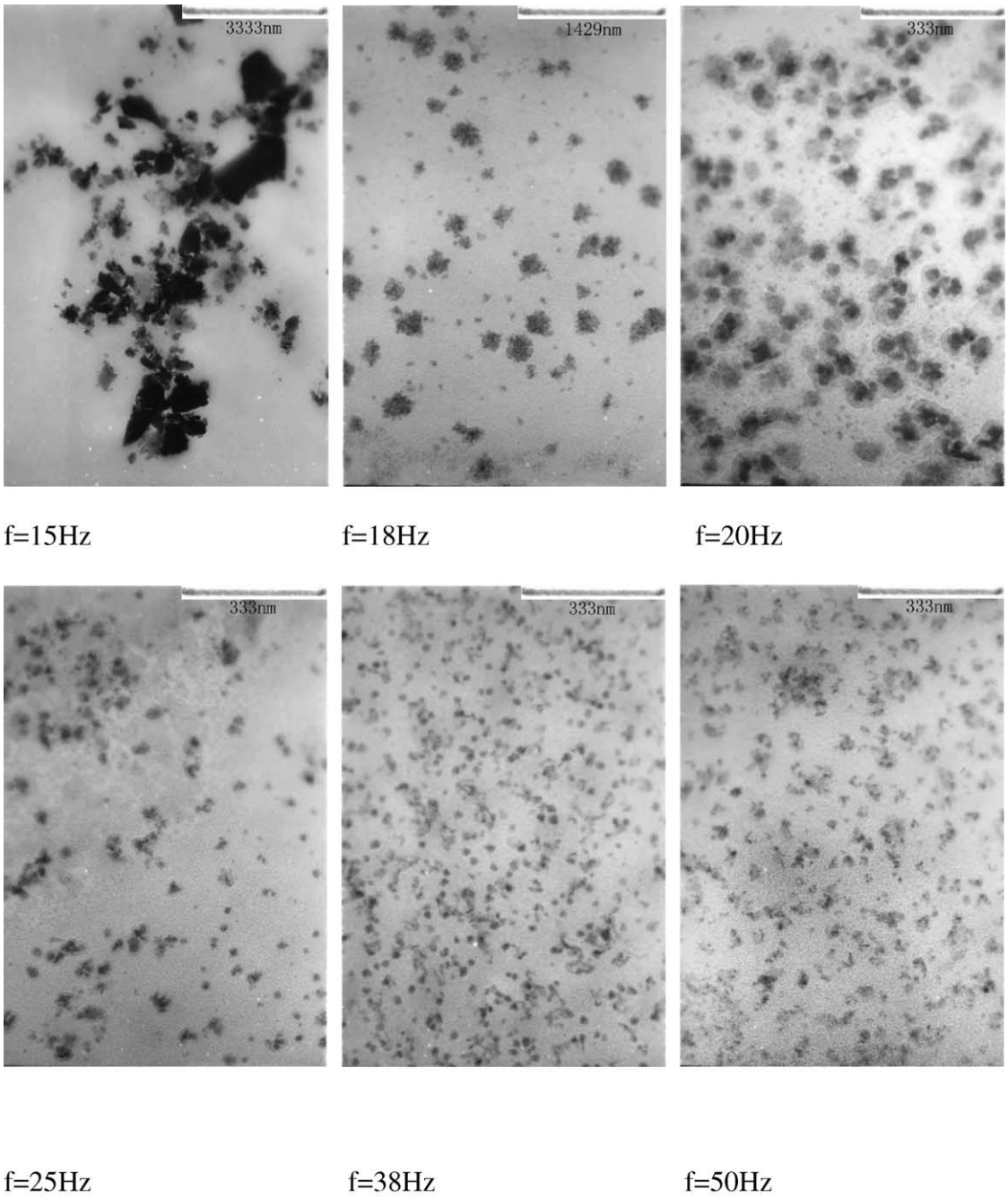


Fig. 2. The influence of rotating speed, *f*, on mean particle size.

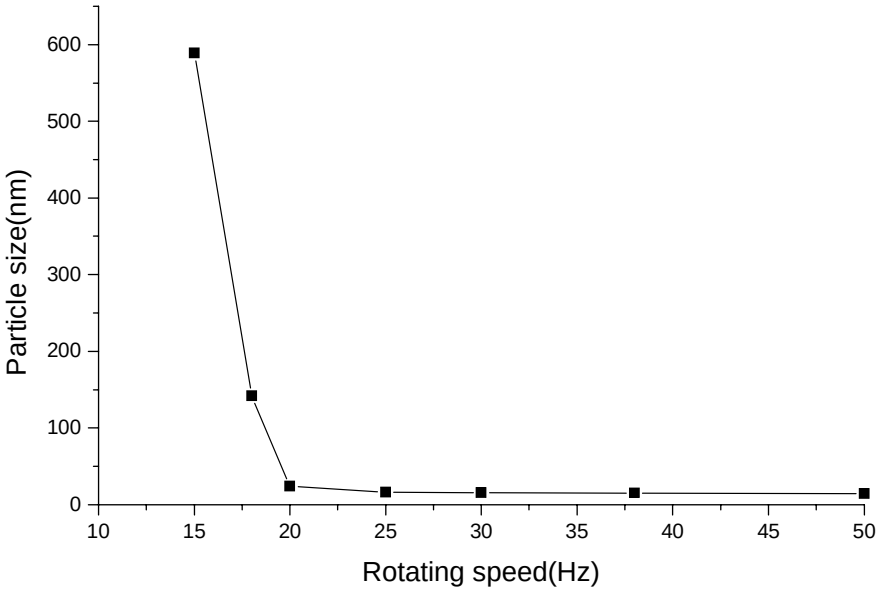


Fig. 3. The influence of rotating speed on mean particle size (graphical representation).

Precipitation consists of several main steps: chemical reaction (and subsequent supersaturation), nucleation, solute diffusion and crystal growth (Dirken and Ring, 1991). Nucleation rate (dN/dt) can be expressed as

$$\frac{\mathrm{d}N}{\mathrm{d}t} = K_{\mathrm{n}}(C_i - C^*)^a \tag{1}$$

where K_{n} is the solute nucleation constant, C_i and C^* are the solute concentration on the crystal surface and saturation concentration, respectively. The value of the parameter a is usually between 5 and 18.

The diffusion rate of solute to the crystal surface is

$$\frac{\mathrm{d}m}{\mathrm{d}t} = K_{\mathrm{d}}(C - C_i) \tag{2}$$

where K_{d} is the solute diffusion rate constant and C is the supersaturated concentration.

The growth rate of crystal is

$$\frac{\mathrm{d}l}{\mathrm{d}t} = K_{\mathrm{g}}(C_i - C^*)^b \tag{3}$$

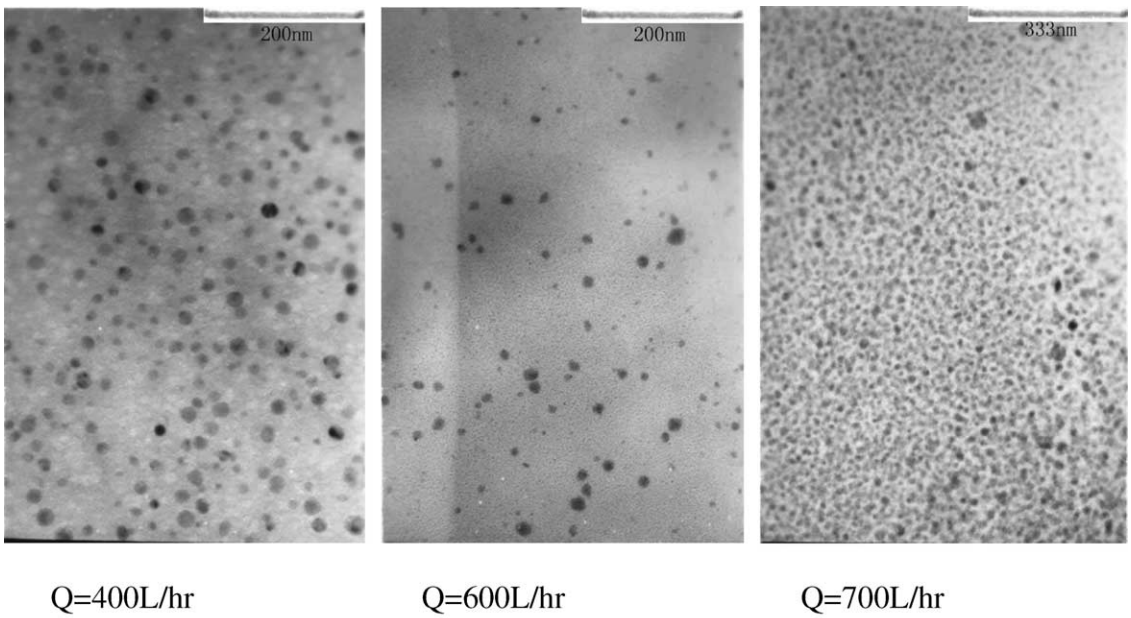
where K_{g} is the crystal growth rate constant. The value of b is usually between 1 and 3, and increases with temperature.

Particles in nanosize range can be obtained by rapid micro-mixing of reactants to enhance nucleation while suppressing crystal growth. Eqs. (1)–(3) indicate that both the nucleation and crystal growth depend on the level of supersaturation. In particular, C_i is closely related to the level of micro-mixing. Thorough micro-mixing leads to the same C_i for all the nuclei in the liquid, resulting in uniform growth and particle size. On the other hand, insufficient micro-mixing will lead to growth disparity among different nuclei, resulting in a wide particle size distribution. There are two characteristic time parameters in crystallisation: the induction time (τ) and the micro-mixing time (t_{m}). The induction time, τ, which is to establish a steady-state nucleation rate (normally in μs to ms), is given by $6d^2n/[D\ln(C_i/C^*)]$ (Dirken and Ring, 1991) where d is the molecular size, n is the number of molecule in a nucleus, D is the diffusion coefficient of the molecule. When $t_{\mathrm{m}} \ll \tau$, the nucleation rate will be nearly uniform spatially, and the particle size distribution can be controlled at a uniform level. This is achieved in the present study by the high-gravity technology which utilises a rotating packed bed to intensify mass and heat transfer in multiphase systems (Chen et al., 1996, 2000). During rotation, the fluids going through the packed bed are spread and split into thin films, threads and very fine droplets under the high shear created by the high gravity. This

results in intense micro-mixing between the fluid elements by 1–3 orders of magnitude. The micro-mixing time (t_m) in this process is estimated to be around the magnitude of the order of 10–100 μs in the present study.

2. Effect of reactant flow rate

At a fixed volume flow of sodium benzoate, the particle size of the precipitated benzoic acid was decreased with increasing volume flow of HCl (Fig. 4).



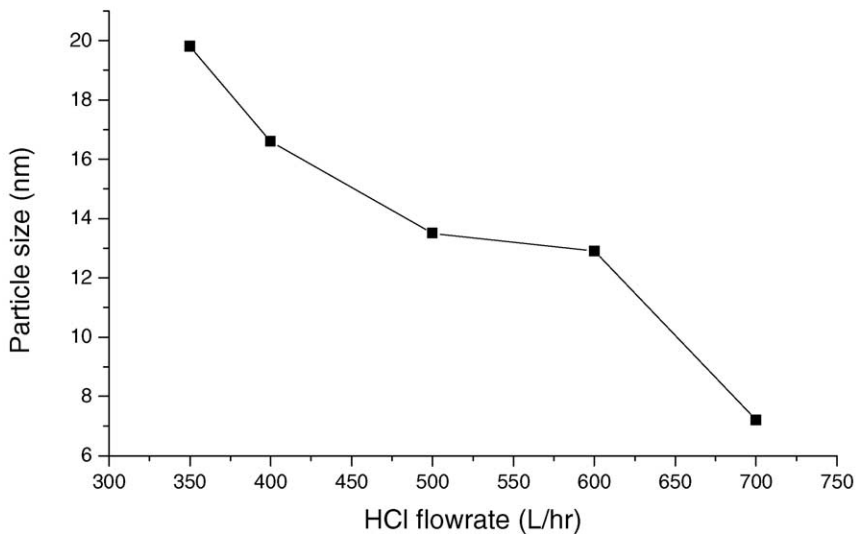


Fig. 4. The influence of HCl flow rate on mean particle size.

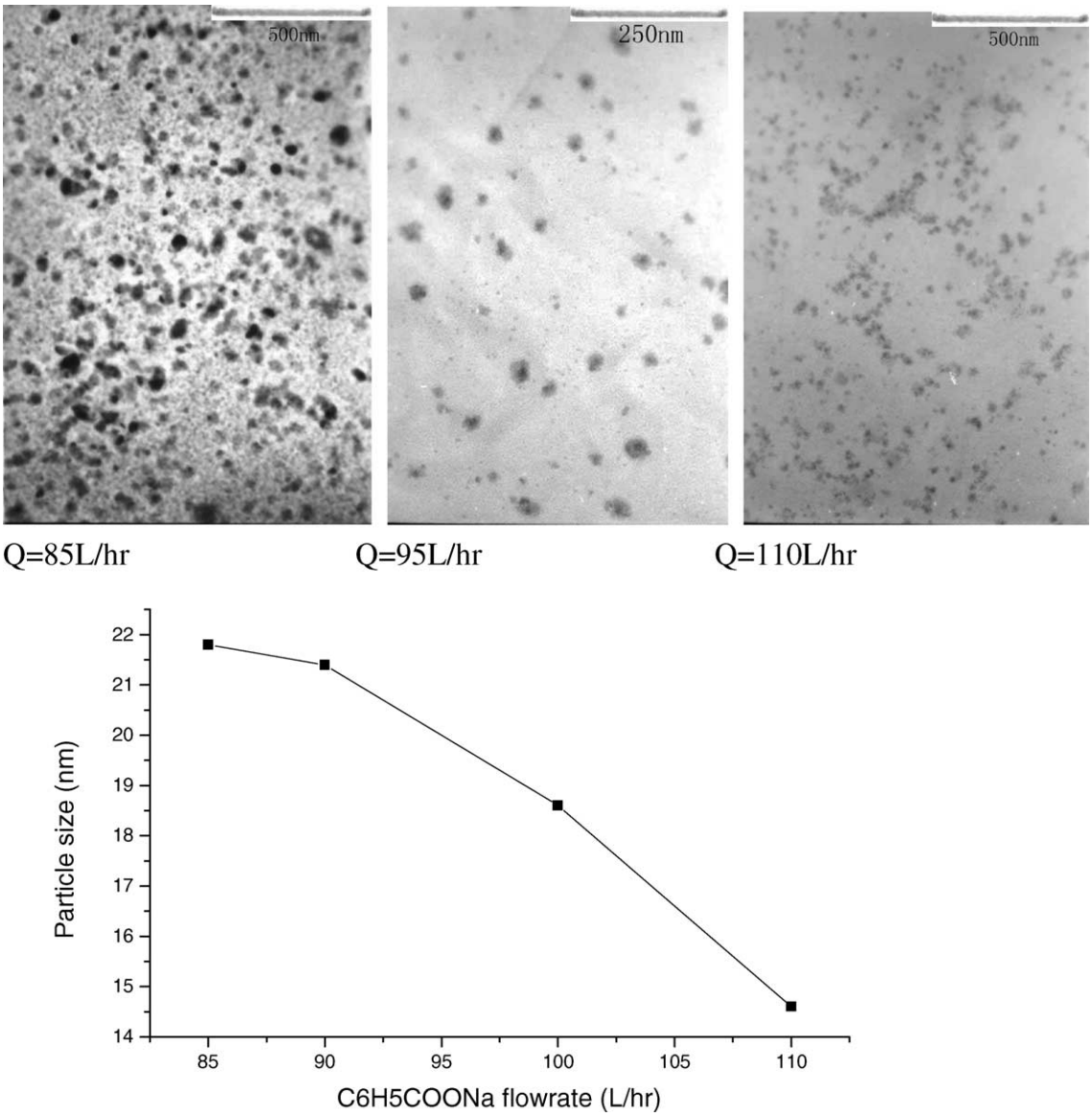


Fig. 5. The influence of sodium benzoate flow rate on mean particle size.

This was due to the higher initial supersaturation level leading to high nucleation rate which depleted the solute rapidly, thus many small nuclei instead of large crystals were formed. A similar trend in particle size was obtained when the volume flow of sodium benzoate was increased at a fixed volume flow of HCl (Fig. 5).

3. Effect of reactant concentration

The particle size of benzoic acid was inversely proportional to the concentration of HCl (Fig. 6). Similar to the effect of increased volume flow, a high reactant concentration will create a high supersaturation level and nucleation rate, resulting in small sized crystals.

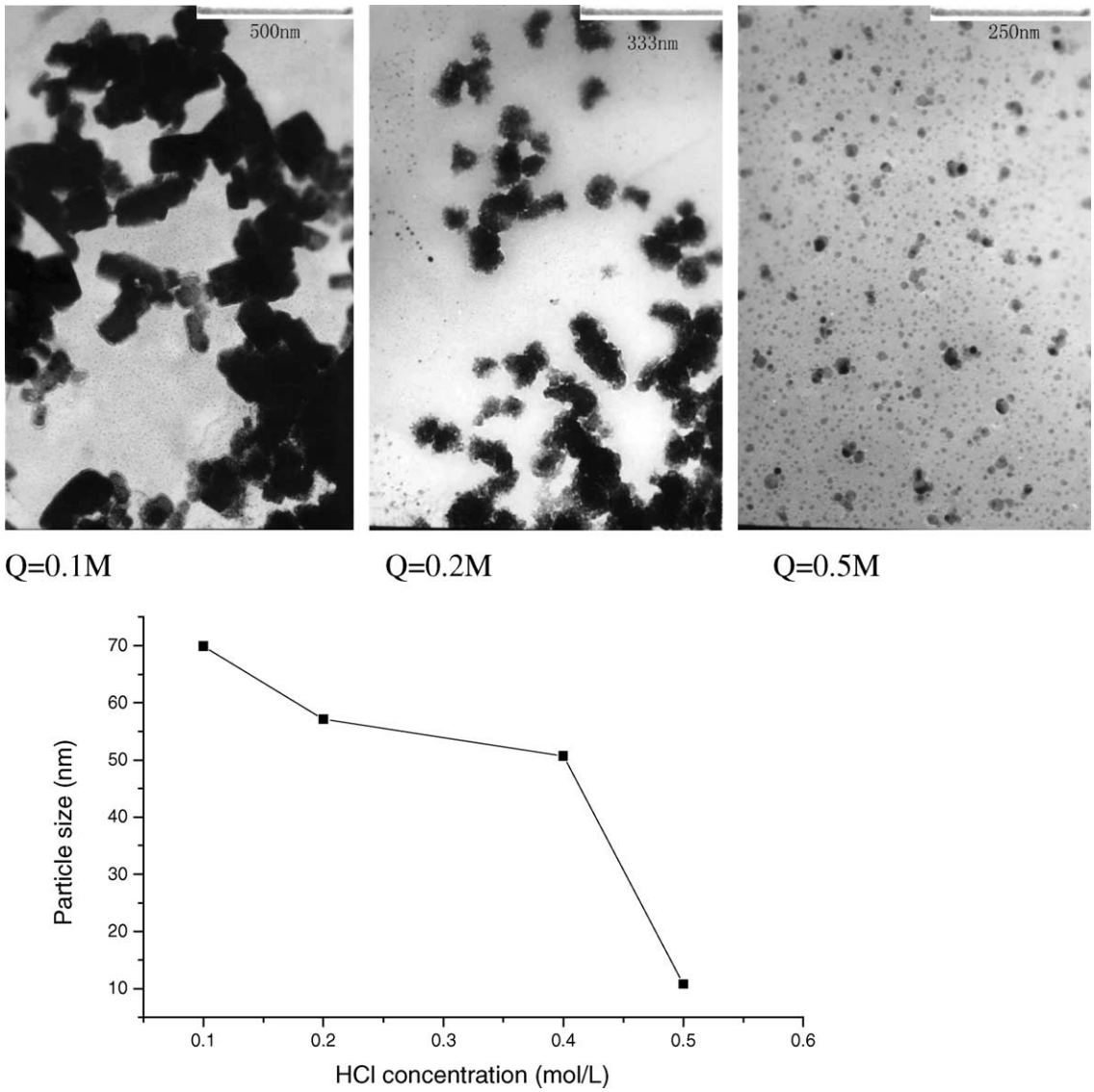


Fig. 6. The influence of HCl concentration on mean particle size.

In summary, using benzoic acid as a model compound, the present results have shown the feasibility to produce nanodrugs by the rotating packed bed method under high gravity. The rotating speed (high-gravity level), reactant concentration and volume flow rate have been identified as key factors affecting the particle size.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant Nos. 20146002, 20236020) and “863” Plan of China (Grant No. 2001AA218061). Dr. Jimmy Yun would like to acknowledge the support as a visiting scientist to the

Key Laboratory of the Ministry of Education for Controllable Reactions, China.

References

Bustami, R.T., Chan, H.K., Dehghani, E., Foster, N.R., 2000. Generation of microparticles of proteins for aerosol delivery using high pressure modified carbon dioxide. Pharm. Res. 17, 1360–1366.

Chen, J.F., Zhou, X.M., Zheng, C., 1995. Ultrafine particle synthesis by high-gravity reactive precipitation. Chinese Patent No. 95105344.2.

Chen, J.F., Zheng, C., Chen, G.T., 1996. Interaction of macro- and micro-mixing on particle size distribution in reaction precipitation. Chem. Eng. Sci. 51, 1957–1966.

Chen, J.F., Zhou, X.M., Wang, Y.H., Zheng, C., 1998. Synthesis of ultrafine calcium carbonate. Chinese Patent No. ZL95105343.4.

Chen, J.F., Wang, Y.H., Guo, F., Wang, X.M., Zheng, C., 2000. Synthesis of nanoparticles with novel technology: high-gravity reactive precipitation. Ind. Eng. Chem. Res. 39, 948–954.

Dirken, J.A., Ring, T.A., 1991. Fundamentals of crystallization—kinetic effects on particle size distributions and morphology. Chem. Eng. Sci. 46, 2389–2427.

Eiffel Technologies, 2002. http://www.eiffeltechnologies.com.au/erd. Accessed 24 April 2002.

Fowler, R., 1989. Higee—a status report. Chem. Eng. 35, 456–473.

Guo, K., Guo, F., Feng, Y.D., Chen, J.F., Zheng, C., Gardner, N.C., 2000. Synchronous visual and RTD study on liquid flow in rotating packed-bed contactor. Chem. Eng. Sci. 55, 1699–1706.

Roco, M.C., 2001. From vision to the implementation of the U.S. national nanotechnology initiative. J. Nanoparticle Res. 3, 5–11.

Ultrasound, 2002. Ultrasound—the key to better crystals for the pharmaceutical industry. http://www/aeat.com/sono/feature1.html. Accessed 23 April 2002.

York, P., Hanna, M., 1996. Particle engineering by supercritical fluid technologies for powder inhalation drug delivery. In: Dalby, R.N., Byron, P.R., Farr, S.J. (Eds.), Respiratory Drug Delivery, vol. V. Interpharm Press, IL, pp. 231–239.