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Influence of the solvent composition on the aerosol synthesis of pharmaceutical polymer nanoparticles

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Abstract

Spherical, Eudragit L100 polymer nanoparticles with and without a ketoprofen drug were prepared by a novel aerosol flow reactor method. In this method, the polymer solution is sprayed to form nanosized droplets followed by the evaporation of a solvent. A purpose of the work was to explore the effect of solvent, solvent mixture, and co-solute (ketoprofen) on the formation of polymer particle, and particularly on particle morphology. The solvents used, i.e. ethanol, THF, toluene, and water, were selected according to their vapor pressure and dissolution capability for the polymer. At the polymer concentration range from 0.2 to 1.5 g/l of the starting solution, the geometric number mean diameters (GMD) of the particles increased from 75 to 130 nm and from 65 to 100 nm from the solutions of ethanol and THF, respectively. Particle morphology was observed by a scanning electron microscope (SEM). Particles changed from collapsed to irregular via spherical shape in the course of the decreasing solubility of the polymer in the medium. This is critically dependent on the solvent evaporation rate as well as the solute solubility, i.e. fast evaporative removal of solvent results in collapsed particles whereas low solubility results in irregular particles. Interplay between the vapor pressure of the solvents and the polymer solubility in the medium made possible to prepare particles with more complicated structures such as shriveled and blistery structures. The particle morphology as detected by SEM did not change when 10 wt.% of ketoprofen was added to the precursor solution.

Keywords: Nanoparticles; Aerosol; Polymer; Eudragit; Drug

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1. Introduction

Applications in a variety of areas like catalyst and pharmaceutical manufacturing have a demand for small particles (Edelstein and Cammarata, 1996; Ravi Kumar, 2000). Solid-state drug nanoparticles that are unstable in morphology could be stabilized by

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polymers. In these composite particles, the polymer may act, in addition to stabilizer, as functional material that controls the release and diffusion of a drug depending on the environmental conditions such as pH, temperature, ionic strength, humidity, and so on (Galaev and Mattiasson, 1993; Yuk and Bae, 1999). Moreover, ionic and non-ionic polymers may behave like surfactants on the particle surface thereby sustaining colloidal stability if needed. This is particularly important in biomedical applications where drug delivery could be carried out either by oral or intravenous administration. It has been shown that systemic side-effects in the drug targeting into cancerous tumor can be minimized by the decrease of the particle size (Brigger et al., 2002).

The morphology of the nano- and micronsized particles can be controlled by different preparation methods and compositions (Edwards et al., 1997; Che et al., 1998; Maa et al., 1999; Tsapis et al., 2002). For the production of nano- and micronsized particles, techniques such as dry and wet milling, emulsification–diffusion, precipitation, polymerization, and spray drying have been demonstrated (Masters, 1991; Allèmann et al., 1993; Peltonen et al., 2002; Chen and Chew, 2003). Wet milling and high-pressure homogenization produce nanosized particles but the particles should be stabilized with surfactants to prevent aggregation and coalescence (Merisko-Liversidge et al., 2003). Several papers treat the preparation of micronsized polymer particles by routes of aerosol (Shin et al., 1996; Zhou et al., 2001; Wang and Wang, 2002). Commonly, the polymer solution is sprayed to form droplets, but the polymerization of monomers in droplets has also been studied (Shin et al., 1996). In the latter case, the micronsized particles should be purified from residual monomers after experiment. In pharmaceutics, however, the production and handling of clean dry powders are an integral part.

The dispersibility of powder depends on physical properties of the particles. Interparticle cohesion and the adhesion between particle and surface can be manipulated by the nature of the material, and size, size distribution, shape, and morphology of the particle (Hickey et al., 1994; Maa et al., 1997). For instance, Chew et al. prepared corrugated particles whose rough surface lowered the area of contact between particles, thus reducing powder cohesiveness (Chew and Chan, 2001). Therefore, from the point of applications such as drug delivery by respiration, the particle morphology should be taken carefully into account in the particle design.

This study was a continuation to our previous work with drug nanoparticles produced by the aerosol flow reactor method (Eerikäinen et al., 2003). The polymer used was a pH-responsive Eudragit L100 that has been used as an enteric coating material for drugs (Weiss et al., 1993; Esposito et al., 2000). In the method, the polymer solution was atomized, and resulting droplets were transferred to a heated tubular laminar flow reactor with the aid of a carrier gas, and then collecting dry particles. This aerosol method produces dry nanoparticles directly without a need for further purification of the particles. Also, during the solvent evaporation, the formation and resulting morphology of the particle can be modified. This study aimed to enlighten the mechanism of polymeric nanoparticle formation during droplet drying and subsequent heating, and to understand the influences of solvents and a drug molecule, ketoprofen, on the morphology of the particles.

2. Material and methods

2.1. Materials

The polymer Eudragit L100 (Röhm Pharma, Germany) was used as received. Eudragit L100 is a random copolymer of methyl methacrylate and methacrylic acid. The drug ketoprofen (2-(3-benzoylphenyl)propionic acid) (Sigma, USA) was used as received. Solvents ethanol (99.6%, Alko Oyj, Finland), THF (J.T. Bakers, USA), and toluene (J.T. Bakers, USA) were used as received. Water was purified by ion-exchange, and was measured to have pH 6 (Millipore).

2.2. Preparation of the solutions

Both Eudragit L100 and ketoprofen are well-soluble in ethanol and THF. The polymer concentrations, which ranged from 0.2 to 1.5 g/l, were prepared from the 2.0 g/l stock solution by dilution. One hundred milligrams of polymer was dissolved in 100 ml of toluene or water and the solutions were stirred overnight. The equilibrium concentrations for Eudragit L100 were determined after filtration and solvent evaporation, and those were 0.058 and 0.029 g/l in toluene and in water, respectively. For solutions having solvent mixtures, the polymer was first dissolved in either THF or ethanol followed by the slow addition of water or THF while stirring the mixture. The volume ratios of the solvents were 0.1, 1.0, and 9.0.

The polymer solutions containing the drug were prepared in the similar way. The solvents were ethanol, THF, and THF/water solutions with the volume ratios of 0.1 and 9.0. Polymer and drug were dissolved separately in a good solvent followed by the mixing of the solutions while stirring. Water was added slowly to the stirred mixture. The polymer concentration of 0.2 g/l and ketoprofen concentration of 10 wt.% of the polymer mass were used for the experiments.

2.3. *Preparation of the nanoparticles*

The experimental set-up is presented in our previous paper (Eerikäinen et al., 2003). The solution was atomized using a collision-type air jet atomizer (TSI 3076, TSI Inc. Particle Instruments, St. Paul, USA). The generated droplets were carried into a heated reactor using dry nitrogen with a flow rate of 1.5 l/min. The aerosol flow in the reactor tube was calculated to be laminar (Eerikäinen et al., 2003). The reactor tube was stainless steel with the inner diameter and length of 30 and 800 mm, respectively. The temperature of the reactor was kept constant at 50 °C, and was controlled with four separate heaters. After the heating, the dry nanoparticles were diluted by dry nitrogen gas with the ratio of 1:17 in a porous diluter tube at ambient temperature. The particles were collected by an electrostatic precipitator (InTox Products, Albuquerque, USA) onto either a plain or carbon-coated copper grid (Agar Scientific Ltd., Essex, UK).

2.4. *Instrumentation and characterization*

The morphology of the particles was analyzed with a field-emission scanning electron microscope (SEM; Leo DSM982 Gemini, LEO Electron Microscopy Inc., Oberkochen, Germany) using an acceleration voltage of 2 kV. The samples for SEM images were coated with platinum in order to stabilize the particles under electron beam and to enhance image contrast.

The particle size (geometric mean number diameter, GMD) and size distribution (geometric standard deviation, GSD) were determined with a TSI scanning mobility particle sizer (SMPS) equipped with a differential mobility analyzer (DMA, model 3081) (TSI Inc. Particle Instruments, St. Paul, USA) and a condensation particle counter (CPC, model 3027) (TSI Inc. Particle Instruments, St. Paul, USA). The average values of GMD and GSD were determined from 3–6 measurements. The maximum standard errors were 5 and 0.5% for GMD and GSD, respectively.

3. Results and discussion

The formation of spherical nanoparticles and their morphology can be influenced by proper experimental conditions. The solubility of the polymer in the solvent and the volatility of the solvent are probably the most important factors that influence on the particle formation.

A concept of solvent quality for a polymer is noteworthy (Grosberg and Khokhlov, 1997). As the solubility of the polymer increases, the solvent quality for the polymer improves, and vice versa. The solvent medium is, therefore, good or poor for the polymer, respectively. In a good solvent, polymer chains are expanded, whereas they shrink and eventually phase separates when the solvent quality worsens. In the good solvent, the polymer–solvent interactions dominate, whereas this is replaced by the interactions between polymer chains in the poor solvent.

The vapor pressure of the solvent, as it mainly determines the drying rate of the droplets at fixed temperature, is essential. The particle formation from inorganic molecules has been studied for spray pyrolysis techniques (Leong, 1987a,b; Che et al., 1998). In general, hollow particles could be obtained if a solute concentration gradient is created during evaporation of the solvent and/or removal of the gases from the melted particles. However, not only the diffusion and viscosity of the polymer, but also the interactions between the chains, i.e. physical entanglements (Sperling, 1992), differ drastically from the ones of small molecules. Therefore, during the solvent evaporation, the behavior of the polymer chains might generate particles with unusual morphologies. Protein and synthetic polymer microparticles with different morphologies such as corrugated, wrinkled, and highly porous have been prepared by spray drying or spray freeze drying techniques

(Edwards et al., 1997; Maa et al., 1997, 1999; Chew and Chan, 2001).

3.1. Influence of the polymer concentration in different solvents

The vapor pressures of the solvents THF, ethanol, toluene, and water at 25 °C are 21.6, 7.87, 3.79, and 3.17 kPa, respectively. The solubility of Eudragit L100 in used solvents was experimentally observed, and found to decrease in following order: ethanol > THF > toluene > water.

In these experiments, the temperature of the reactor was kept constant at 50 °C. In general, the size of the dry particles increased with increasing polymer concentration; see Fig. 1. For concentration range from 0.2 to 1.5 g/l, the GMD increased from ca. 75 to 130 nm, and from ca. 65 to 100 nm for the particles prepared from ethanol and from THF, respectively. The size distribution, however, showed notable difference between the polymer solutions. With increasing polymer concentration in THF, the GSD of the particle size increased from 1.9 to 2.2, whereas that from ethanol remained the same, <1.85. The atomizer produces droplets with the GSD less than 1.9. The broadening of the size distribution of the particles from THF was repeatable, and thereby, significant.

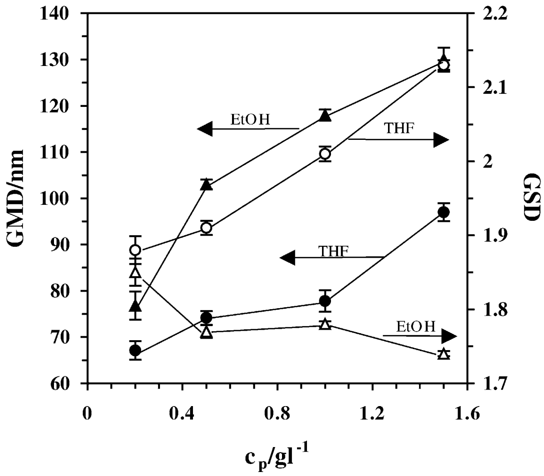


Fig. 1. Geometric mean diameter, GMD (filled symbols), and standard deviation, GSD (open symbols), as a function of polymer concentration. Triangles and circles stand for the particles prepared from ethanol and THF, respectively. Number of measurements for every concentration varied 3–6 times. The standard errors for the GMD and GSD were <5% and <0.5%, respectively.

Fig. 2 shows the SEM images of the particles as a function of polymer concentration. The particles from ethanol were spherical and most likely solid, i.e. non-porous and non-hollow. The particles from THF with the diameter less than 100 nm were solid spheres, whereas the particles larger than that were collapsed. Our previous study by a transmission electron microscope (TEM) showed that the collapsed particles were hollow (Eerikäinen et al., 2003). Therefore, the largest particles in this study might also be hollow besides being collapsed.

Polymer particles from toluene and water were small with the GMD around 35 nm and the GSD less than 1.9. The particles had irregular shape most likely having solid interior.

Scheme 1 is illustrative and based on other studies (Messing et al., 1993; Zhou et al., 2001) how the particles are formed depending on various conditional factors. Solid nanospheres are formed if the vapor pressure of the solvent is low and/or the droplet size is small enough; see Scheme 1A. This applies also to the case of volatile solvent (particle diameter (D_p) <100 nm in this work for the particles prepared from THF). The particles are collapsed if the vapor pressure of the solvent is high enough and/or droplet size is large enough; see Scheme 1B. During the evaporation of the solvent, a polymer film is formed on the surface of the droplet. The remaining solvent in the interior breaks through the film resulting in collapsed, and supposedly hollow, particles. The irregular wrinkled particles can be prepared when a polymer is at its solubility limit in the single liquid medium, i.e. poor solvent; see Scheme 1C. In the poor solvent, the polymer chains have shrunken conformation. At the very early stage of the solvent evaporation, the polymers precipitate and solvent molecules are expulsed fast from the droplet. According to the discussion, the particle formation in the poor solvent is controlled mainly by the precipitation of the polymer than the evaporation of the solvent.

3.2. Influence of the solvent composition

The particle formation from solvent compositions was expected to be dependent on both the vapor pressures of the solvents and the solubility of the polymer in the medium. In the experiments conducted

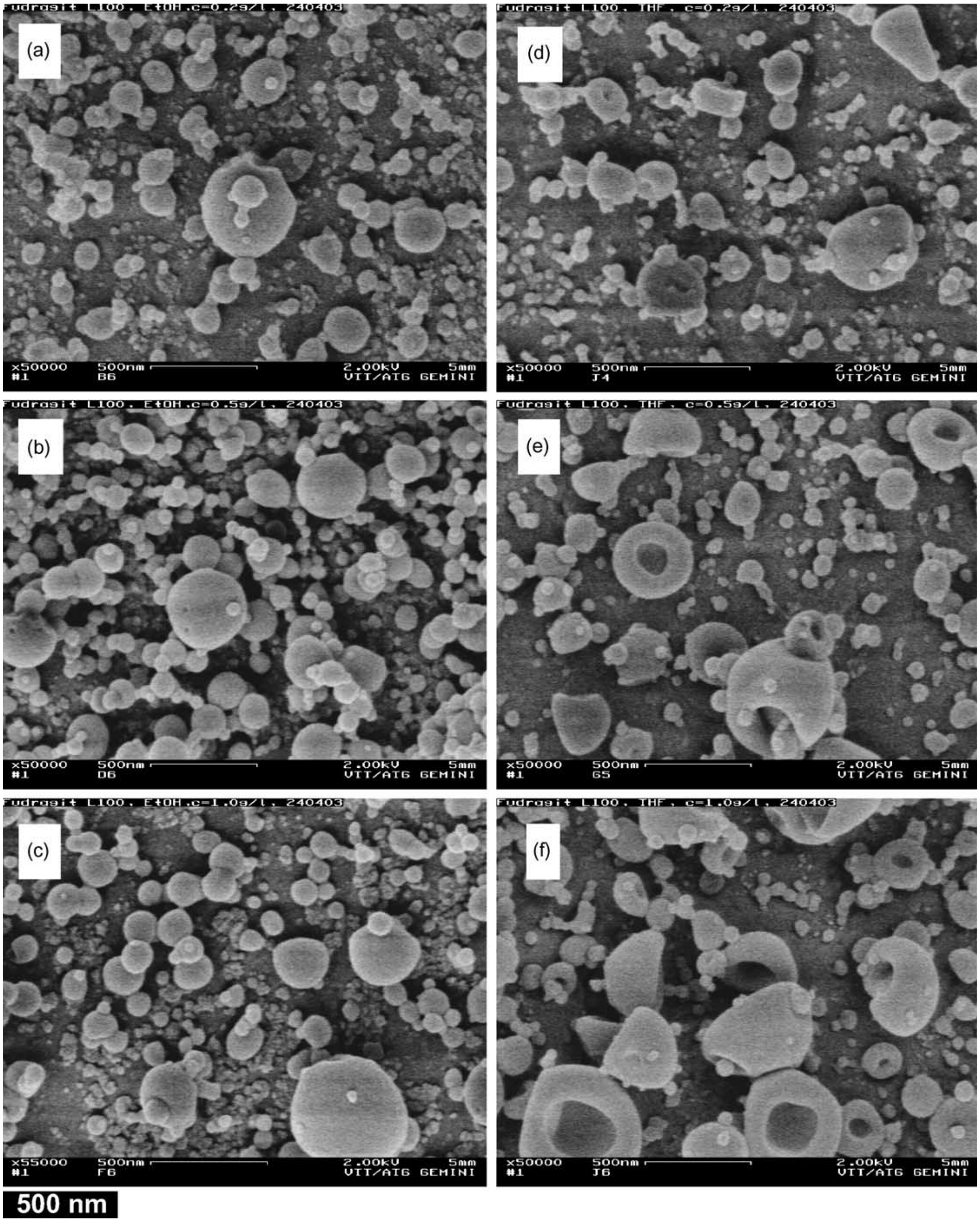
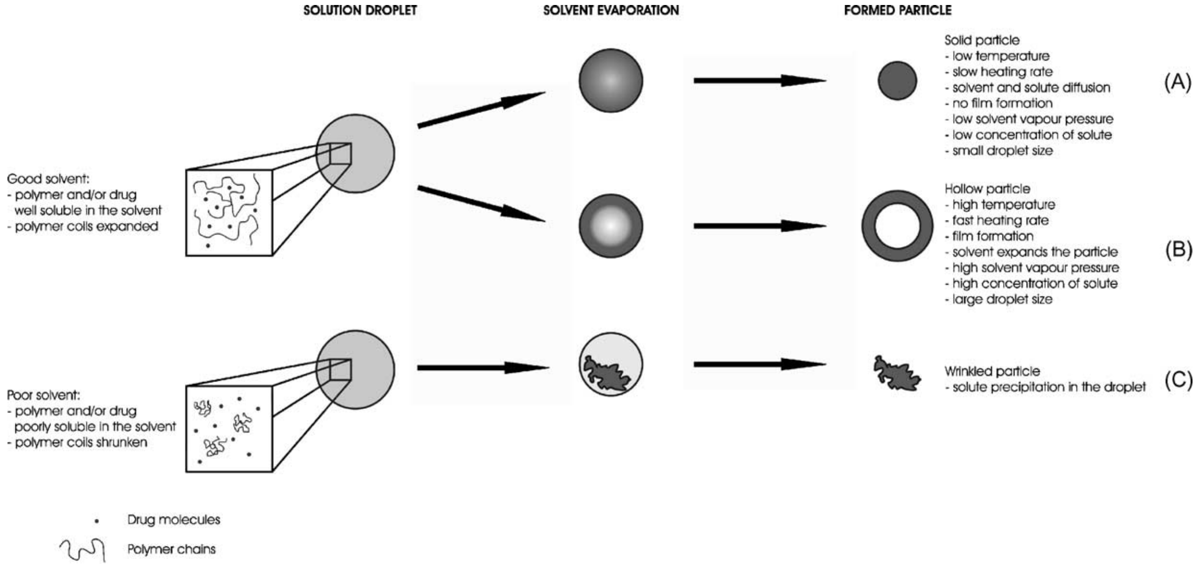


Fig. 2. The morphology of the particles imaged by SEM. Samples from ethanol: (a) 0.2 g/l, (b) 0.5 g/l, and (c) 1.0 g/l. Samples from THF: (d) 0.2 g/l, (e) 0.5 g/l, and (f) 1.0 g/l.



Scheme 1. Models for the formation of the particles at different experimental conditions.

at 50 °C, two polymer concentrations were used, 0.2 and 1.0 g/l.

3.2.1. Ethanol–water solution

Because of the non-solvent characteristics of water for the studied polymer, the solubility of the polymer in the solvent mixture can be varied by the amount of water. With increasing content of water in the solution, the geometric mean diameter of the particles decreased from 80 to 55 nm and from 120 to 80 nm for the solutions of 0.2 and 1.0 g/l, respectively; see Fig. 3. The GSD also decreased in the same respect. The particles were spherical; however, some deformed irregular particles were observed from the 0.2 g/l solutions with increasing water content. The polymer precipitated in the 1.0 g/l solution with volume ratio of 0.1 for ethanol.

3.2.2. Ethanol–THF solution

Both ethanol and THF are good solvents for the studied polymer. The addition of THF, however, resulted in particles whose size decreased from 80 to 65 nm and from 120 to 80 nm and increased size distribution (>1.9) for the both 0.2 and 1.0 g/l solutions, respectively. Moreover, the morphology of the particles changed with respect to solvent composition. From ethanol and THF concentrated solutions, the majority of particles appeared to be spherical and collapsed, respectively, as discussed earlier; see Fig. 2.

3.2.3. THF–water solution

The addition of water affected the particle formation more notably in the case of THF solution than in

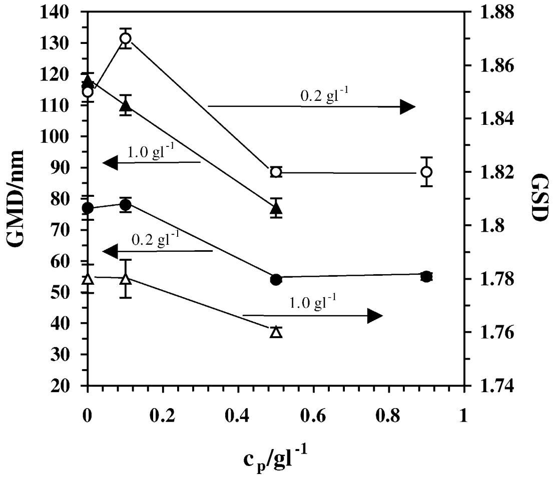


Fig. 3. Geometric mean diameter, GMD (filled symbols), and standard deviation, GSD (open symbols), as a function of water fraction in ethanol. Triangles and circles stand for the polymer concentrations of 1.0 and 0.2 g/l, respectively. Number of measurements for every concentration varied 3–6 times. The standard errors for the GMD and GSD were <5% and <0.5%, respectively.

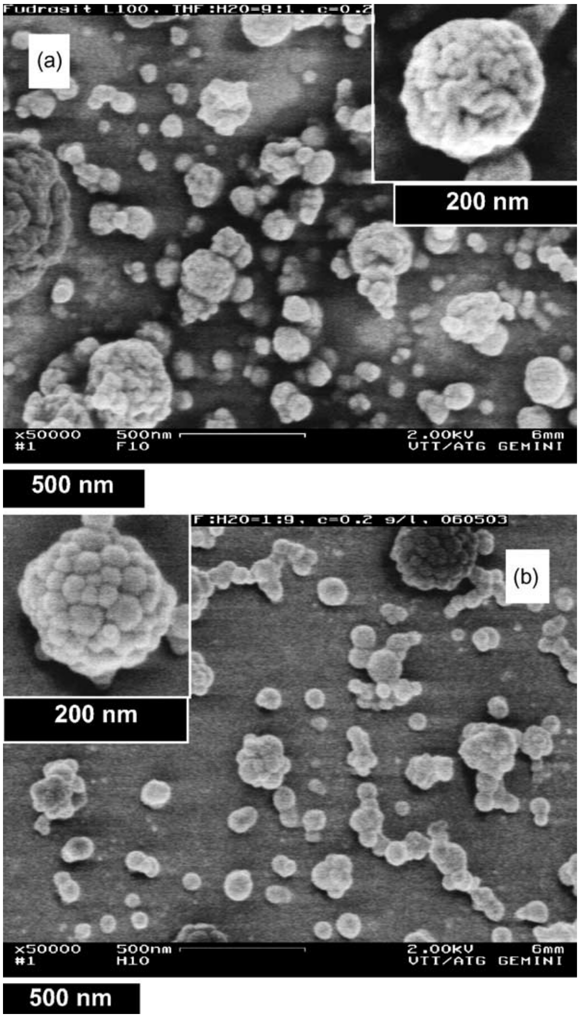


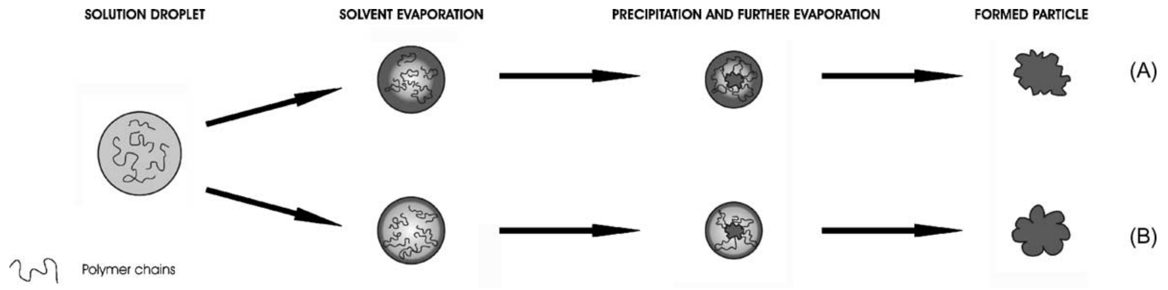
Fig. 4. The morphology of the particles from THF/water imaged by SEM. Images a and b show the shriveled and blistery particles from the solutions of the volume ratios of THF/water = 9 and THF/water = 0.1, respectively.

the case of the ethanolic solution. The 0.2 g/l polymer solution was opaque whereas in the 1.0 g/l solution, the polymer already precipitated, respectively, at the volume ratio of 0.1 and 1.0 for THF. The prepared particles were spherical with the GMD varying between 75 and 85 nm, and their size distribution narrowed with added water. The morphologies of the particles, however, were completely different depending on the volume ratio of the solvents. As shown in Fig. 4a, all the particles from the solution of high THF content showed that the particle surface had a shriveled and brain-like structure. On the other hand, the particles from the solution of high water content exhibited both blistery ($D_p > 100$ nm) and smooth ($D_p < 100$ nm) surface structures; see Fig. 4b.

With the increasing amount of water, the phase separation of the polymer takes increasingly part in the formation and surface structure of the particle. This induces an accelerated precipitation of polymer during solvent removal. Besides this, the difference in the vapor pressures between THF and water is significant. The particle formation from the solution with a high THF content may be explained as follows; see Scheme 2A. Fast evaporation of THF forms a thick polymer film on the surface of the droplet. At the same time, the solvent quality worsens for the polymer and the solution becomes viscous. At some critical concentration, the polymer chains collapse and precipitate. It is assumed that the polymer chains on the surface and in the interior of the drying droplet are highly entangled to each other. Therefore, the precipitating polymers in the droplet interior pull the polymers on the dried surface inwards, thus resulting in shriveled particles; see Fig. 4a. The appearance of the particles prepared from the low THF content solution was different depending on the particle size. The particle formation for the particles with $d > 100$ nm could be understood in the following way; see Scheme 2B. Now, the evaporation of THF induces a thin polymer film on the surface of the droplet. In very beginning of the solvent removal, the phase separation of the polymer takes place. In the interior, large amount of water molecules slowly penetrate through the film, simultaneously swelling the thin and flexible polymer film. Eventually, the blisters are formed up on the particle surface. The structure is characterized as popcorn-structure; see Fig. 4b. For small particles, the blister formation was not observed that could be explained by the faster removal of water the smaller is the drying particle. The interior of shriveled particles is assumed to be solid (Chew and Chan, 2001), but that of blistery particles has not been investigated.

3.3. Influence of a drug

Fig. 5(a and b) shows the exemplary polymer particles containing 10 wt.% ketoprofen. The composite particles appeared to be similar regarding to surface structure as those of the particles without the drug (compare with Fig. 2d and Fig. 4a). Ketoprofen



Scheme 2. Models for the formation of shriveled (A) and blistery (B) particles from the solutions of volume ratios of THF/water = 9 and 0.1, respectively.

apparently did not influence the particle formation with particular drug–polymer compositions, although the dimer formation between carboxylic acid groups of ketoprofen and polymer was observed in our studies by FTIR (Eerikäinen et al., 2004). The results in this work indicate that the polymer, being a much larger molecule than ketoprofen, controls the particle formation. However, further studies with other drug molecules or drug concentrations were not conducted, and the conclusion is not fully warranted by the results in this work.

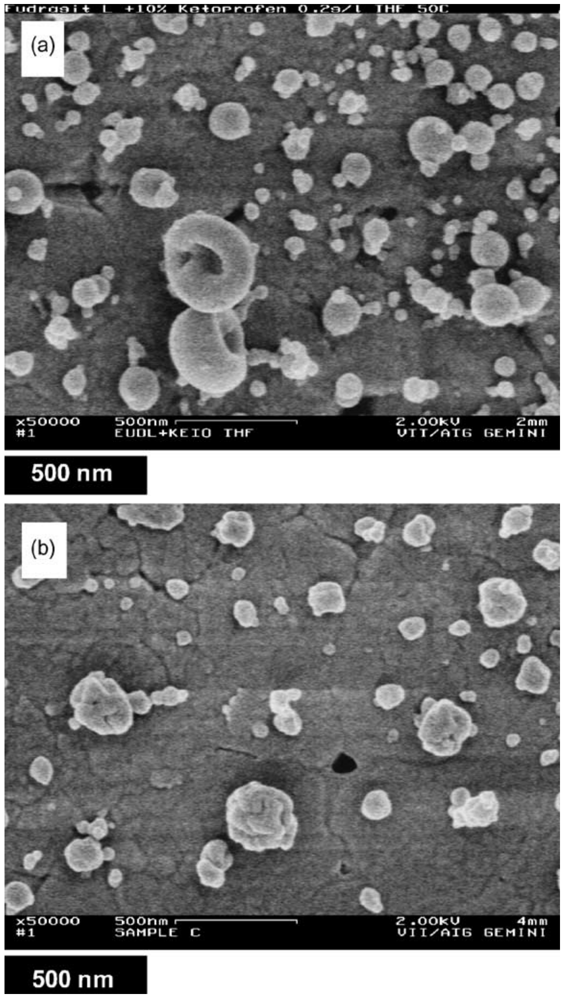


Fig. 5. The morphology of the particles from the 0.2 g/l polymer solutions containing 10 wt.% of ketoprofen to polymer mass. Images: (a) THF, and (b) THF/water = 9.

4. Conclusions

In this work, the polymer nanoparticles with different morphological structures were prepared by the aerosol flow reactor method. This work suggested the mechanisms for particle formation from various solvent media. The morphology of Eudragit L100 polymer particles can be modified by a solvent or solvent mixtures. The particle formation from a single solvent markedly depended on the vapor pressure of solvent, droplet size, and polymer concentration, resulting in various morphologies, such as solid, hollow, and collapsed. Besides these factors, the polymer concentration being close to the saturation concentration, the precipitation of the polymer starts to dominate the particle formation over the evaporation of the solvent or solvents. The mechanisms for the formation of shriveled and blistery particles have been proposed to be interplay between the evaporation of the solvent and the precipitation of the polymer. The particles having spherical but deformed surface structure are expected to exhibit reduced interparticle contacts, and therefore the particles would be easy to separate. However, the adhesion forces and flowability of the particles depend on their physicochemical properties. The SEM observations give only a general impression about the surface morphological features, not the internal structure of the particle. Therefore, the physical testing of the particles will be studied in the future work.

References

Allémann, E., Gurny, R., Doelker, E., 1993. Drug-loaded nanoparticles—preparation methods and drug targeting issues. Eur. J. Pharm. Biopharm. 39, 173–191.

Brigger, I., Dubernet, C., Couvreur, P., 2002. Nanoparticles in cancer therapy and diagnosis. Adv. Drug Deliv. Rev. 54, 631–651.

Chan, H.-K., Chew, N.Y.K., 2003. Novel alternative methods for the delivery of drugs for the treatment of asthma. Adv. Drug Deliv. Rev. 55, 793–805.

Che, S., Sakurai, O., Shinozaki, K., Mizutani, N., 1998. Particle structure control through intraparticle reactions by spray pyrolysis. J. Aerosol Sci. 3, 271–278.

Chew, N.Y.K., Chan, H.-K., 2001. Use of solid corrugated particles to enhance powder aerosol performance. Pharm. Res. 18, 1570–1577.

Edelstein, A.S., Cammarata, R.C., 1996. Nanomaterials: Synthesis, Properties and Applications. J W Arrowsmith Ltd, Bristol.

Edwards, D.A., Hanes, J., Caponetti, G., Hrkach, J., Ben-Jerbia, A., Eskew, M.L., Mintzes, J., Deaver, D., Lotan, N., Langer, R., 1997. Large porous particles for pulmonary drug delivery. Science 276, 1868–1871.

Eerikäinen, H., Watanabe, W., Kauppinen, E.I., Ahonen, P.P., 2003. Aerosol flow reactor method for synthesis of drug nanoparticles. Eur. J. Pharm. Biopharm. 55, 357–360.

Eerikäinen, H., Peltonen, L., Raula, J., Hirvonen, J., Kauppinen, E.I., 2004. Nanoparticles containing ketoprofen and acrylic polymers prepared by an aerosol flow reactor method. AAPS PharmSciTech. (submitted for publication).

Esposito, E., Roncarati, R., Cortesi, R., Cervellati, F., Nastruzzi, C., 2000. Production of Eudragit microparticles by spray-drying technique: influence of experimental parameters on morphological and dimensional characteristics. Pharm. Dev. Technol. 5, 267–278.

Galaev, I.Yu., Mattiasson, B., 1993. Thermoreactive water-soluble polymers, nonionic surfactants, and hydrogels as reagents in biotechnology. Enzyme Microb. Technol. 15, 354–366.

Grosberg, A.Yu., Khokhlov, A.R., 1997. Giant Molecules, Here, There and Everywhere . . .. Academic Press, USA, p. 117.

Hickey, A.J., Concessio, N.M., Van Oot, M.M., Platz, R.M., 1994. Factors incluencing the dispersion of dry powders as aerosols. Pharm. Technol. 18, 58–82.

Leong, K.H., 1987a. Morphological control of particles generated from the evaporation of solution droplets: theoretical considerations. J. Aerosol Sci. 18, 511–524.

Leong, K.H., 1987b. Morphological control of particles generated from the evaporation of solution droplets: experiment. J. Aerosol Sci 18, 525–552.

Maa, Y.-F., Costantino, H.R., Nguyen, P.-A., Hsu, C.C., 1997. The effect of operating and formulation variables on the morphology of spray-dried protein particles. Pharm. Dev. Technol. 2, 213–223.

Maa, Y.-F., Nguyen, P.-A., Sweeney, T., Shire, S.J., Hsu, C.C., 1999. Protein inhalation powders: spray drying vs. spray freeze drying. Pharm. Res. 16, 249–254.

Masters, K., 1991. The Spray-Drying Handbook. Longman Scientific and Technical, New York.

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.

Messing, G.L., Zhang, S.-C., Jayanthi, G.V., 1993. Ceramic powder synthesis by spray pyrolysis. J. Am. Ceram. Soc. 76, 2707–2726.

Peltonen, Koistinen, P., Karjalainen, M., Häkkinen, A., Hirvonen, J., 2002. AAPS PharmSciTech., 3, article 32.

Ravi Kumar, M.N.V., 2000. Nano and microparticles as controlled drug delivery devices. J. Pharm. Pharm. Sci. 3, 234–258, and references therein.

Shin, D.-S., Oh, E.-K., Kim, S.-G., 1996. Formation of polymer particles in aerosol-phase reaction. Aerosol Sci. Technol. 24, 243–254.

Sperling, L.H., 1992. Introduction to Physical Polymer Science, second ed. John Wiley & Sons, Inc., USA.

Tsapis, N., Bennett, D., Jackson, B., Weitz, D.A., Edwards, D.A., 2002. Trojan particles: large porous carriers of nanoparticles for drug delivery. Appl. Phys. Sci. 99, 12001–12005.

Wang, F.-J., Wang, C.-H., 2002. Sustained release of etanidazole from spray dried microspheres prepared by non-halogenated solvents. J. Controlled Release 81, 263–280.

Weiss, G., Knoch, A., Laicher, A., Stanilaus, F., Daniels, R., 1993. Microencapsulation of ibuprofen by a coacervation process using Eudragit L100-55 as an enteric polymer. Drug Dev. Ind. Pharm. 19, 2751–2764.

Yuk, S.H., Bae, Y.H., 1999. Phase-transition polymers for drug delivery. Crit. Rev. Ther. Drug Carrier Syst. 16, 385–423.

Zhou, X.D., Zhang, S.C., Huebner, W., Ownby, P.D., Gu, H., 2001. Effect of the solvent on the particle morphology of spray dried PMMA. J. Mater. Sci. 36, 3759–3768.