International Journal of Pharmaceutics 397 (2010) 218–224

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Pharmaceutical Nanotechnology

Effective polymeric dispersants for vacuum, convection and freeze drying of drug nanosuspensions

Sujung Kim, Jonghwi Lee*

Department of Chemical Engineering and Materials Science, Chung-Ang University, 221 Heukseok-dong, Dongjak-gu, Seoul 156-756, South Korea

ARTICLE INFO

Article history:
Received 18 March 2010
Received in revised form 26 June 2010
Accepted 8 July 2010
Available online 15 July 2010

Keywords:
Milling
Particle size
Nanoparticles
Nanocrystals
Freeze drying
Suspensions
Dispersion

ABSTRACT

Drying nanosuspensions into redispersable powders is a critical issue in developing solid dosage forms of drug nanoparticles. The particle fusion and chain entanglement of polymeric steric stabilizers adsorbed onto the nanoparticle surface should be prevented to retain redispersibility after drying. Herein, we report that only a small amount of polymeric dispersants such as carrageenan, gelatin, and alginic acid between 0.5 and 3 wt.% in various drug nanosuspensions can provide sufficient redispersibility in vacuum, convection, and freeze drying. In vacuum and freeze drying of naproxen nanosuspensions, the addition of only 0.5 wt.% carrageenan resulted in the formation of redispersable nanoparticulate powders. The amounts of polymeric dispersants required for redispersibility was lowest for carrageenan and highest for gelatin. The specific interactions between the dispersants and steric stabilizers (or drugs), in addition to viscosity increase during drying, appeared to effectively prevent irreversible particle aggregation.

1. Introduction

Particle size engineering of drugs is a convenient tool to control the bioavailability of a solid dosage form (Amidon et al., 1995; Lee, 2003; Liu, 2000). The recent development of nano-comminution technology has widely increased the range of particle sizes available for processing into solid dosage forms. So far, it has successfully improved the bioavailability of various poorly water-soluble drugs, e.g., Rapamune®, Emend®, Tricor®, and Megace® ES (Lee et al., 2008; Serajuddin, 1999; Yamada et al., 1999; Yin et al., 2005; Zheng and Bosch, 1997).

As the particle size of drugs decreases, the Gibbs free energy increases mainly due to the extra subdivision potential term related to the increase in surface energy (Hill, 2001). Thus, nano-comminution uses mechanical energy and surface steric stabilization to compensate for the extra energy (Lee et al., 2008; Liversidge and Conzentino, 1995; Liversidge and Cundy, 1995; Merisko-Liversidge et al., 2004). Steric stabilization using polymers is an effective mechanism for nanoparticles, as it is more effective for smaller particles than for ionic stabilization (Berglund et al., 2003a,b; Ploehn and Russel, 1990). A liquid medium is used in the preparation of nanoparticles by nano-comminution. Therefore, reliable conversion methods of nanoparticle suspensions to solid powders are required for the preparation of oral solid dosage forms. However, the drying unit operations are still quite challenging in the pharmaceutical industry (Eerdenbrugha et al., 2008; Grau et al., 2000; Kesisoglou et al., 2007; Schmidt and Bodmeier, 1999).

Properly dried powders are able to restore their original emulsion or suspension states of nanoparticles when they are redispersed in water ('redispersibility'), since they did not go through irreversible aggregation during drying (Saez et al., 2000). Freeze drying is a commonly chosen method because of its ability to retain the structure of an emulsion or suspension. A significant amount of cryoprotectant such as sucrose (usually more than drug content) is commonly used for effective structure preservation (Abdelwahed et al., 2006a,b; Bakaltcheva et al., 2000; Berejnov et al., 2006; Goldblith et al., 1975; Hirsjarvi et al., 2006; Konan et al., 2002; Layre et al., 2006; Lee, 2003; Quintanar-Guerrero et al., 1998). With the aid of large amount of dispersants, spray or fluidized bed drying was also attempted in some cases (Chaubal and Popescu, 2008; Sonner et al., 2002). However, to the best of our knowledge, simple vacuum or convection drying has never been reported because they are thought to inevitably impair the stabilization mechanism used in the preparation.

Furthermore, the use of a significant amount of dispersant limits its drug loading in a final dosage form. While the amount of liquid medium is continually diminished, the effect of the dispersants will be determined both by the kinetic parameters and by the thermodynamic parameters (Philip et al., 2003; Ryde and Ruddy, 2002). Therefore, it is strongly needed to develop a reli-

* Corresponding author. Tel.: +82 2 820 5269; fax: +82 2 824 3495.
E-mail address: jong@cau.ac.kr (J. Lee).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.07.010

able drying method for nanosuspensions using a limited amount of dispersant.

In this study, we attempted to minimize the amount of dispersants and to apply common drying methods for nanosuspensions. Mucoadhesive water-soluble polymers of limited concentrations were used as dispersants for three common drying processes in order to retain the redispersibility of nanoparticles. The restricted diffusion of nanoparticles and repulsive forces provided by the water-soluble polymer chains effectively led to redispersable nanoparticulate powders.

2. Materials and methods

2.1. Materials

Naproxen ((±)-2-(6-methoxy-2-naphthyl)propionic acid) from Tokyo Kasei Kogyo (Japan), itraconazole from Kapex Chemicals (Maharashtra, India), sofalcone (Dae He Chemical, South Korea), cilostazol (PacificPharma, South Korea), gelatin from Geltech (South Korea), and chitosan from KittoLife (chitosan oligosaccharide lactate, 3000 g/mol, South Korea) were used without purification. λ-Carrageenan, fenofibrate, alginic acid, and hydroxypropyl cellulose (HPC) were purchased from Sigma–Aldrich (St. Louis, MO, USA). Water (HPLC) from J.T. Baker (NJ, USA) was used without purification.

2.2. Preparation and drying of nanosuspensions

A media milling method (nano-comminution) was used to produce the drug nanosuspensions. A polymeric steric stabilizer, hydroxypropyl cellulose (HPC), was first dissolved in water, and the solution was mixed with drug powders (naproxen, itraconazole, sofalcone, and fenofibrate) and yittria-stabilized zirconia (1 mm diameter, 50 v/v%) in a 30 mL vial. The final drug concentration in the liquid medium was 8 wt.%, and the weight ratio of HPC to drug was 1–6. Comminution proceeded for 5 days at room temperature and 125 rpm.

Before mixing with the nanosuspensions, the polymeric dispersants, carrageenan, gelatin, and alginic acid, were prepared in water to produce homogeneous solutions. Carrageenan and alginic acid were dissolved at room temperature, and gelatin was dissolved at 40 °C overnight. The prepared solutions were mixed with nanosuspensions at a 1:1 weight ratio for 30 min (final concentrations of dispersant before drying = 5, 3, 2, 1, 0.5, and 0.1 wt.%). The solutions underwent either vacuum drying at room temperature for 24 h (chamber 64 L, 76 cm Hg), drying in a convection oven for 24 h (40, 60, 80 °C, accuracy ±2 °C) or freezing in a −25 °C freezer for 3 h and subsequent freeze drying for 24 h (FD-1000, EYELA, Tokyo, Japan).

2.3. Characterizations

The redispersibilities of the dried powders were assessed by measuring the volume-averaged particle sizes before and after drying. After complete drying, 0.01 g of dried powder was mixed with 10 mL of water, and immediately after mixing, the dispersion was placed into the sample chamber of a particle size analyzer. Volume-averaged particle sizes were measured in 150 mL water using a laser light scattering particle size analyzer (LA-910, Horiba Co., Kyoto, Japan) (relative refractive index = 1.06, Mie & Fraunhofer type). A 1-min sonication (40 W, 39 Hz) was applied before measurement at a stirring speed of 340 mL/min. The rheological properties of the suspensions before drying were measured by an AR2000 rheometer (TA Instrument, DE, USA) using a 40 mm cone and plate (1°, stain rate from 0.01 to 200/s) at room temperature. Zeta potential was measured for 5 wt.% dispersant cases by a dynamic electrophoretic light scattering spectrophotometer ELS-Z2 (Otsuka Electronics, Japan, avg. electric field −16.53 V/cm, conversion equation: Smoulchowski) at 25 °C.

For the examination of the particle morphology, a scanning electron microscope S-4800 (Hitachi, Tokyo, Japan) was used at 4 kV, and the specimens for SEM were coated with carbon (ca. 3 nm). For atomic force microscopy (AFM), 1 mg of dried particles was dispersed in 1 mL of water, and the dispersion was used to coat a glass slide using a spin coater SPIN-1200D (MIDAS SYSTEM, South Korea, 3000 rpm, 33 s). The particle morphology was visualized by an AFM XE-100 (Park systems, Gyeonggi, South Korea) at 0.5 Hz in non-contact mode. Etched silicon tips on a cantilever (NSC15, Park Systems, South Korea) with a force constant of 40 Nm^{-1} (as specified by the manufacturer) were used.

3. Results

3.1. Polymeric dispersants

Five different drugs were first processed into submicron particles in the presence of a steric stabilizer, HPC, as shown in Table 1. Since the same polymeric stabilizer was used for all of the drugs, the drug surfaces were covered by the same polymer chains, which provided a similar balance between inter-particular attraction and repulsion. The volume-averaged particle size varied from 100 to 320 nm. The differences in the particle sizes showed the stabilizing ability of HPC on the surfaces of the different drugs. The bulk physical chemical properties of the individual drugs may also be the reason for the differences, such as the melting point, molecular weight, solubility, or hydrophobicity (Lee et al., 2008). However, in this study, the differences in the particle sizes listed in Table 1 are not significant, as the redispersibilities of the dried particles were assessed by a much larger difference in particle size (typically far less than 1 μm (bold numbers in Tables 2–4) or several microns) (Lee and Cheng, 2006).

Table 2 shows the volume-averaged particle sizes from the redispersion experiments of vacuum and freeze-dried powders. First of all, vacuum drying successfully produces redispersable powders with the use of a small amount of polymeric dispersants between 0.5 and 3 wt.%. The redispersibilities of drug particles significantly depended on the concentration of the polymeric dispersant. When carrageenan was used as a dispersant in vacuum drying, the particle size increased from 200–300 nm to 2–22 μm as the concentration of carrageenan decreased from 3 to 0 wt.%. A critical concentration was observed as the transition in particle size primarily occurred between 0.5 and 0.1 wt.%. Therefore, for good redispersibility, a small amount of carrageenan greater than 0.5 wt.% was necessary in the vacuum drying of the naproxen nanosuspension. The transition from 200 to 300 nm to several microns occurs at a different concentration for each polymer. For gelatin, the transition appeared to exist between 1 and 3 wt.%, and for alginic acid it existed between 0.5 and 1 wt.%. Among the three polymeric dispersants, carrageenan seems to be the most effective dispersant for improving the redispersibility of drug nanoparticles, as it requires the smallest amount of dispersant.

Table 1
Volume-averaged particle sizes of drug suspensions prepared by nano-comminution for 5 days (parenthesized numbers are standard deviations).

Drug	Mean particle size (μm)
Naproxen	0.10 (±0.06)
Itraconazole	0.11 (±0.06)
Fenofibrate	0.16 (±0.09)
Sofalcone	0.32 (±0.11)
Cilostazol	0.20 (±0.10)

Table 2
Effect of dispersant concentration on the redispersability of naproxen nanoparticles. The redispersability was verified by the volume-averaged particle size (μm) after reconstitution of the dried powder in water by changing the type of dispersant and the drying method.

Concentration of dispersant solution (wt.%)	Vacuum drying			Freeze drying	
	Carrageenan	Gelatin	Alginic acid	Carrageenan	Gelatin
5	–	–	–	**0.12** (±**0.05**)	**0.16** (±**0.05**)
3	**0.23** (±**0.06**)	**0.36** (±**0.10**)	–	**0.26** (±**0.07**)	**0.13** (±**0.06**)
2	**0.21** (±**0.06**)	–	**0.19** (±**0.05**)	**0.23** (±**0.06**)	**0.16** (±**0.08**)
1	**0.26** (±**0.06**)	1.75 (±5.60)	**0.31** (±**0.41**)	**0.28** (±**0.08**)	**0.45** (±**0.89**)
0.5	**0.36** (±**0.71**)	–	2.02 (±4.05)	**0.31** (±**0.10**)	3.89 (±86.7)
0.1	2.32 (±4.63)	–	–	**0.91** (±**2.00**)	–
0	22.2 (±16.1)	22.2 (±16.1)	22.2 (±16.1)	16.2 (±14.4)	16.2 (±14.4)

Table 3
Effect of drying temperature on the redispersability of naproxen nanoparticles dried in a convection oven (with carrageenan 2 wt.%).

Temperature (°C)	Mean particle size (μm)	Standard deviation (μm)
40	**0.36**	0.29
60	**0.39**	1.01
80	20.79	2.70

When freeze drying was employed instead of vacuum drying, a smaller amount of polymeric dispersant prevented irreversible aggregation as shown in Table 2. However, the differences in the required amounts of polymeric dispersants were surprisingly small. When gelatin was used, a higher concentration (>1 wt.%) than that of carrageenan was necessary; however it was still lower than the concentration required for vacuum drying (>3 wt.%). When 5 wt.% carrageenan was used, particles of 0.12 μm size were obtained, which was quite close to the original particle size (0.10 μm) before drying.

An average particle size between 400 and 1000 nm was observed only for freeze-dried carrageenan/naproxen composite powders (0.91 μm in Table 2). In all the other cases, irreversible aggregation produced a relatively sharp transition in particle size, i.e., from a few hundred nanometers to several microns. Fig. 1 demonstrates a reason for the sharp transition; the particle size distributions had two distinct peaks, one less than 1 μm and the other greater than several microns. As the concentration of carrageenan increases, the peak greater than several microns disappears and the peak less than 1 μm increases. No other significant peak between the two peak areas was observed, which indicates the possible unstable energy states of aggregation in the size range.

Although the presence of carrageenan improved the redispersibility of the nanosuspensions, the volume-average particle size after reconstitution was slightly larger than the original particle size before drying (Tables 1 and 2). The peaks of the reconstituted cases less than 1 μm in size were indeed slightly different from the original peak before drying, as shown Fig. 1. This difference could be meaningful in bioavailability.

The similar particle size distributions were observed in the cases of Table 3. When the naproxen nanosuspensions with 2 wt.% carrageenan were dried in a convection oven at 40 and 60 °C, their reconstitution in water produced average particle sizes of 300–400 nm. As the drying temperature increased, faster drying resulted, and the redispersibility of dried powders could be improved, since the structures in nanosuspensions could be retained (Lee and Cheng, 2006). However, Table 3 shows contradictory data. Between 60 and 80 °C, the particle size had a sharp transition from 0.39 to 20.79 μm. An increase in temperature induced more irreversible particle aggregation, possibly because of the decrease in solution viscosity (changes in the chain dynamics of polysaccharide). In the cases of convection drying (Table 3), 2 wt.% carrageenan was observed to be the smallest amount required for sufficient redispersibility (data not given). When 0.5 or 1 wt.% carrageenan was used, the particle sizes after reconstitution were all greater than 12 μm. The required amount of polymer, 2 wt.%, was slightly larger than the amounts required for the vacuum and freeze drying methods in Table 2; however convection drying is still a cost-effective drying method.

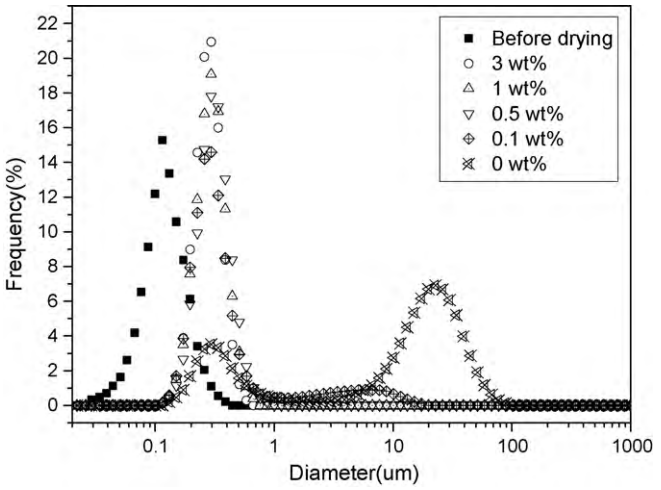


Fig. 1. Redispersability (particle size distribution curves) of naproxen particles vacuum dried with carrageenan.

3.2. Drugs

The results of the naproxen nanosuspensions may not simply be generalized for the nanosuspensions of other drugs. Table 4 shows the particle sizes from the redispersion experiments of different

Table 4
Effect of carrageenan concentration, drying method and drug on the redispersability of drug nanoparticles (volume-averaged particle size (μm)).

Concentration of dispersant (wt.%)	Drying methods					
	Vacuum drying				Freeze drying	
	Itraconazole	Sofalcone	Fenofibrate	Cilostazol	Itraconazole	Sofalcone
3	**0.62** (±1.15)	–	**0.50** (±0.80)	–	**0.72** (±1.85)	**0.37** (±0.14)
2	1.11 (±2.32)	**0.64** (±0.80)	**0.73** (±1.29)	**0.30** (±0.08)	1.28 (±3.11)	**0.39** (±0.17)
1	3.59 (±5.36)	2.01 (±3.49)	**0.59** (±0.98)	**0.45** (±0.35)	–	**0.53** (±0.77)
0.5	–	–	1.04 (±2.13)	1.24 (±2.33)	–	–

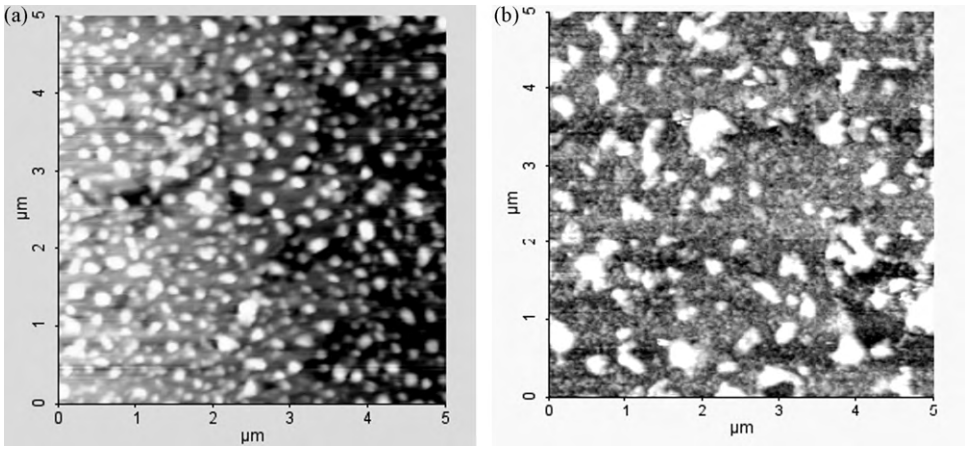
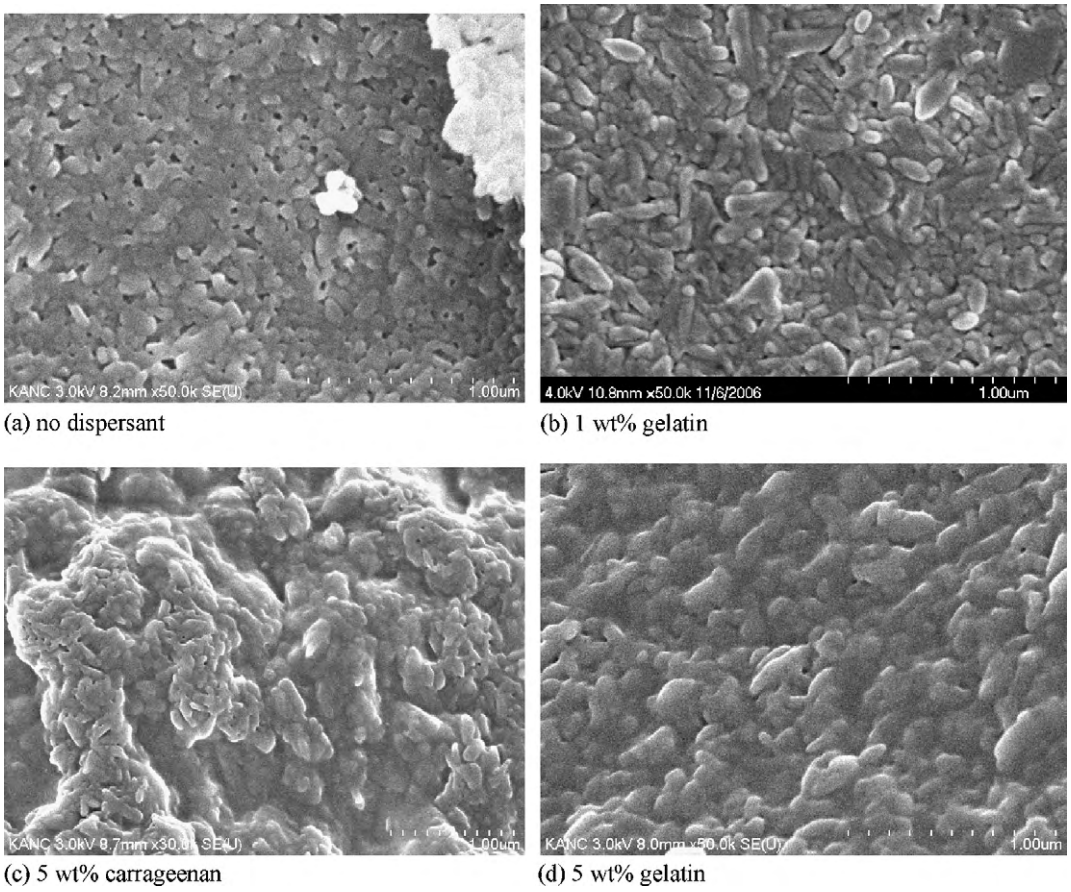


Fig. 2. AFM images of redispersed naproxen particles: (a) 0.5 wt.% carrageenan solution and (b) 0.1 wt.% carrageenan solution.

drugs with 0.5–3 wt.% carrageenan, where successful redispersion cases could be found. Compared to naproxen, a relatively smooth transition in particle size existed. In many cases, the smallest particle sizes were larger than the original particle sizes before drying (Table 1).

Although the same dispersant was used, the concentration required for good redispersibility depended on the kind of drug. While naproxen required a minimum concentration of 0.5 wt.%, itraconazole required a concentration of 3 wt.%, which was the highest requirement among the drugs used in our experiment (Table 4). This result implies that the high viscosity caused by the addition of polymeric dispersants may not be the only factor in determining the redispersibility of drug nanoparticles. If their particle sizes are similar, the viscosities of nanosuspensions are more dependent on the concentration of polymers than the properties related to the type of drug (Bałdyga et al., 2008).

Similar to the cases of Table 2, the freeze drying of sofalcone required a smaller amount of carrageenan than did the vacuum drying of sofalcone. However, itraconazole required similar amounts of carrageenan in both drying processes to produce a particle size of 600–700 nm. Therefore, not only the type of dispersant but also the type of drug significantly influenced the redispersibility of dried powders.



(a) no dispersant
(b) 1 wt% gelatin
(c) 5 wt% carrageenan
(d) 5 wt% gelatin

Fig. 3. SEM micrographs of vacuum-dried naproxen particles: (a and b) poor redispersion cases, and (c and d) good redispersion cases.

3.3. Morphology observations

Two microscopic investigations were used to visualize the differences in particle sizes. Fig. 2 shows the AFM observation of drug particles spin-coated onto a glass slide. Spin coating produced more well dispersed particles than particles slowly dried from a solution drop. Therefore, it was easier to observe individual submicron particles. Fig. 2a shows naproxen particles of approximately 200 nm. A decrease in the concentration of carrageenan resulted in larger particles (aggregates in Fig. 2b). The non-spherical morphology of Fig. 2b indicates that the particles were not the primary particles but aggregates of the primary particles. Aggregates larger than 1 μm were occasionally observed in Fig. 2b case.

During drying of the nanosuspension, dissolved polymers (extra HPC and polymeric dispersant) precipitated out of solution in addition to the polymer (HPC) physically adsorbed onto the surface of drug nanoparticles. Fig. 3a and b shows the cases of poor redispersion in which no significant polymer phases were observed. Alternatively, Fig. 3c and d shows polymer phases surrounding the drug particles. The individual drug particles were difficult to identify in the micrographs. The polymer phases can serve as protective layers, preventing irreversible aggregation of drug nanoparticles.

3.4. Viscosities of the nanosuspensions

The polymeric dispersants used in this experiment are often used as thickening agents due to the intrinsic high viscosities of their solutions. More effective protection of drug nanoparticles by polymer chains can occur with greater solution viscosity. Fig. 4 shows the typical shear viscosity results of carrageenan cases as a function of shear rate. Distinct shear thinning behavior existed except for cases of relatively low concentration and high shear rate.

Since the irreversible aggregation of naproxen nanoparticles becomes negligible above 0.5 wt.% (Table 2), the viscosities between 0.1 and 0.5 wt.% may be a critical value. The difference between 0.1 and 0.5 wt.% was more distinct at a relatively high shear rate. Nanoparticles may indeed experience a relatively high shear rate in their nanoscopic environment, although a quantitative comparison cannot be made.

However, the viscosity of alginic acid cases ranged from 0.07 to 6 poise in the same range of shear rate (data not given), and aggregation became serious at a different viscosity range. Overall, no single common critical value of viscosity was observed to predict the redispersibility of nanosuspensions. This is a natural consequence since the dependence of redispersibility on the types of both polymeric dispersant and drug was observed to be significant (Tables 2 and 4). The viscous media and appropriate chemical interactions between a drug (or HPC on drug surface) and a dispersant appear to be critical for the preparation of redispersable drug nanoparticles.

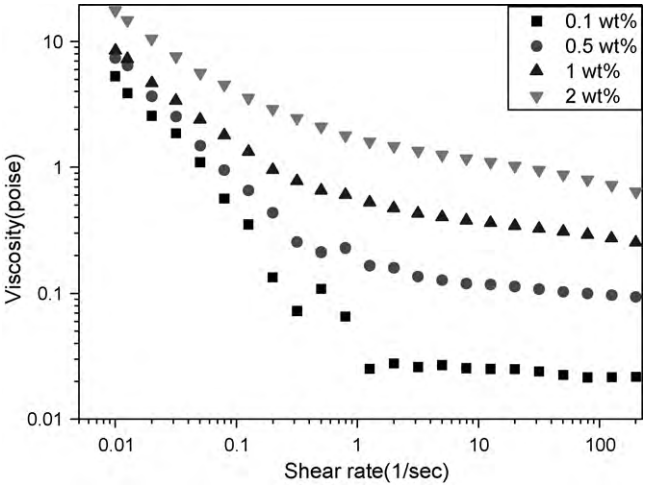


Fig. 4. Shear viscosities of naproxen nanosuspensions containing carrageenan. The concentration of carrageenan varied from 0.1 to 2 wt.%.

4. Discussion

During drying of nanosuspensions, the ceaseless motion of HPC chains and the subsequent steric repulsion mechanism become inactive. Removal of water between nanoparticles induces entanglement of HPC chains, and the entanglement or particle fusion results in irreversible aggregation (Fig. 5). To prevent the irreversible aggregation and retain the redispersibility of nanoparticles, dispersants such as sucrose and lactose are often used (even HPC). The dispersants fill the gaps between the nanoparticles after the removal of water. Therefore, a significant amount of dispersant, typically greater than that of the drug, is needed. Fast drying often provides better conditions for the prevention of chain entanglement (Lee and Cheng, 2006; Searles et al., 2001).

The additions of carrageenan, gelatin, and alginic acid were able to successfully protect drug nanoparticles from irreversible

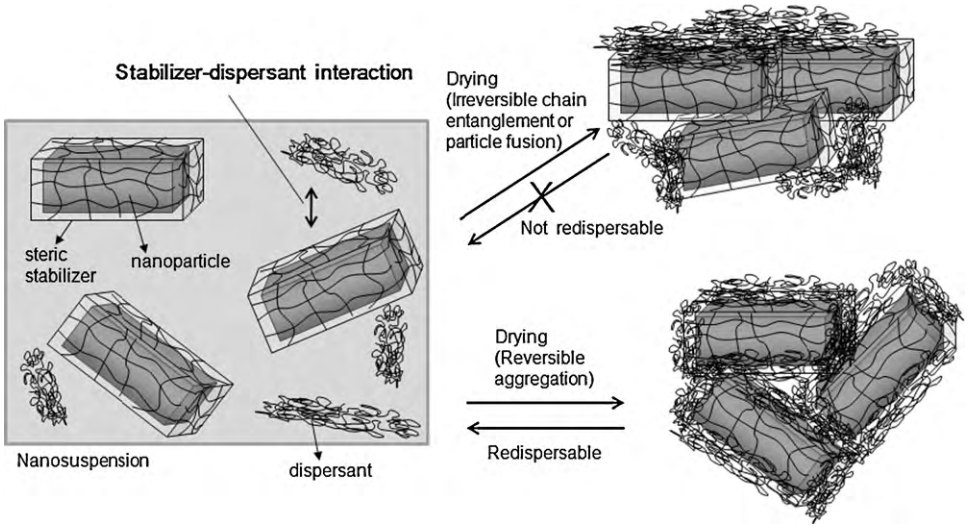


Fig. 5. Schematic diagram of nanosuspension drying processes of reversible and irreversible aggregation.

aggregation in this study, particularly the addition of only 0.5 wt.% carrageenan. It appears to be difficult for a small concentration of polymeric dispersant (even smaller than the amount of HPC, steric stabilizer) to form a continuous matrix and physically block the entanglement between the HPC chains on nanoparticle surfaces. Instead, the polymeric dispersant can interact with the HPC chains and prevent entanglements between them (Fig. 5). Differences in the specific interactions between polymeric dispersants and HPC may be why the carrageenan cases had the best redispersibility.

Zeta potential of drug particles could provide a clue for the interactions between stabilizer and dispersant. Among the three dispersants, the changes in zeta potential was the greatest in the cases of carrageenan (-28.4 ± 1.34 mV) compared to the naproxen control without any dispersant (-17.1 ± 0.34 mV). The use of alginic acid (-19.9 ± 0.60 mV) and gelatin (-18.24 ± 0.45 mV) slightly modified the zeta potential of naproxen nanoparticles. Therefore, carrageenan seems to have strong attractive interactions with HPC-covered naproxen nanoparticles, which result in an existence of a significant amount of carrageenan at the slipping plane of particles resulting in more negative zeta potential. After drying and redispersion, the zeta potential values slightly changed (carrageenan = -38.5 ± 0.68; alginic acid = -18.4 ± 0.42; gelatin = -13.6 ± 0.74 mV). It needs to be mentioned that a dispersant for drying processes mainly filled the space between particles in a dried state, and the surface property (zeta potential) of suspension itself may or may not directly predict the bulk powder properties (redispersibility of powder).

The polymeric dispersants can also significantly increase the viscosity of the nanosuspension. Their aqueous solutions can be physically gelled at a high concentration because of their strong interactions between polar functional groups. It is generally accepted that carrageenan undergoes gelation through coil–helix transition followed by aggregation (Loret et al., 2009). Similar mechanisms will be active during drying and will restrict the motions of drug nanoparticles and HPC chains. The retarded motions of HPC chains in the viscous solution can reduce the occurrence of chain entanglement and particle aggregation.

Carrageenan and alginic acid are polysaccharides, one with hydroxyl and sulfonyl groups and the other with hydroxyl and carboxyl groups, respectively. Gelatin is a protein obtained from the hydrolysis of collagen. The chemical structures of drugs and polymers are relatively diverse, and the interactions between polymers and HPC (or drugs) cannot be readily compared. However, specific interactions between them can be expected based on their structures. Indeed, strong interactions between cellulose (HPC) and carrageenan were reported based on the rheological properties of the polymer mixtures (Gomez-Diaz et al., 2008). The specific interactions will reduce the chances of entanglement between HPC chains and subsequent particle aggregation. The functional groups are thought to bring the mucoadhesive property to the polymers, and this can additionally help the performance of the resulting nanoparticulate formulations.

The specific interactions between a polymeric dispersant and a steric stabilizer and the viscosity effects will become more important as drying progresses. Fortunately, irreversible aggregation will become more active as drying progresses too. This coincidence might be a reason why the use of the small amounts of the polymeric dispersants is unexpectedly effective. For the development of the solid nanoparticulate formulations, the effective polymeric dispersants seems to be the best choices.

5. Conclusions

Nanosuspensions of different drugs were prepared by wet comminution and dried by conventional methods (vacuum, freezing and convection drying) in the presence of polymeric dispersants (carrageenan, gelatin and alginic acid). The polymeric dispersants of only 3 wt.% or less was able to successfully prevent irreversible aggregation between nanoparticles in all of the drying methods. The minimum amount of polymer required for sufficient redispersibility depended on the type of polymeric dispersant, the type of drug, and the drying method. Generally, carrageenan was more effective than the other two polymers. When carrageenan was used for naproxen nanosuspensions, vacuum and freeze drying required a minimum concentration of 0.5 wt.% for good redispersibility, and convection drying required a minimum concentration of 2 wt.%. Among the three drying methods, freeze drying generally required the smallest amount of dispersants. The use of a relatively small amount of polymeric dispersant will provide more freedom in drug contents, processing windows and choices for drying processes.

Acknowledgements

This research was supported by Ministry of Health and Welfare in South Korea (A090996). SK would like to thank Human Resource Development BK21 (KRF) and the Human Resource Training Project for strategic technology (MKE & KOTEF).

References

Abdelwahed, W., Degobert, G., Fessi, H., 2006a. Investigation of nanocapsules stabilization by amorphous excipients during freeze-drying and storage. Eur. J. Pharm. Biopharm. 63, 87–94.
Abdelwahed, W., Degobert, G., Stainmesse, S., Fessi, H., 2006b. Freeze-drying of nanoparticles: formulation, process and storage considerations. Adv. Drug Deliv. Rev. 58, 1688–1713.
Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.
Bakaltcheva, I., Ganong, J.P., Holtz, B.L., Peat, R.A., Reid, T., 2000. Effects of high-molecular-weight cryoprotectants on platelets and the coagulation system. Cryobiology 40, 283–290.
Bałdyga, J., Orciuch, W., Makowski, L., Krasiński, A., Malski-Brodzicki, M., Malik, K., 2008. Shear flow of aggregated nanosuspensions. Fundamentals and model formulation. J. Dispersion Sci. Technol. 29, 564–572.
Berejnov, V., Husseini, N.S., Alsaied, O.A., Thorne, R.E., 2006. Effects of cryoprotectant concentration and cooling rate on vitrification of aqueous solutions. J. Appl. Cryst. 39, 244–251.
Berglund, K.D., Przybycien, T.M., Tilton, R.D., 2003a. Coadsorption of sodium dodecyl sulfate with hydrophobically modified nonionic cellulose polymers. 1. Role of polymer hydrophobic modification. Langmuir 19, 2705–2713.
Berglund, K.D., Przybycien, T.M., Tilton, R.D., 2003b. Coadsorption of sodium dodecyl sulfate with hydrophobically modified nonionic cellulose polymers. 2. role of surface selectivity in adsorption hysteresis. Langmuir 19, 2714–2721.
Chaubal, M.V., Popescu, C., 2008. Conversion of nanosuspensions into dry powders by spray drying: a case study. Pharm. Res. 25, 2302–2308.
Eerdenbrugha, B.V., Froyenb, L., Humbeeckb, J.V., Martensc, J.A., Augustijnsa, P., den Mootera, G.V., 2008. Drying of crystalline drug nanosuspensions. The importance of surface hydrophobicity on dissolution behavior upon redispersion. Eur. J. Pharm. Sci. 35, 127–135.
Goldblith, S.A., Rey, L., Rothmayr, W.W., 1975. Freeze Drying and Advanced Food Technology. Academic Press, New York.
Gomez-Diaz, D., Navaza, J.M., Quintans-Riveiro, L.C., 2008. Influence of mixing and temperature on the rheological properties of carboxymethyl cellulose/κ-carrageenan mixtures. Eur. Food Res. Technol. 227, 1397–1402.
Grau, M.J., Kayser, O., Muller, R.H., 2000. Nanosuspensions of poorly soluble drugs—reproducibility of small scale production. Int. J. Pharm. 196, 155–157.
Hill, T.L., 2001. A different approach to nanothermodynamics. Nano Lett. 1, 273–275.
Hirsjarvi, S., Peltonen, L., Kainu, L., Hirvonen, J., 2006. Freeze-drying of low molecular weight poly(L-lactic acid) nanoparticles: effect of cryo- and lyoprotectants. J. Nanosci. Nanotechnol. 6, 3110–3117.
Kesisoglou, F., Panmai, S., Wu, Y., 2007. Nanosizing—oral formulation development and biopharmaceutical evaluation. Adv. Drug Deliv. Rev. 59, 631–644.
Konan, Y.N., Gurny, R., Allemann, E., 2002. Preparation and characterization of sterile and freeze-dried sub-200 nm nanoparticles. Int. J. Pharm. 233, 239–252.
Layre, A.M., Couvreur, P., Richard, J., Requier, D., Ghermani, E.N., Gref, R., 2006. Freeze-drying of composite core–shell nanoparticles. Drug Dev. Ind. Pharm. 32, 839–846.
Lee, J., 2003. Drug nano- and microparticles processed into solid dosage forms: physical properties. J. Pharm. Sci. 92, 2057–2068.
Lee, J., Cheng, Y., 2006. Critical freezing rate in freeze drying nanocrystal dispersions. J. Control. Release 111, 185–192.
Lee, J., Choi, J.-Y., Park, C.H., 2008. Characteristics of polymers enabling nano-comminution of water-insoluble drugs. Int. J. Pharm. 355, 328–336.

Liu, R. (Ed.), 2000. Particle Size Reduction, in Water-insoluble Drug Formation. Interpharm Press, Buffalo Grove, pp. 455–492.
Liversidge, G.G., Conzentino, P., 1995. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int. J. Pharm. 125, 309–313.
Liversidge, G.G., Cundy, K., 1995. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs. I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int. J. Pharm. 125, 91–97.
Loret, C., Ribelles, P., Lundin, L., 2009. Mechanical properties of κ-carrageenan in high concentration of sugar solutions. Food Hydrocolloids 23, 823–832.
Merisko-Liversidge, E., McGurk, S.L., Liversidge, G.G., 2004. Insulin nanoparticles: a novel formulation approach for poorly water soluble Zn-insulin. Pharm. Res. 21, 1545–1553.
Philip, J., Gnanaprakash, G., Jayakumar, T., Kalyanasundaram, P., Raj, B., 2003. Three distinct scenarios under polymer, surfactant, and colloidal interaction. Macromolecules 36, 9230–9236.
Ploehn, H.J., Russel, W.B., 1990. Interactions between colloidal particles and soluble polymers. Adv. Chem. Eng. 15, 137–228.
Quintanar-Guerrero, D., Ganem-Quintanar, A., Allemann, E., Fessi, H., Doelker, E., 1998. Influence of the stabilizer coating layer on the purification and freeze-drying of poly (D,L-lactic acid) nanoparticles prepared by an emulsion diffusion technique. J. Microencapsulation 15, 107–120.
Ryde, N.P., Ruddy, S.B., 2002. Solid dose nanoparticulate compositions comprising a synergistic combination of a polymeric surface stabilizer and dioctyl sodium sulfosuccinate. US Patent 6,375,986.
Saez, A., Guzman, M., Molpeceres, J., Aberturas, M.R., 2000. Freezedrying of polycaprolactone and poly (D,L-lactic-glycolic) nanoparticles induce minor particle size changes affecting the oral pharmacokinetics of loaded drugs. Eur. J. Pharm. Biopharm. 50, 379–387.
Schmidt, C., Bodmeier, R., 1999. Incorporation of polymeric nanoparticles into solid dosage forms. J. Control. Release 57, 115–125.
Searles, J.A., Carpenter, J.F., Randolph, T.W., 2001. The ice nucleation temperature determines the primary drying rate of lyophilization for samples frozen on a temperature-controlled shelf. J. Pharm. Sci. 90, 860–871.
Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.
Sonner, C., Maa, Y.F., Lee, G., 2002. Spray-freeze-drying for protein powder preparation: particle characterization and a case study with trypsinogen stability. J. Pharm. Sci. 91, 2122–2139.
Yamada, T., Saito, N., Imai, T., 1999. Effect of grinding with hydroxypropyl cellulose on the dissolution and particle size of a poorly water-soluble drug. Chem. Pharm. Bull. 47, 1311–1313.
Yin, S.X., Franchini, M., Chen, J., Hsieh, A., Jen, S., Lee, T., Hussain, M., Smith, R., 2005. Bioavailability enhancement of a COX-2 inhibitor, BMS-347070, from a nanocrystalline dispersion prepared by spray-drying. J. Pharm. Sci. 94, 1598–1607.
Zheng, J.Y., Bosch, H.W., 1997. Sterile filtration of nanocrystal drug formulation. Drug Dev. Ind. Pharm. 23, 1087–1093.