Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 355 (2008) 328–336
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

Characteristics of polymers enabling nano-comminution of water-insoluble drugs

J. Lee *, J.-Y. Choi, C.H. Park

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

Received 8 August 2007; received in revised form 22 October 2007; accepted 18 December 2007
Available online 28 December 2007

Abstract

Comminution has evolved into an effective method to prepare drug nanoparticles. Although nano-comminution has advantages, such as cost-effectiveness and easy scale-up, the processing is significantly sensitive to the selection of a polymeric stabilizer, which suffers from a lack of systematic understanding in this field. Herein, the combinations of various water-insoluble drugs and pharmaceutical polymers were systematically compared to assess the general relationships between the properties of the drugs and polymers. As a rule of thumb, drugs of high molecular weight, low solubility, high melting points, and a surface energy similar to that of the polymers, can be successfully processed into nanoparticles of unimodal particle size distribution. The addition of small molecular weight surfactants results in an additional size reduction in certain polymer/drug pairs, generally by reducing the size of larger particles. Both anionic and cationic surfactants produce similar size reductions in a polymer/drug pair indicating that the charge–charge interaction between polymer and surfactant is not important.

Keywords: Nanoparticles; Solubility; Bioavailability; Nanosuspension; Particle size; Surfactants

1. Introduction

Nanoparticles are inevitably more unstable than microparticles because of the extra Gibbs free energy contribution related to the particle size and primarily due to surface energy (Adamson and Gast, 1997; Hill, 2001; Lee et al., 2005; Morrison and Ross, 1992). Therefore, a convenient and efficient method to address the extra contribution is the key to preparing active pharmaceutical ingredient (API) nanoparticles.

The current preparation techniques of nanoparticles can be classified into two major groups, depending on their mechanisms to compensate the extra energy penalty (Lee et al., 2000, 2006). The first is the thermodynamic approach which uses stabilizers or a proper medium, such that stable nanoparticles can be prepared. The emulsion-type method uses surfactants or block copolymers, such as the spraying process using supercritical fluids. The second approach is kinetic, using an energy input to compensate, such as impinging jet processes, electrospraying techniques, and extrusion processes using relatively high shear force. For maximum efficiency, the two approaches are often combined.

Among the preparation methods, nano-comminution has conveniently been utilized to prepare solid nanoparticles due to simplicity and cost-effectiveness (Craig, 2002; Grau et al., 2000; Liversidge and Conzentino, 1995; Liversidge and Cundy, 1995; Leuner and Dressman, 2000; Merisko-Liversidge et al., 1996; Serajuddin, 1999; Six et al., 2004; Takano et al., 2006; Yamada et al., 1999; Zheng and Bosch, 1997). The drug crystallinity remains largely intact during the processing, thus relieving any stability concerns. Furthermore, no organic solvent or harsh environment is needed. The wet nano-comminution process can be easily scaled to industrial pharmaceutical unit operations. Recently, API nanoparticles have been successfully processed into solid dosage forms, such as Emend® (Merck & Co.).

Unfortunately, the process is sensitive to the choice of stabilizer (Lee, 2003; Lee et al., 2005). This critical point distinguishes nano-comminution from simple milling processes. Only a few polymeric stabilizers are known to be effective in reducing the drug size to nanometers. The additional use of small molecular weight surfactants is a common method to

* Corresponding author. Tel.: +82 2 8165269; fax: +82 2 8243495.
E-mail address: jong@cau.ac.kr (J. Lee).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.12.032

further decrease the particle size; however, the choice is also based on empirical approaches. Currently, the preparation of drug nanoparticles via nano-comminution requires a series of trial and error experiments because there is a lack of systematic knowledge of the process (Grau et al., 2000; Lee et al., 2005; Liversidge and Conzentino, 1995; Liversidge and Cundy, 1995; Merisko-Liversidge et al., 1996). In spite of the industrial importance of the process, a systematic study of stabilizer selection is far from completed. Furthermore, it is hard to compare the results of previous reports, since each study used different processing and characterization conditions.

In our previous studies, a systematic change of the hydrophilicity of amino acid copolymers was performed to elucidate the role of polymer properties in the nano-comminution of API (Lee et al., 2005). To attain successful nano-comminution, a certain level of hydrophobic moieties in the copolymer is needed. This approach, using tailored polymers, was useful in investigating the effect of hydrophobicity; however, it was impractical due to the difficulty in using the tailored amino acid copolymers for actual pharmaceutical formulation. Therefore, it is necessary to have knowledge of common pharmaceutical polymers to develop a more useful guideline in developing nano-comminution systems (Rowe et al., 2003).

In this study, the combinations of 5 common polymer stabilizers, 2 low molecular weight surfactants and 11 insoluble drugs were investigated with keeping processing and characterization conditions the same. An attempt at establishing the relationship among the properties of polymers, drugs, and surfactants was made by analyzing the results of mean particle sizes.

2. Materials and methods

2.1. Materials

Poorly soluble drugs, such as ibuprofen (Dr. Reddy's, India, 48.3 μm), glimepiride (Hanseo Chem., South Korea), biphenyl dimethyl dicarboxylate (BDD, Pharma Mar S. A., Spain), digitoxin (HPLC, >99%, Fisher, USA, 2.8 μm), naproxen (Tokyo Kansei Kogyo, Japan, 67.0 μm), paclitaxel (95%, Samyang Genex, South Korea), lipoic acid (Antibioticos, Italy), prednisolone acetate (M-030402, Shaanxi Rainbow Pharm., China, 19.6 μm), nifedipin (DY-Mach, India, 23.9 μm), hydrocortisone acetate (HAC030304, Tianjin Tianyao Pharm., China, 4.1 μm), and itraconazole (Choongwae Pharm, South Korea, 9.3 μm) were used without further preparation. The particle sizes were all greater than one micron. (The original particle sizes were checked following the method described below.) The basic physical properties of the drugs are provided in Table 1. Polymers used without further preparation were hydroxypropyl cellulose (HPC, $\bar{M}_w$ = 80k, Aldrich, USA), polyvinyl pyrrolidone (PVP, C-30, $\bar{M}_w$ = 50k, ISP Tech., USA), poly(ethylene glycol-*co*-propylene glycol) F127 (PEG:PPG:PEG = 100:65:100, $\bar{M}_w$ = 12.6k) and poly(ethylene glycol-*co*-propylene glycol) F68 (PEG:PPG:PEG = 78:30:78, $\bar{M}_w$ = ca. 8.4k) (Pluronic, Sigma–Aldrich, USA), and polyethylene glycol (PEG, $\bar{M}_w$ = ca. 80k, Sigma–Aldrich). Sodium dodecyl sulfate (SDS, Fisher, USA) and benzethonium chloride (Hyamine, ≥97%, Sigma–Aldrich, USA) were used as anionic and cationic surfactants, respectively.

2.2. Preparation of nanosuspensions

Drug particles (8 wt%) were mixed with the polymer (1.33 wt%) in distilled water. The mixture slurry (0.375 g) and polystyrene beads (0.354 g, 500 μm) were added to a 2 mL vial. The comminution process was performed on a high-speed shaker (Mini Beadbeater, Biospec Product, USA) at 4800 rpm at room temperature for 30 min. When an additional ionic surfactant was used, such as SDS and benzethonium chloride (Hyamine), the material was added at 1% the amount of polymer. After filtering the polystyrene beads, the resulting suspension was stored at 5 °C for further characterization. When other preparation equipment, such as a ball and rotational bead mill was employed, the concentrations of ingredients remained constant, with changes only in the total slurry amount according to the scale of the milling chamber. For ball milling, yttria-stabilized zirconia beads (500 μm, SamWha Ceramics, South Korea) were used and the same polystyrene beads and volume fraction were used for rotational bead milling.

2.3. Characterizations after comminution

Particle size analysis was performed using a Horiba Laser Light Scattering Particle Size Analyzer LA-910 (refractive

Table 1
Physical properties of API

Drugs	Molecular weight (g/mol)	Solubility (mM)	Melting temperature (°C)
Itraconzazole	705.65	1.4×10^{-6} (RT, neutral pH) (Verreck et al., 2005)	166.2
Paclitaxel	853.9	0.0035 (37 °C, water) (Elkharraz et al., 2006)	213–216
Glimepiride	490.62	0.0082 (37 °C, water) (Frick et al., 1998)	205–207
Digitoxin	765.95	0.013 (20 °C, water) (Merck index, 13ed)	256–257
BDD	270.28	0.013 (25 °C, water) (Kim et al., 2001)	210–212
Nifedipin	346.33	0.023 (Haltner, 2005)	172–174
Hydrocortisone acetate	404.5	0.025 (RT, water) (from Schwarz Pharma, USA)	220
Prednisolone acetate	402.49	0.042 (25 °C, water) (Gani and Pistikopoulos, 2002)	235
Ibuprofen	206.28	0.063 (RT, water) (Godwin et al., 2006)	75–77
Naproxen	230.26	0.12 (25 °C, water) (Mura et al., 2005)	152–154
Lipoic acid	206	3.9 (20 °C, water) (Schuhbauer et al., 2002)	50

index = 1.06, ultrasonic chamber power = 40 W and 39 kHz, 340 mL/min stirring flow (level 3), 95–100 mL water medium). The drug concentration in the analyzer chamber was 0.02 wt%. The measurements were repeated at least three times to calculate the error range of the volume averaged mean size. Particle morphology was investigated using a Hitachi (S-4700, Japan) scanning electron microscope at 4 kV and 0.5 Hz. Samples were prepared by drying suspension droplets on clean SEM sample stages, followed by coating with Pt-Pd at 7 nm/min for 2 min.

Static contact angles of the drugs and polymers were examined using a contact angle analyzer (Phoenix 450, SEO Co., South Korea) at room temperature (15–25 °C). The values were converted to approximate surface energy values. Various liquids were dropped over polymer films or drug compacts at 1 μL/s. The polymer films were prepared by evaporation of 100 μL polymer aqueous solutions (5 wt%) on a glass slide for 24 h under a vacuum. The drug compacts (diameter = 1 cm, thickness = ca. 1 mm) were prepared from compaction of 0.04 g of drug powder at 31.4 kg/cm^2 for 30 s by a Hydraulic Press 3912 (Carver, USA). Distilled water, ethanol (Sigma–Aldrich, USA), *n*-octane (>99%, Acros, USA), decane (95%, Junsei, Japan), chloroform (99%, HPLC grade, Sigma–Aldrich, Canada), tetrahydrofuran (99%, Samchun Pure Chem., South Korea), polyethylene dibenzoate ($\bar{M}_n$ = 410, Sigma–Aldrich, USA), isopropyl acetate (99%, Sigma–Aldrich, USA), and *N*,*N*-dimethylformamide (Samchun Pure Chem., South Korea) were used in the static contact angle measurements.

3. Results

3.1. Characteristics of particle size reduction

Comminution proceeds via particle fracture, suggesting that the balance and the type of applied energy are critical in understanding the particle size reduction as a function of time (Schonert, 1989, 1995). However, it is more important for the nano-comminution process whether the surface of drug particles is fully stabilized (Lee, 2003; Lee et al., 2005). It determines the steady state (i.e., smallest) particle sizes.

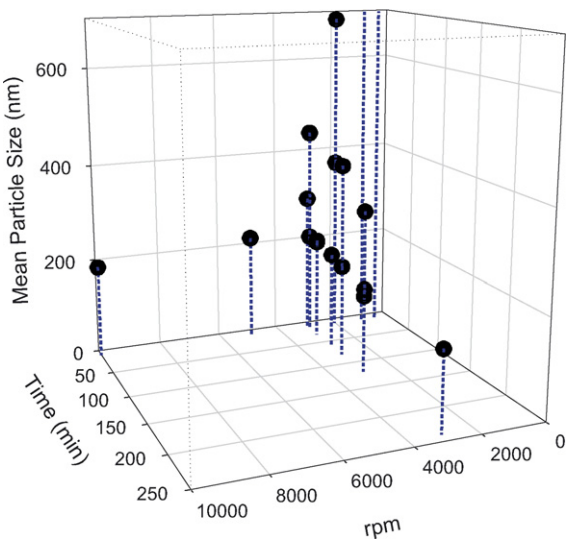

Fig. 1. Particle size reduction as a function of time and rpm in the comminution of naproxen particles using the three different processing methods. The drop lines without data points (near the time and rpm = 0 axis) have mean particle sizes near those of naproxen particles as received (67 μm).

Three types of the comminution apparatus were attempted in the initial trials of this study, with varying rotating or shaking speed and processing time (Fig. 1). After applying mechanical energy greater than approximately 2k rpm for 30 min, the mean particle size reached the steady state value, regardless of the equipment used. (Only a few data points are plotted in Fig. 1 for a comprehensible 3D plot.) Herein, the discussion will focus on the steady state particle sizes.

As stated in earlier reports, the relationship between the original sizes and steady state particle sizes attained after comminution were difficult to determine (Lee, 2003; Lee et al., 2005, 2006; Liversidge and Conzentino, 1995; Liversidge and Cundy, 1995). The as received drug particle sizes ranged from 4 to 70 μm, however the discussion of the original sizes before comminution are not meaningful in this study. It was also difficult to determine the steady state mean particle sizes between 0.5 and 1 μm after significant comminution (Tables 2–4). Further-

Table 2
Particle sizes of drugs after nano-comminution in the presence of different polymeric stabilizers

Drugs (surface energy, dyn/cm^2)	Polymers (surface energy, dyn/cm^2)				
	HPC (49 ± 2)	PVP (43 ± 3)	F127 (41 ± 3)	PEG (38 ± 3)	F68 (37 ± 5)
Ibuprofen (52 ± 5)	421 (±76)	m	m	m	m
Glimepiride (46 ± 2)	317 (±85)	141 (±67)	351 (±73)	m	537 (±200)
BDD (44 ± 3)	186 (±50)	330 (±72)	276 (±72)	430 (±139)	398 (±133)
Digitoxin (43 ± 4)	312 (±312)	302 (±324)	364 (±317)	m	347 (±96)
Naproxen (43 ± 3)	119 (±37)	208 (±77)	287 (±35)	m	505 (±155)
Paclitaxel (43 ± 3)	368 (±83)	406 (±116)	443 (±160)	381 (±109)	394 (±124)
Lipoic acid (41 ± 3)	m	m	m	m	m
Prednisolone acetate (40 ± 3)	m	m	m	m	361 (±102)
Nifedipin (39 ± 3)	190 (±68)	m	m	m	417 (±118)
Hydrocortisone acetate (38 ± 3)	m	m	m	m	421 (±120)
Itraconazole (36 ± 3)	305 (±132)	m	279 (±90)	m	448 (±140)

The standard deviations of particle sizes are given in the parentheses. The 'm' indicates systems of mean particle size above 1 μm.

Table 3
Particle sizes of drugs after nano-comminution in the presence of a polymeric stabilizer and sodium dodecyl sulfate (SDS, an anionic surfactant)

Drugs (surface energy, dyn/cm^2)	Polymers (surface energy, dyn/cm^2)				
	HPC (49 ± 2)	PVP (43 ± 3)	F127 (41 ± 3)	PEG (38 ± 3)	F68 (37 ± 5)
Ibuprofen (52 ± 5)	△ m	▼ 277 (±20)	m	m	m
Glimepiride (46 ± 2)	416 (±146)	483 (±203)	281 (±65)	▼ 547 (±224)	394 (±112)
BDD (44 ± 3)	310 (±86)	316 (±90)	382 (±117)	460 (±163)	368 (±114)
Digitoxin (43 ± 4)	449 (±129)	181 (±76)	212 (±98)	m	426 (±145)
Naproxen (43 ± 3)	250 (±93)	188 (±74)	△ m	m	△ m
Paclitaxel (43 ± 3)	△ m	132 (±102)	379 (±82)	326 (±89)	△ m
Lipoic acid (41 ± 3)	m	m	m	m	m
Prednisolone acetate (40 ± 3)	▼ 412 (±81)	m	m	m	424 (±145)
Nifedipin (39 ± 3)	287 (±67)	▼ 176 (±85)	m	m	535 (±153)
Hydrocortisone acetate (38 ± 3)	▼ 405 (±123)	▼ 560 (±840)	▼ 295 (±93)	m	493 (±150)
Itraconazole (36 ± 3)	229 (±94)	▼ 549 (±269)	215 (±96)	m	469 (±161)

The standard deviations of particle sizes are given in the parentheses. The 'm' indicates systems of mean particle size above 1 micron. The △ and ▼ indicate an increase and a decrease in particle size from the systems without using SDS (Table 2) respectively.

more, particle sizes greater than 0.5 μm were relatively unstable and sensitive to measuring conditions, such as stirring and sonication. The instability appears to be related to the insufficient surface steric stabilization by the adsorption of polymers on the drug crystal surface. As the amount of polymer adsorption decreases, the particle size increases (Lee, 2003). When the physical adsorption of the polymer occurred, the mean particle size easily decreased to less than 0.5 μm. Based on these observations, any particle sizes above 1 μm were labeled 'm'.

3.2. Properties of polymers

The steady state particle size was unique for a drug/polymer pair, showing that the stabilization ability of the polymer for the drug surface was critical. Table 2 shows the volume-averaged mean particle sizes of various drugs comminuted in the presence of various polymers. (They are not the smallest sizes because the preparation method was not optimized for each drug.) Comparison between 'm' and submicron particle sizes was more meaningful than the detailed comparison between two submicron sizes due to large batch-to-batch errors.

The surface energies of the drugs and polymers calculated from the static contact angle measurements are in the parentheses of Table 2. Previous studies have shown that contact angle measurements for surface energy are only a rough assessment with possible kinetic and environmental influences (Adamson and Gast, 1997; Morrison and Ross, 1992).

Table 2 shows that the prediction of steady state particle size is not straightforward, as can be expected. However, several interesting points were derived. PEG was not a successful stabilizer in most cases, except with BDD and paclitaxel due to no distinct hydrophobic units driving the adsorption of polymer chains. All other polymers were successful in the particle size reduction of glimepiride, BDD, digitoxin, naproxen, and paclitaxel. Interestingly, the surface energies of drugs were similar to those of the polymers, suggesting the influence of surface energy.

In addition to the five drugs, four more drugs, prednisolone acetate, nifedipin, hydrocortisone acetate, and itraconazole, showed successful size reduction in the presence of F68. F68 appeared to be the most versatile stabilizer, successfully stabilizing 9 out of 11 drugs possibly by strong chain adsorption via the hydrophobic PPG units.

Table 4
Particle sizes of drugs after nano-comminution in the presence of a polymeric stabilizer and benzethonium chloride (Hyamine, a cationic surfactant)

Drugs (surface energy, dyn/cm^2)	Polymers (surface energy, dyn/cm^2)				
	HPC (49 ± 2)	PVP (43 ± 3)	F127 (41 ± 3)	PEG (38 ± 3)	F68 (37 ± 5)
Ibuprofen (52 ± 5)	△ m	m	m	m	m
Glimepiride (46 ± 2)	167 (±47)	170 (±41)	336 (±73)	▼ 465 (±132)	300 (±79)
BDD (44 ± 3)	304 (±83)	273 (±72)	382 (±117)	668 (±468)	360 (±110)
Digitoxin (43 ± 4)	312 (±86)	272 (±94)	336 (±530)	m	507 (±144)
Naproxen (43 ± 3)	△ m	△ m	210 (±114)	m	397 (±121)
Paclitaxel (43 ± 3)	△ m	370 (±82)	479 (±231)	391 (±118)	698 (±2128)
Lipoic acid (41 ± 3)	m	m	m	m	m
Prednisolone acetate (40 ± 3)	m	m	m	m	458 (±165)
Nifedipin (39 ± 3)	304 (±31)	▼ 328 (±32)	▼ 209 (±24)	m	510 (±151)
Hydrocortisone acetate (38 ± 3)	▼ 713 (±168)	▼ 923 (±408)	▼ 328 (±32)	m	487 (±161)
Itraconazole (36 ± 3)	376 (±49)	m	298 (±130)	m	440 (±147)

The standard deviations of particle sizes are given in the parentheses. The 'm' indicates systems of mean particle size above 1 μm. The △ and ▼ indicate an increase and a decrease in particle size from the systems without using SDS (Table 2), respectively.

Compared to the hydrophobic F127, F68 had a lower molecular weight. Generally, the higher the molecular weight, the more physical adsorption (Morrison and Ross, 1992; Ploehn and Russel, 1990). However, it is possible that the 30-min processing time was not sufficient for the higher molecular weight F127 which physically adsorbed to the drug surface. The lower molecular weight F68, may have a less kinetically restricted adsorption process. Therefore, the difference between F127 and F68 may originate from the different molecular weights. [The similar effect of molecular weight was recently observed in our lab using 7 different HPC (Mn = 7200–29,000 g/mol) and itraconazole.]

F68, HPC and F127 showed good performance in terms of the number of successful nano-comminutions. Besides PEG, PVP appeared to be the worst polymer. PVP has amide functional groups, while all other polymers had ether or hydroxyl functional groups.

3.3. Drug properties

In Table 2, chemically similar to prednisolone acetate, hydrocortisone acetate with an additional double bond in the 6-membered ring, produced similar results. On the other hand, although the chemical structures were similar, ibuprofen was significantly different than naproxen. The effect of comminution heat was related to the crystalline melting behavior of the drugs, particularly for the drugs with relatively low melting temperatures. The crystalline melting points of ibuprofen and naproxen are 75–77 and 152–154 °C, respectively. Upon melting of the drug surface, the steric stabilization from polymer adsorption can be disrupted and subsequent aggregation can occur.

Among the drugs used, both α-lipoic acid and ibuprofen have relatively low melting temperatures of 75–77 and 50 °C, respectively (Table 1). α-Lipoic acid showed distinct evidence of melting after comminution, such that it appeared as gum. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis was performed to confirm melting. The heat induced melting and polymerization through disulfide interactions, such that by maintaining the processing temperature below 5 °C, a successful nanosuspension was possible (mean particle size = 90–400 nm) (Park et al., 2006).

Ibuprofen was not observed to look like gum, however cooling affected the mean particle size. Additionally, a decrease in particle size occurred with decreasing rpm, which contradicts the behavior that is usually observed in other comminution systems. As a result, other than HPC/ibuprofen, most ibuprofen and α-lipoic acid systems were unable to produce enough size reduction, as shown in Table 2. Comminution at a low temperature could suppress the melting related problems, however understanding crystal melting and related solubility issues were not straightforward. Detailed experimental results will be discussed in a separate study of the two drug systems.

A simple rule for selection of a proper polymer was not determined; consequently, alternative approaches were attempted in order to determine general rules of thumb. To this end, the number of successful cases was plotted as a function of drug solubility of Table 1 (Fig. 2). Fig. 2 generally shows more successful

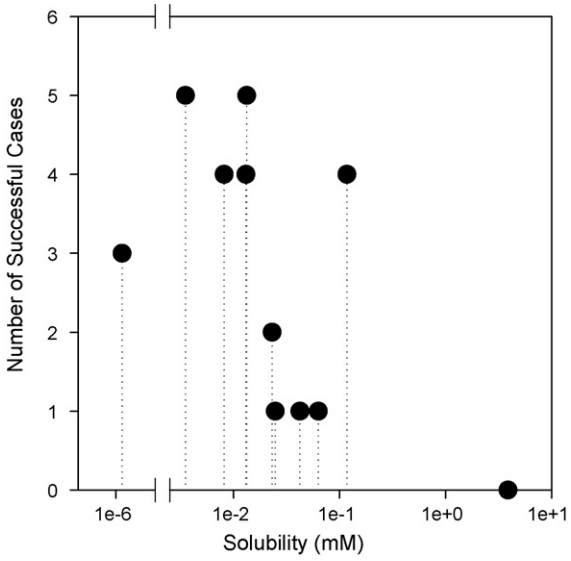

Fig. 2. The number of successful cases of drugs in Table 2 vs. the solubility (molar concentration) of drugs.

cases for the less soluble drugs. Nano-comminution appears to be good for relatively insoluble compounds, however, due to the diversity of chemical structures and physical properties, it is hard to expect a deterministic dependence on solubility.

In addition to surface energy and solubility, the molecular weight of the drug may be a determining factor in the nano-comminution process. Fig. 3 shows the molecular weight dependence for the successful cases. Compared to Fig. 2, the relation is unclear, however when the molecular weight is greater than 500 g/mol, the number of successful cases is above three, indicating that the higher molecular weight may be beneficial. A weak relationship between the number of successful cases and functional groups of the drugs was also observed, which was similar to Fig. 3.

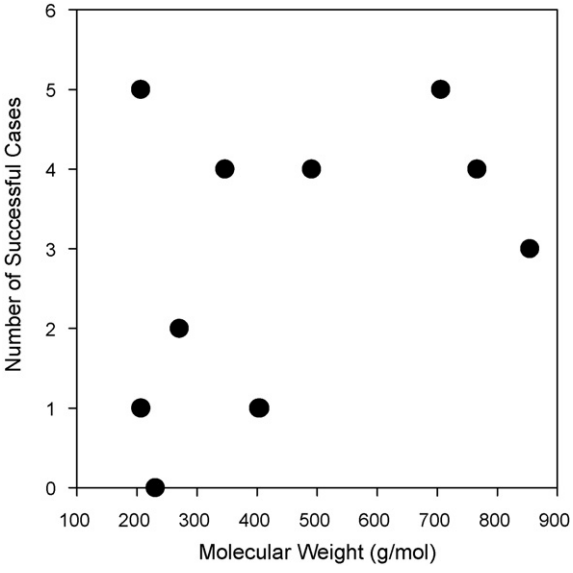

Fig. 3. The number of successful cases of drugs in Table 2 vs. the molecular weight of drugs.

3.4. Effect of anionic and cationic surfactants

The addition of a small molecular weight surfactant often has a significant effect on nano-comminution. In Tables 3 and 4, the same polymer/drug pairs of Table 2 were processed in the presence of an anionic and cationic surfactant.

In Table 3, the eight polymer/drug pairs decreased in particle size and five increased. In Table 4, six cases decreased and four increased. To this end, the addition of small molecular weight surfactants was not always beneficial. The most successful decreases in particle size were observed for prednisolone acetate, nifedipin, hydrocortisone acetate, itraconazole with HPC, PVP, and F127. Among the drugs and materials, these drugs were of relatively low surface energy and the polymers were of relatively high surface energy.

Among the drugs, only itraconazole, nifedipin, paclitaxel, and glimepiride have amine or amino groups. The amine groups might cause repulsive interactions with the cationic surfactants and attractive interactions with the anionic surfactants; however, no significant difference existed between the results shown in Tables 3 and 4. Therefore, the interactions between the polymers and drugs appear to be more important than those between the polymers and surfactants. The addition of surfactants appears to

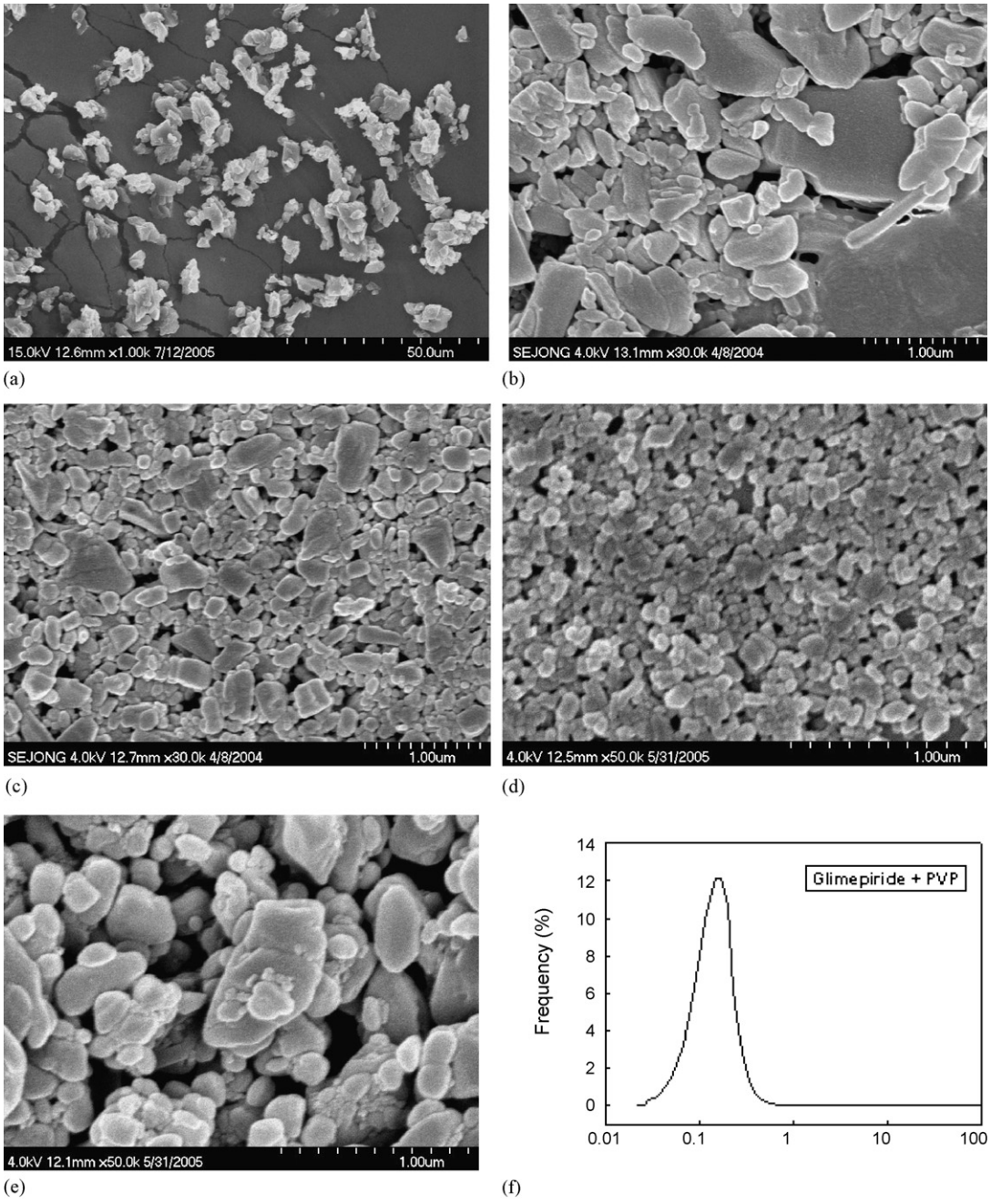

Fig. 4. Typical SEM micrographs and a particle size distribution curve of drug particles after nano-comminution. (a) Hydrocortisone acetate as received, (b) hydrocortisone acetate with HPC, (c) hydrocortisone acetate with HPC and SDS, (d) glimepiride with PVP, (e) glimepiride with PEG and (f) glimepiride with PVP.

aid the interaction between the polymers and drugs, resulting in an additional decrease in particle size.

On the other hand, an increase in mean particle size was observed for cases with naproxen and paclitaxel of Tables 3 and 4. The addition of a surfactant might hinder the physical interactions between the polymers and drugs.

3.5. Particle morphology and size distribution

The particle morphology of the as received materials was diverse. The particle morphologies before and after comminution were not simply related. Fig. 4a–c shows the hydrocortisone acetate particles before and after comminution. The sharp edges in Fig. 4a were rounded by the comminution processing, as shown in Fig. 4b. When SDS was used, the particle size further decreased (Fig. 4c). Additionally, the smallest particle size was similar in both Fig. 4b and c. Therefore, the addition of SDS aids in breaking and stabilization of the larger particles in Fig. 4b.

Fig. 4d shows an example of well-prepared nanosuspension. The particle morphology was close to spherical due to significant attrition. In Table 2, when PEG was used as a stabilizer instead of PVP, the mean particle size of glimepiride increased from 141 nm to greater than 1 μm. Fig. 4e indicates that the smallest particle size may be larger than the smallest particle of Fig. 4d.

The particle size distribution of successfully prepared nanosuspensions was unimodal, as shown in Fig. 4f, which was consistent with the SEM results of Fig. 4d. However, poorly processed nanosuspensions often had bimodal distributions which were consistent with Fig. 4b and e.

4. Discussion

Nano-comminution is more complex than emulsifying processes using surfactants. It involves fracture of drug crystals, adsorption and desorption of polymers on drug surfaces, dissolution and precipitation of drug, aggregation and segregation of particles, and micelle formation of polymers. Therefore, it may not be possible to find a simple rule guiding selection of a proper polymeric stabilizer for a specific drug. The surface energy, solubility, molecular weight, type and number of functional groups, crystal structure, and thermal properties of the drug crystals have an effect on nano-comminution.

For effective surface adsorption, a polymer should have a hydrophobic moiety to drive the free energy reduction associated with adsorption. Longer desorption time is also beneficial. The hydrophobic surface of the drug is better than a hydrophilic surface for adsorption, due to reversible dissolution and precipitation. To prevent particle aggregation and promote segregation, a hydrophilic moiety of a polymer with sufficient kinetic energy is necessary, such as F68. Among the polymers, HPC had relatively semi-flexible chains, however it did not show any distinct differences in performance (Park et al., 2006).

The fracture process of drug crystals depends on two major types of parameters: the transfer of mechanical energy and intrinsic physical properties of the crystals. The transfer of mechanical energy involves the slurry viscosity, the size and density of milling media, and energy input, which influence particle size reduction as a function of time and not the steady state drug particle sizes. The intrinsic physical properties involves the stress intensity factor, yield stress, plastic and elastic nature of the crystals. Irwin's equation predicts the size of the damage zone ahead of the crack propagation in a crystal, which might determine the smallest size of drug particles that can be attained by nano-comminution (Lee, 2003). Although these are important parameters, they are difficult to consider in the discussion of the nano-comminution results, due to fact that the basic physical properties of drug crystals remain largely unknown.

The micelle formation of polymers can compete with surface adsorption, which significantly depends on the concentration of the polymers. Some of the drug can be solubilized by micelle formation, although based on the DSC and XRD analysis in this study, that amount was small. The micelle formation is an unwanted (amorphous) state of the drug in the 'nanocrystal' comminution process.

The use of polymer/surfactant mixtures is often considered to have synergistic effects in numerous applications such as suspensions and slurries (Berglund et al., 2003a,b; Evertsson and Nilsson, 1997). Depending on the type of polymers, surfactants, and drug surfaces, either attractive or repulsive interactions between the polymers and surfactants and either co-adsorption or selective adsorption can occur. Therefore, four different combinations can be identified, depending on the types of interactions and adsorption (Berglund et al., 2003a,b; Evertsson and Nilsson, 1997; Ploehn and Russel, 1990).

Attractive interactions will lead to polymer/surfactant aggregates, according to the string of pearls model (Berglund et al., 2003a,b; Evertsson and Nilsson, 1997; Ploehn and Russel, 1990). HPC and SDS are known to have attractive (strongly cooperative) interactions (Berglund et al., 2003a,b; Evertsson and Nilsson, 1997). It is unclear whether hyamine has an attractive interaction with HPC, however, this study showed the synergistic effect of polymer/surfactant aggregates does not always occur. Alternately, the synergistic effects can be found in the certain drug and polymer pairs. For example, HPC/ibuprofen, PEG/glimepiride, HPC/hydrocortisone acetate, HPC/paclitaxel, PVP/nifedipin, PVP/hydrocortisone acetate, and F127/hydrocortisone acetate had the same result after surfactant addition, regardless of the surfactant types. Therefore, selective adsorption or co-adsorption of the polymer on the drug surface appears to be more critical to induce an effect of surfactant addition than on the interaction type between the polymer and surfactant.

Previous reports show that the total adsorption amount of the polymer and surfactant decreases with an increase in SDS concentration (Berglund et al., 2003a,b; Evertsson and Nilsson, 1997). The same phenomenon does not seem to occur in this study due to the relatively low concentration of SDS (~1 mM). However, if the concentration of surfactant increases, the same 'washing out' effect may occur and the polymer/surfactant interaction may be more significant.

5. Conclusions

The steady state particle sizes of insoluble drugs attained after sufficient nano-comminution were determined mainly by the selection of a polymeric stabilizer. The steady state particle sizes of various systems obtained under the same processing and characterization conditions were compared. Among the five common polymers, F68 was the most versatile in terms of the number of drugs successfully processed into nanoparticles. Surface energy appears to be an important factor, however it does not provide full predictability. The number of successful cases was plotted as a function of solubility or molecular weight. Generally, lower solubility, higher molecular weight, and higher melting point drugs were found to be better candidates for nano-comminution. The additional use of small molecular weight surfactants did not always reduce the particle size, however the results strongly depended on which pair of polymer/drug was used, regardless of anionic or cationic surfactants. The particle size distribution of successfully processed systems was unimodal, and poorly processed systems often had bimodal distribution.

Acknowledgements

Financial support from the Korea Institute of Industrial Technology Evaluation and Planning (project number 10011410) is gratefully acknowledged. CHP thanks Korea Research Foundation for BK21 Fellowship, and JL thanks the Chung-Ang University Excellent Researcher Grant in 2008.

References

Adamson, A.W., Gast, A.P., 1997. Physical Chemistry of Surfaces. John Wiley & Sons, p. 348, p. 506.

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.

Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231, 131–144.

Elkharraz, K., Faisant, N., Guse, C., Siepmann, F., Arica-Yegin, B., Oger, J.M., Gust, R., Goepferich, A., Benoit, J.P., Siepmann, J., 2006. Paclitaxel-loaded microparticles and implants for the treatment of brain cancer: preparation and physicochemical characterization. Int. J. Pharm. 314, 127–136.

Evertsson, H., Nilsson, S., 1997. Microviscosity in clusters of ethyl hydroxyethyl cellulose and sodium dodecyl sulfate formed in dilute aqueous solutions as determined with fluorescence probe techniques. Macromolecules 30, 2377–2385.

Frick, A., Möller, H., Wirbitzki, E., 1998. Biopharmaceutical characterization of oral immediate release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin. Eur. J. Pharm. Biopharm. 46, 305–311.

Gani, R., Pistikopoulos, E.N., 2002. Property modeling and simulation for product and process design. Fluid Phase Equilib. 194-197, 43–59.

Godwin, D.A., Wiley, C.J., Felton, L.A., 2006. Using cyclodextrin complexation to enhance secondary photoprotection of topically applied ibuprofen. Eur. J. Pharm. Biopharm. 62, 85–93.

Grau, M.J., Kayser, O., Müller, R.H., 2000. Nanosuspensions of poorly soluble drugs—reproducibility of small scale production. Int. J. Pharm. 196, 155–157.

Haltner, E., 2005. Cell culture as a tool to verify coating concepts of low soluble substances. Innovative approaches for granulation, coating, drying. TTC Workshop No. 88, pp. 21–23.

Hill, T.L., 2001. A different approach to nanothermodynamics. Nano Lett. 1, 273–275.

Kim, C.-K., Cho, Y.-J., Gao, Z.-G., 2001. Prepartion and evaluation of biphenyl dimethyl dicarboxylate microemulsions for oral delivery. J. Control. Release 70, 149–155.

Lee, J., 2003. Drug nano- and microparticles processed into solid dosage forms: physical properties. J. Pharm. Sci. 92, 2057–2068.

Lee, J., Lee, S.-J., Choi, J.-Y., Yoo, J.Y., Ahn, C.-H., 2005. Amphiphilic amino acid copolymers as stabilizers for the preparation of nanocrystal dispersion. Eur. J. Pharm. Sci. 24, 441–449.

Lee, J., Lim, G.-B., Chung, H., 2006. Preparation methods of drug nanoparticles. In: Kumar, C.S.S.R. (Ed.), Biological and Pharmaceutical Nanomaterials (Nanotechnologies for the Lifesciences), vol. 2. Wiley Science.

Lee, R.W., Mcshane, J., Shaw, J.M., Wood, R.W., 2000. Particle size reduction. In: Liu, R. (Ed.), Water-insoluble Drug Formation. Interpharm Press, Buffalo Grove, pp. 455–492.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Liversidge, G.G., Conzentino, P., 1995. Drug particle size reduction for decreasing gastic 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.

Merisko-Liversidge, E., Sarpotdar, P., Bruno, J., Hajj, S., Wei, L., Peltier, N., Rake, J., Shaw, J.M., Pugh, S., Pollin, L., Jones, J., Corbett, T., Cooper, E., Liversidge, G.G., 1996. Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. Pharm. Res. 13, 272–278.

Morrison, I.D., Ross, S., 1992. Colloidal Dispersions. Wiley-Interscience, p. 402.

Mura, P., Furlanetto, S., Cirri, M., Maestrelli, F., Corti, G., Pinzauti, S., 2005. Interaction of naproxen with ionic cyclodextrins in aqueous solution and in the solid state. J. Pharm. Biomed. Anal. 37, 987–994.

Park, C.H., Kim, A.R., Yun, H.L., Lee, J., 2006. Ring opening and polymerization of alpha-lipoic acid. Polymer (Korea) 30, 357–361.

Ploehn, H.J., Russel, W.B., 1990. Interactions between colloidal particles and soluble polymers. Adv. Chem. Eng. 15, 137–228.

Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients. Pharmaceutical Press.

Schonert, K., 1989. Aspects of very fine grinding. In: Sastry, K.V.S., Fuerstenau, M.C. (Eds.), Challenges in Mineral Processing. Society of Mining Engineers Inc., Littleton, Colorado, pp. 155–172.

Schonert, K., 1995. Comminution from theory to practice. In: The Proceedings of the XIX International Mineral Processing Congress. SME, Littleton, Colorado, pp. 7–14.

Schuhbauer, H., Winkler, S., Rudholzner, M., Mussner, R., Huber, E., 2002. Stable, acid, aqueous solution containing alpha-liponic acid (derivatives), method for the production thereof and use of the same. US Patent 20,020,495,600 (28 November).

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.

Six, K., Verreck, G., Peeters, J., Brewster, M., van den Mooter, G., 2004. Increased physical stability and improved dissolution properties of itraconazole, a class II drug, by solid dispersions that combine fast- and slow-dissolving polymers. J. Pharm. Sci. 93, 124–131.

Takano, R., Sugano, K., Higashida, A., Hayashi, Y., Machida, M., Aso, Y., Yamashita, S., 2006. Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test. Pharm. Res. 23, 1144–1156.

Verreck, G., Decorte, A., Heymans, K., Adriaensen, J., Cleeren, D., Jacobs, A., Liu, D., Tomasko, D., Arien, A., Peeters, J., Rombaut, P., Mooter, G.V., Brewster, M.E., 2005. The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. Eur. J. Pharm. Sci. 26, 349–358.

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.

Zheng, J.Y., Bosch, H.W., 1997. Sterile filtration of nanocrystal drug formulation. Drug Dev. Ind. Pharm. 23, 1087–1093.