Nanoparticulation of Poorly Water Soluble Drugs Using a Wet-Mill Process and Physicochemical Properties of the Nanopowders

Yusuke TANAKA,*[,a,c] Mitsugi INKYO,[b] Ryoko YUMOTO,[c] Junya NAGAI,[c] Mikihisa TAKANO,[c] and Shunji NAGATA[a]

[a] *Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Hiroshima International University; 5–1–1 Hiro-koshingai, Kure, Hiroshima 737–0112, Japan:* [b] *Kotobuki Industries Co., Ltd.; Ohashi-Gyoen-Bldg. 2F, 1–8–1 Shinjuku, Shinjuku-ku, Tokyo 160–0022, Japan: and* [c] *Department of Pharmaceutics and Therapeutics, Graduate School of Biomedical Sciences, Hiroshima University; 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8553, Japan.*
Received March 4, 2009; accepted July 23, 2009; published online July 29, 2009

In order to improve the dissolution and oral absorption properties of poorly water soluble drugs such as omeprazole, albendazole and danazol, various dispersing agents were added to prepare nanopowder formulations using an ULTRA APEX MILL, which is a wet-mill instrument, and their physicochemical properties were evaluated. Using Pluronic F-108 or F-68 as dispersing agents, slurries containing drug particles having nanometer size were obtained for all model drugs tested. Omeprazole, a heat labile drug, was not degraded by wet-milling and the omeprazole nanoparticles in a milled slurry did not aggregate for 24 h after wet-milling. After lyophilization of these milled slurries containing drug nanoparticles, fine solid white nanopowders were obtained. Scanning electron microscopy (SEM) suggested that the model drugs were milled into nanometer size. X-ray powder diffraction (XRPD) patterns and Differential Scanning Calorimetry (DSC) curves confirmed that all milled drug nanopowders were crystalline, although milling of albendazole nanopowder transformed it to another crystal form. Wet-milling using an ULTRA APEX MILL offers a highly effective approach to produce stable drug nanopowders and is a very useful tool for bioavailability enhancement of poorly water soluble and heat labile drugs.

Key words nanoparticle; milling; nanotechnology; lyophilization; X-ray powder diffractometry

Oral drug administration is the most convenient and common type of drug therapy due to good patient compliance and low medicine production costs. Currently, more than 60% of marketed drugs are used as oral products. Therefore, pharmaceutical manufacturers generally prefer to develop oral products. Recently, the introduction of techniques such as combinatorial chemistry and high-throughput screening has made it possible to quickly synthesize many new drug candidate compounds. Many of these candidate compounds, however, are poorly soluble and/or are poorly absorbed. Such candidate compounds now comprise 40% or more of all newly synthesized candidate drugs.[1,2] Thus, oral bioavailability, dissolution rate and solubility are serious concerns in the development of new oral products, because the main factors affecting drug absorption from the gastrointestinal tract are the permeability of the gastrointestinal membrane and the products' dissolution rate and solubility in water.[3] Pharmaceutical techniques to improve the aqueous solubility, dissolution rate and oral absorption of poorly water soluble drugs are needed to further the development of new oral products.

The dissolution rate of solid drugs increases in proportion to the surface area according to the Noyes–Whitney equation.[4] One common approach to increase the surface area and to improve dissolution rate is milling of a solid drug to reduce the particle size, and this process has been investigated widely. Milling is a useful technique that is relatively cheap, fast and easy to scale up. Most of the mills currently used to reduce particle size are dry-mills such as rod-mills, hammer-mills or jet-mills. However, the particle size of drugs produced by dry-mills is 1—10 μm at best[5—8] and it is difficult to reduce particle size to sub-micron level using this type of equipment. In addition, some drugs are degraded by the thermal energy generated by dry-mills.[9]

Wet-milling technique is one of the most efficient ways to generate sub-micron drug crystals to improve dissolution rate and oral absorption. The thermal energy generated during wet-milling is lower than that generated by dry-mills because drugs are suspended in aqueous solution. Several techniques have already reported concerning wet-milling such as high speed homogenization and high pressure homogenization.[10—15] However, almost of these techniques were not sufficient to manufacture the drug products because it needed long treatment period or it was not drown to powders from the suspension.

ULTRA APEX MILL, which is a wet-mill using beads, is practically used primarily for inorganic substances such as titanium oxide or aluminum oxide to produce particles having nanometer size[16] and have wide production scale ranges from gram to kilogram (up to 20 kg). Wet-mill instruments using beads are usually equipped a screen type separater to isolate a wet-milled substrate from beads.[13] However, the available beads size is limited by use of this separater on wet-milling (0.3 mm at smallest).[17] Thus, there are some problems with attrition and clog of beads at screen segment. The ULTRA APEX MILL makes it possible to use fine beads (down to 0.015 mm at smallest) by using centri-separater instead of a screen type.[17] Thus, it is easy to operate the ULTRA APEX MILL because attrition and clog of beads at screen segment are improved and filtration and decantation are not needed to isolate a wet-milled substrate from beads. In addition, it is anticipated that wet-milling using fine beads enables to produce much smaller particles than other wet-mills using larger size beads.

In order to develop pharmaceutical techniques to improve dissolution rate and oral bioavailability, we have utilized the ULTRA APEX MILL to produce nanopowders of poorly

* To whom correspondence should be addressed. e-mail: y-tanaka@ps.hirokoku-u.ac.jp

water soluble and heat labile model drugs. Omeprazole, albendazole and danazol were selected as model drugs for this study. Omeprazole is a poorly soluble (106 μg/ml: Determined experimentally in pH 6.8 Japanese Pharmacopoeia 2nd solution) and heat labile drug[18—20] and albendazole (solubility: 10 μg/ml) and danazol (solubility: 0.56 μg/ml) are also poorly soluble.[21—23] Furthermore, we carried out a physico-chemical characterization of these drugs after they were subjected to wet-milling.

Experimental

Materials Omeprazole was a gift from Sawai Pharmaceutical Co., Ltd. (Osaka, Japan). Albendazole and danazol were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). Poloxamers (Pluronic F-68 and F-108) were purchased from ADECA Alcohol Delivery Company (Japan). Tween 80 and methanol were purchased from Bio Medical Science Inc. (Japan) and WAKO Pure Chemical Industries, Ltd. (Japan), respectively. All other reagents were analytical grade commercial products.

Preparation of Various Mixed Slurries and Powders The compositions of mixed omeprazole, albendazole and danazol slurries used in this study are presented in Table 1. Each dispersing agent, *i.e.* Tween 80, methanol, Pluronic F-108 or Pluronic F-68, was added to 500 ml distilled water at 0.05—5 (w/v) % and 5 g (1%, w/v) of omeprazole, albendazole or danazol was suspended in each of these solutions. The resulting mixed slurries were then lyophilized to create mixed powders.

Preparation of Various Milled Slurries and Nanopowders Using the ULTRA APEX MILL A schematic of the ULTRA APEX MILL, Kotobuki Industries Co., Ltd. (Japan) used to prepare various milled slurries and powders is illustrated in Fig. 1. The experiments were performed as follows: The milling chamber of the ULTRA APEX MILL was filled with 500 g of fine zirconia beads (diameter: 0.05 mm). The beads were stirred by a rotor pin (8.0 m/s) and then a mixed slurry containing a drug (omeprazole, albendazole or danazol) and dispersing agent (Tween 80, methanol, or Pluronic F-68 or F-108) was poured into the slurry tank and infused into the lower part of the milling chamber by a feed pump. The drug particles were milled by impact with zirconia beads in the milling chamber. The milled drug, which reached to the upper part of the milling chamber, was separated from the zirconia beads by a Centri-Separator and the separated slurry was poured into the slurry tank again. This process was repeated for 30—60 min to obtain a milled slurry. The milling chamber and slurry tank were cooled by 13 °C water during milling to maintain the slurry at a low temperature.

The particle sizes of drugs in the various milled slurries were measured immediately. In order to measure the stability of the omeprazole nanoparticles in the milled slurry, small amounts were taken from the milled omeprazole slurries with 0.1% Pluronic F-68 or 0.05% Pluronic F-108 and were stored at 4 °C for 24 h. The omeprazole particle sizes were then measured again. The milled slurries containing drug nanoparticles were readily lyophilized to obtain nanopowders, which were resuspended, and the particle sizes were measured after sonication.

Particle Size Measurement The particle size distribution of each drug slurry was measured by using a Laser Scattering Analyzer (LA-950, Horiba, Japan) and the median particle size was calculated.

Scanning Electron Microscopy (SEM) Analysis A scanning electron microscope (JSM-6340F, JEOL Ltd., Japan) operating at 3 keV was used to determine particle shapes of the various powders. Prior to SEM analysis, the powders were dispersed onto a carbon-tape-coated aluminum stub and then coated with gold.

Evaluation of Omeprazole Degradation The degradation of omeprazole prepared by mixing, wet-milling and lyophilization was evaluated by HPLC. The various omeprazole powders were dissolved in methanol and diluted with methanol to a final concentration of 100 μg/ml omeprazole. The intact omeprazole in each sample was quantitated by HPLC.

Differential Scanning Calorimetry (DSC) DSC curves were obtained using a Differential Scanning Calorimeter (DSC-60, Shimadzu, Japan). Each powder (3 mg) was encapsulated in a sealed aluminum pan. The samples were heated from 30 to 200 °C or 250 °C at a heating rate of 10 °C/min.

X-Ray Powder Diffraction (XRPD) Patterns X-ray powder diffraction was performed using a D8 ADVANCE (Bruker AXS, Germany). Measurements were performed at 40 kV and 40 mA. The powders were compressed into the sample holder and the surface was smoothed with a flat block. The measurements were carried out over a range of 2θ values, from 5° to 40°.

HPLC Analysis Omeprazole concentrations were determined by HPLC using an HPLC pump (LC-20AD, Shimadzu Co., Kyoto, Japan) and a UV detector (SPD-20A, Shimadzu Co.). An analytical column (YMC-Pack Pro C18, 150×6.0 mm i.d., YMC Co., Ltd. Japan) was used at 40 °C. The mobile phase consisted of 50 mM phosphate buffer (pH 7.0) and acetonitrile at a 5 : 3 ratio. Omeprazole was detected at 302 nm.

Table 1. Compositions of Mixed Slurries Used in This Study

Drugs (w/v%)	Dispersing agents (w/v%)
Omeprazole (1%)	Methanol (5%)
	Tween 80 (5%)
	Pluronic F-68 (0.05%)
	Pluronic F-68 (0.1%)
	Pluronic F-108 (0.05%)
Albendazole (1%)	Pluronic F-68 (0.15%)
Danazol (1%)	Pluronic F-68 (0.05%)
	Pluronic F-68 (0.1%)

All reagents were added 500 ml distilled water.

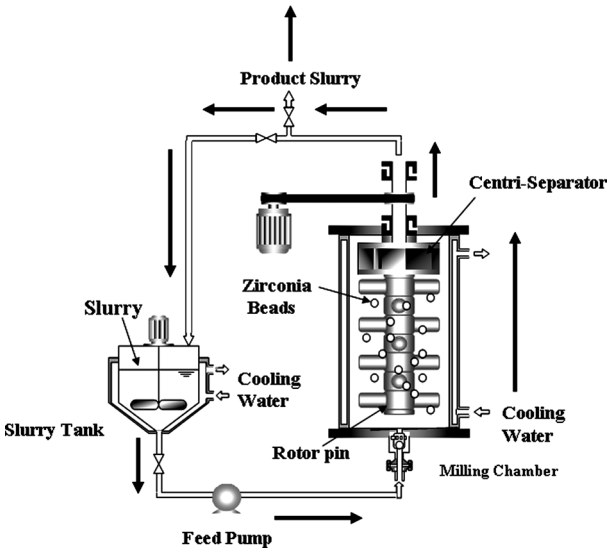

Fig. 1. Wet-Milling Process by ULTRA APEX MILL Shown in Schematic Representation

A mixed slurry was put into the slurry tank and infused into the milling chamber by a feed pump. The mill was operated in re-circulation mode.

Results

Particle Size Measurement Each bulk powder was suspended in water to make a bulk slurry and the median particle sizes of each drug in three types of slurry, *i.e.* bulk (drug only), mixed (drug and a dispersing agent) and milled (milled drug and a dispersing agent) slurries were measured using a Laser Scattering Analyzer (Table 2).

Particle sizes of omeprazole, albendazole and danazol in bulk slurries were 74.2, 75.1 and 30.1 μm, respectively. The drug particle sizes decreased to 5.88—8.63 μm after mixing with various dispersing agents. It is considered that aggregates in bulk slurries dispersed by adding various dispersing agents. After adding 5% Tween 80, 0.1% Pluronic F-68 or 0.05% Pluronic F-108 to omeprazole followed by wet-milling using the ULTRA APEX MILL, the particles in the milled slurries became nano-sized particles with sizes ranging from 127 to 187 nm. However, extraction of milled omeprazole particles with Tween 80 was impossible because the particles did not solidify upon lyophilization. The other

Table 2. Median Particle Sized in Various Slurries Calculated by Measured Particle Size Distribution

Drug (w/v%)	Dispersing agent (w/v%)	Median particle size (μm)		
		Bulky slurry	Mixed slurry	Milled slurry
Omeprazole (1%)	—	74.2		
	Methanol (5%)		5.88	2.39
	Tween 80 (5%)		6.26	0.127
	Pluronic F-68 (0.05%)		7.13	6.70
	Pluronic F-68 (0.1%)		7.29	0.187
	Pluronic F-108 (0.05%)		7.17	0.164
Albendazole (1%)	—	75.1		
	Pluronic F-68 (0.15%)		6.84	0.185
Danazol (1%)	—	30.1		
	Pluronic F-68 (0.05%)		8.44	5.81
	Pluronic F-68 (0.1%)		8.63	0.102

omeprazole particle sizes in the milled slurries (milled with 5% methanol or 0.05% Pluronic F-68) were somewhat influenced by wet-milling, although their particle sizes decreased only slightly. The albendazole particle size in a slurry was 185 nm after adding 0.15% Pluronic F-68 and milling. The particle size of the milled danazol slurry with 0.1% Pluronic F-68 also decreased to nanometer size, but the particle size did not decrease when 0.05% Pluronic F-68 was added followed by milling. Twenty-four hours after milling, the particle sizes of milled omeprazole slurries containing 0.1% Pluronic F-68 or 0.05% F-108 were the same as the initial particle sizes (Table 3). Furthermore, after lyophilization of milled omeprazole, albendazole and danazol slurries containing 0.1% Pluronic F-68 or 0.05% Pluronic F-108, 0.15% Pluronic F-68 and 0.1% Pluronic F-68, respectively, all of the various nanoparticles retained their nanometer size after resuspension of the obtained nanopowders, although their particle sizes increased slightly compared to the initial milled slurries (Table 4). These results indicate that stable nanopowders can be speedily produced by using Pluronic F-68 or F-108 and the ULTRA APEX MILL than other wet-mill techniques.[10,12]

Table 3. Stability of Particle Sizes in Milled Omeprazole Slurries Containing 0.1% Pluronic F-68 or 0.05% Pluronic F-108

Milled omeprazole slurries	Particle size (μm)	
	Initial milled slurry	Milled slurry after 24 h
Milled omeprazole slurry with 0.1% pluronic F-68	0.187	0.189
Milled omeprazole slurry with 0.05% pluronic F-108	0.164	0.161

Table 4. Particle Sizes after Resuspension of Various Nanopowders

Nanopowder	Particle size (μm)	
	Initial milled slurry	Resuspended nanopowder
Omeprazole with 0.1% Pluronic F-68	0.187	0.242
Omeprazole with 0.05% Pluronic F-108	0.164	0.235
Albendazole with 0.15% Pluronic F-68	0.185	0.176
Danazol with 0.1% Pluronic F-68	0.102	0.440

Degradation of Omeprazole by Mixing or Wet-Milling Intact omeprazole in various powders was quantified by HPLC analysis. The amount of intact omeprazole in all omeprazole samples was the same as in the control sample (data not shown). This confirmed that omeprazole powders were not degraded by physical mixing, wet-milling or lyophilization.

Particle Morphology Scanning electron microscopy (SEM) indicated the morphological characteristics of various omeprazole and danazol powders (Fig. 2). The SEM micrographs of bulk and mixed omeprazole and danazol powders revealed large crystalline blocks. In the case of omeprazole and danazol nanopowders, the morphologies included porous aggregates composed of many nanoparticles having rod-like structures.

Differential Scanning Calorimetry (DSC) In order to observe the crystal transformation of drug nanopowders obtained by wet-milling, the DSC curves of various drug powders were obtained at a heating rate of 10 °C/min (Fig. 3, Table 5). Endothermic peaks, which are caused by melting of poloxamers, were observed at about 50 °C in all mixed powders and nanopowders. With increasing temperature, endothermic reactions due to melting of omeprazole, albendazole or danazol in all powders occurred over the ranges of 148—157, 163—194 and 198—224 °C, respectively. There were some peaks around melting points of albendazole powders. These peaks may be caused by heat degradation because no intact albendazole in remained samples after DSC analysis was detected by HPLC (date not shown). The thermal behavior of the albendazole nanopowder changed drastically compared to bulk powders and mixed powders, indicating that the crystal form of albendazole may have changed during wet-milling.

X-Ray Powder Diffraction (XRPD) The XRPD patterns of various drug powders are shown in Fig. 4. For omeprazole and danazol powders, the XRPD patterns of each mixed powder and nanopowder were similar to those of the corresponding bulk powders, although the peak intensities of both nanopowders decreased to about half the level for each bulk powder and mixed powder, suggesting that the crystal forms of these drugs were unchanged by wet-milling. However, although the crystalline structure of the albendazole mixed powder with 0.15% Pluronic F-68 was the same as that of the bulk powder, the XRPD measurement of albendazole powders indicated that the nanopowder had changed to

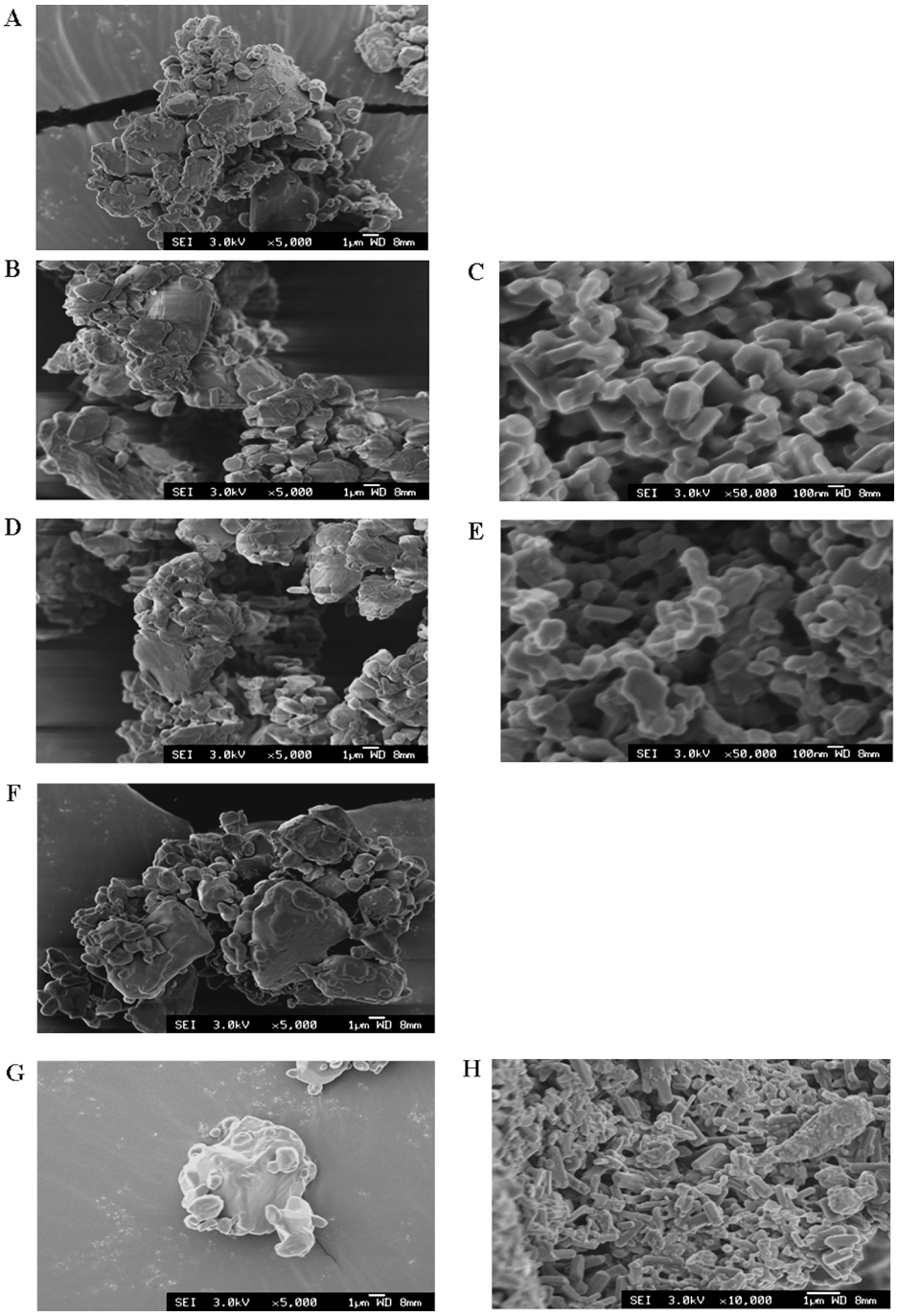

Fig. 2. SEM Micrographs of Omeprazole and Danazol Powders

(A) Omeprazole bulk powder, (B) omeprazole mixed powder with 0.1% Pluronic F-68, (C) omeprazole nanopowder with 0.1% Pluronic F-68, (D) omeprazole mixed powder with 0.05% Pluronic F-108, (E) omeprazole nanopowder with 0.05% Pluronic F-108, (F) danazol bulk powder, (G) danazol mixed powder with 0.1% Pluronic F-68, (H) danazol nanopowder with 0.1% Pluronic F-68.

another crystal form.

Discussion

In order to develop poorly water soluble drugs into oral products, it is very important to improve their solubilities and dissolution rates. Pharmaceutical techniques utilizing ULTRA APEX MILL can overcome some of the problems associated with dry-mills and other wet-mills. However, there are no reports in literature of nanoparticulation of drugs using ULTRA APEX MILL. In this study, we prepared nanopowder formulations of poorly water soluble drugs to improve their dissolution rates and oral absorption.

The ULTRA APEX MILL is a wet-mill instrument used to mill metals such as titanium oxide or aluminum oxide to reduce them to nanometer size. We anticipated that the ULTRA APEX MILL could also be utilized to mill drugs into nanometer size. However, the drugs must be dispersed in water before milling. Therefore, we tested the effects of various dispersing agents. The particle sizes in bulk, mixed and milled slurries of three poorly soluble drugs are listed in Table 2. Although use of 5% Tween 80 to mill omeprazole produced particles having a sub-micron size, these particles

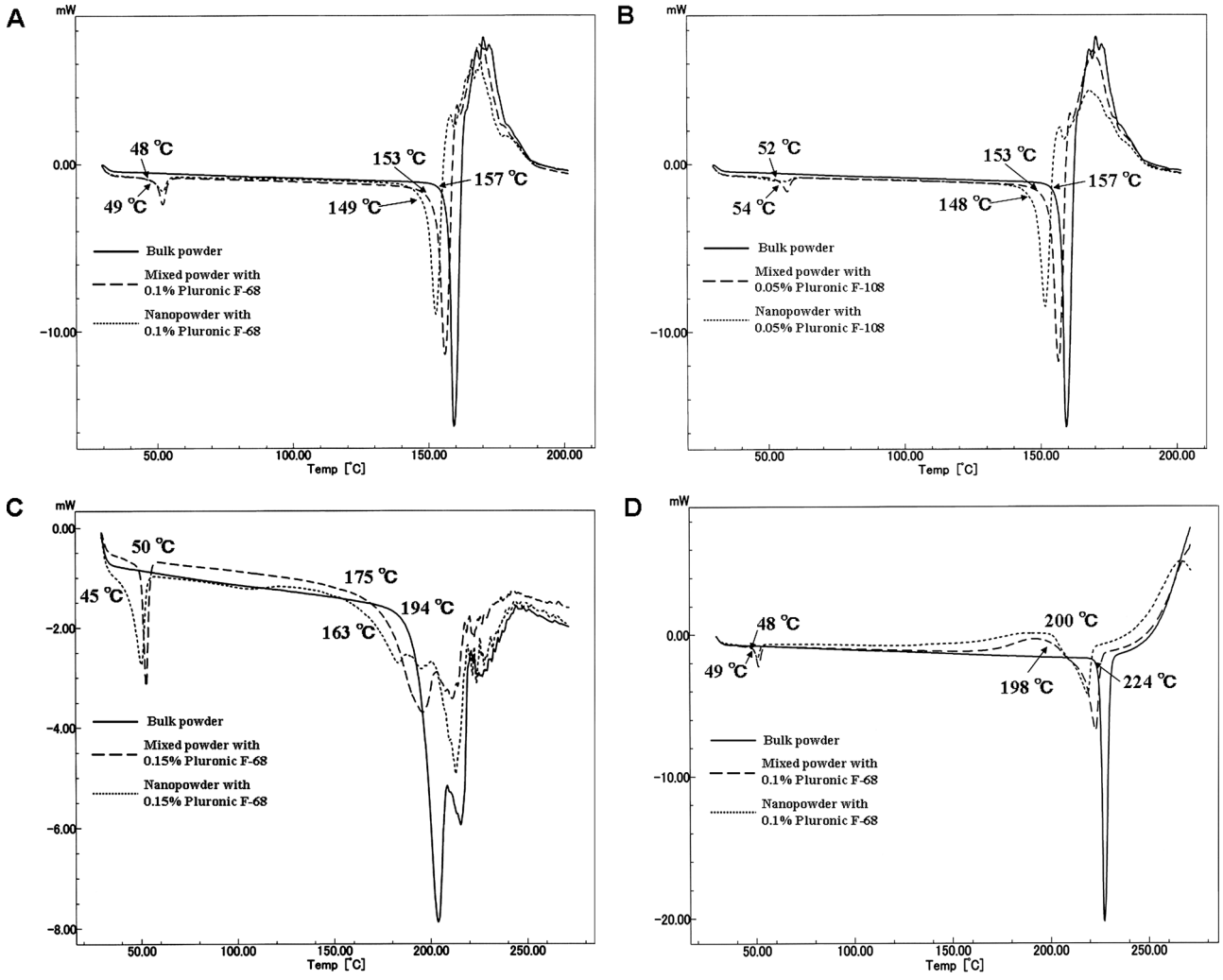

Fig. 3. DSC Curves of Various Powders

(A) Omeprazole bulk powder, mixed powder with 0.1% Pluronic F-68 and nanopowder with 0.1% Pluronic F-68, (B) omeprazole bulk powder, mixed powder with 0.05% Pluronic F-108 and nanopowder with 0.05% Pluronic F-108, (C) various albendazole powders, (D) various danazole powders.

Table 5. Melting Points of Drugs and Poloxamers in Various Powders Determined by DSC

Drug	Formulations	Melting point (°C)	
		Drugs	Poloxamers
Omeprazole	Bulk powder	157	
	Mixed powder with 0.1% Pluronic F-68	153	49
	Nanopowder with 0.1% Pluronic F-68	149	48
	Mixed powder with 0.05% Pluronic F-108	153	54
	Nanopowder with 0.05% Pluronic F-108	148	52
Albendazole	Bulk powder	194	
	Mixed powder with 0.15% Pluronic F-68	175	50
	Nanopowder with 0.15% Pluronic F-68	163	45
Danazol	Bulk powder	224	
	Mixed powder with 0.1% Pluronic F-68	198	49
	Nanopowder with 0.1% Pluronic F-68	200	48

could not be extracted by lyophilization because Tween 80 does not sublimate under reduced pressure and is therefore liquid at room temperature. The omeprazole particle size in the milled slurry decreased only slightly when 5% methanol was used as the dispersing agent. This may have been because the milled omeprazole particles re-aggregated due to the weak dispersion force of methanol. We therefore selected poloxamers as dispersing agents. Poloxamers are block copolymers composed of ethylene oxide and propylene oxide blocks whose properties have been widely investigated in the field of pharmaceutical technology.[24,25] Poloxamers are often utilized in the development of pharmaceutical products. The use of Pluronic F-68 and F-108 was investigated in this study because mixtures of a poloxamer and a model drug produce

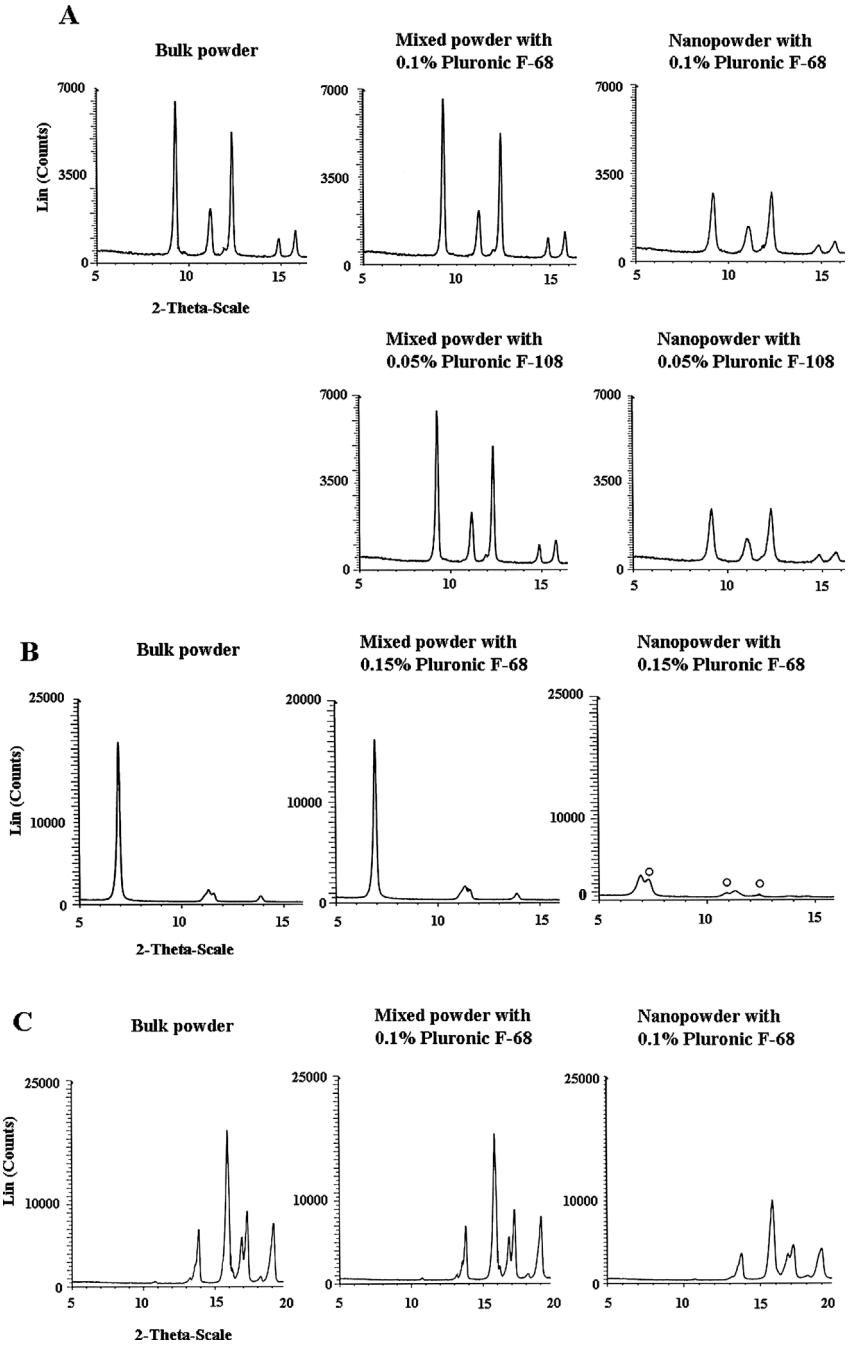

Fig. 4. X-Ray Powder Diffraction (XRPD) Patterns of Various Drug Powders
(A) Omeprazole powders, (B) albendazole powders, (C) danazol powders.

lyophilized solids at room temperature, as these poloxamers melt at about 50 °C.[26] In particular, Pluronic F-68 has been approved for oral administration in humans.[27] Omeprazole particles in milled slurries prepared with 0.1% Pluronic F-68 or 0.05% F-108, but not with 0.05% Pluronic F-68, were reduced to 187 or 164 nm, respectively, and the particles were stable over a period of 24 h. In addition, albendazole and danazol in milled slurries were converted to nanoparticles having particle sizes of 185 and 102 nm, respectively, by using 0.15% or 0.1% Pluronic F-68. The nanopowders retained their sub-micron sizes after lyophilization, although the sizes of albendazole particles were not confirmed by SEM. However, the albendazole nanopowder was considered to be sub-micron size after lyophilization because the particle size after resuspension was 176 nm. We presumed that the poloxamer concentrations used in this study (Pluronic F-68: 0.1%, Pluronic F-108: 0.05% for omeprazole) would provide sufficient solution viscosity as well as steric barriers to inhibit contacts between poloxamer-coated drug nanoparticles. On the other hand, insufficient poloxamer concentration (Pluronic F-68: 0.05% for omeprazole) induced re-aggregation of the particles in some milled slurries. This indicated that the selection and concentrations of dispersing agents are very important to produce stable drug nanopowders of poorly water soluble drugs using the ULTRA APEX MILL. Sommerfeld *et al.* have reported that poly(butyl cyanoacrylate)

(PBCA) nanoparticles prepared using Pluronic F-68 as a stabilizer remained at constant sizes over 8 months in water.[28] Merisko-Liversidge *et al.* have also reported that poloxamers are acceptable stabilizers for generating physically stable nanoparticle dispersions.[13] In our study, similar results were obtained using low concentrations of Pluronic F-68 or F-108. Normally, lyophilization is the recommended method to stabilize particles over months or years.[29—31] However, resuspension of lyophilized nanopowder is often difficult, especially when a stabilizer is not added. The nanoparticles in suspension tend to aggregate, thus forming undesirable larger-particle complexes. In this study, all nanopowders formed nano-sized particles after resuspension, although the particle sizes increased slightly compared to those found in initial milled slurries (Table 4). Liversidge *et al.*, Konan *et al.* and Van Eerdenbrugh *et al.* have reported inhibitory effects of added sugars on nanoparticle aggregation during freeze-drying.[32—34] This merits further investigation for preventing disadvantageous effects such as particle growth and dispersibility in water of agents such as those described here.

The thermal energy generated during wet-milling is lower than that generated by dry-mills because drugs are suspended in aqueous solution. In addition, it is considered that the ULTRA APEX MILL can suppress the thermal energy to lower level than other wet-mills using beads because of using finer zirconia beads (kinetic energy/bead$=1/2\cdot$mass$\cdot$velocity^2).[16] It is generally considered that heat labile drugs are degraded by the heat generated during dry-milling. There are no reports in the literature of nanoparticulation of heat labile drugs without degradation by dry- or wet-milling. It has been reported that omeprazole is a heat labile drug.[18—20] Therefore, the amount of intact omeprazole was quantified by HPLC after wet-milling followed by lyophilization to confirm that this process did not cause significant product degradation. No omeprazole was degraded, indicating that the impact energy generated during wet-milling using the ULTRA APEX MILL is very low (data not shown). Thus, the ULTRA APEX MILL is a useful tool to mill poorly water soluble and heat labile drugs to sub-micron size.

In order to test whether crystal transformations of three drugs occurred during wet-milling, DSC and XRPD analyses were performed. Endothermic peaks caused by melting Pluronic F-68 or F108 were observed for all mixed powders and nanopowders at about 50 °C. This indicated that the drug nanopowders can be extracted as solids by lyophilization because of the higher eutectic temperatures of the tested poloxamers relative to room temperature. About 15 min from the onset of DSC, the endothermal peaks of drugs for all mixed powders and nanopowders shifted to lower temperatures relative to those of drugs for each bulk powder, indicating that the melting points were depressed by mixing the drugs with Pluronic F-68 or F-108. Comparison of the XRPD patterns and DSC curves of albendazole nanopowder with those of the bulk and mixed powders indicated that it may have a crystalline polymorphism. On the other hand, it is also possible that albendazole and Pluronic F-68 formed a complex upon wet-milling. Although the diffraction angles observed for the four mixed powders and nanopowders were in good agreement with those observed for the corresponding bulk powders, except for albendazole nanopowder, all nanopowders showed weaker diffraction intensity than the corresponding mixtures and bulk powders. These results suggested that the four nanopowders were partly amorphous. It is also possible that the reduction of particle sizes to a sub-micron scale reduced the bulk densities of these powders, especially the nanopowders, resulting in better X-ray transmission and hence weaker diffraction intensities. More detailed studies to better understand the mechanisms underlying phenomena described herein are warranted.

Conclusion

In order to improve the dissolution rate of drugs with poor water solubility we have developed a novel technique to produce drug nanoparticles. The reduction of poorly soluble drugs to nanometer size particles can be achieved by adding appropriate amounts of dispersing agents such as Pluronic F-68 and F-108. The dispersed nanoparticles can then be extracted from slurries by lyophilization. This technique is also applicable to heat labile drugs. Results of DSC and XRPD indicated that albendazole changed to a different crystal form upon wet-milling. Although some drugs having crystalline polymorphisms may require lower slurry temperatures than those used in this study, applications of the ULTRA APEX MILL to generate nanopowder drug formulations as described here should prove useful in the pharmaceutical industry.

Acknowledgements We would like to express our gratitude to Sawai Pharmaceutical Co., Ltd. (Japan) for use of D8 ADVANCE to measure X-ray powder diffraction patterns of various samples.

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