# Influence of Manufacturing Factors on Physical Stability and Solubility of Solid Dispersions Containing a Low Glass Transition Temperature Drug

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**In this study, we investigated the effect of manufacturing factors such as particle size, water content and manufacturing method on the physical stability and solubility of solid dispersion formulations of a low-glass-transition-temperature ($T_g$) drug. Solid dispersions were prepared from polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) by hot melt extrusion or spray drying. Water content of solid dispersions prepared by hot melt extrusion determined by dynamic moisture sorption measurement was increased drastically with relative humidity below a certain level of particle size. The blends with a lower water content (0.8%) prepared by hot melt extrusion during storage were more stable than those with a higher water content (3.5%) prepared by spray drying, which caused rapid recrystallization. Physical stability in the hot melt blends may be attributed to reduced molecular mobility due to a higher $T_g$. Dissolution study revealed that solid dispersions prepared by hot melt extrusion with the smallest particle size showed decreased solubility, attributed to reduced wetting properties (surface energy), which is not predictable by the Noyes–Whitney equation. Taken together, these results indicate that the control of particle size concerned in water content or wetting properties is critical to ensuring the physical stability or enhancing solubility of low-$T_g$ drugs. Further, hot melt extrusion, which can reduce water content, is a suitable manufacturing method for solid dispersions of low-$T_g$ drugs.**

**Key words** water content; particle size; low-glass-transition-temperature drug; hot-melt extrusion; stability; solubility

Amorphous solid dispersions have been frequently used to enhance the dissolution properties and bioavailability of poorly water-soluble drugs.[1–3] However, these solid dispersion formulations are physically unstable and are apt to crystallize during storage, which may alter drug absorption properties. Previous studies have reported that one important factor affecting the physical stability of the amorphous state is molecular mobility, with high molecular mobility leading to rapid nucleation and crystal growth.[4,5]

Glass transition temperature ($T_g$), which delineates a temperature range between high and low molecular mobility, is a critical parameter affecting the molecular mobility of amorphous state compounds; solid dispersions with low $T_g$ have relatively high molecular mobility, which can subsequently lead to rapid nucleation and crystal growth above the $T_g$.[6] Numerous studies have investigated the physical stability of amorphous solid dispersions in terms of molecular mobility and thermodynamic quantities at temperatures below $T_g$.[7,8] Further, amorphous solid dispersions are more hygroscopic than their crystalline counterparts, due to their ability to absorb water content into their bulk structure, in addition to surface adsorption.[9] This absorbed water content can induce plasticization and enhance molecular mobility, thereby leading to crystallization. Because an increase in a compound's water content increases the risk of crystallization, moisture control may be a critical factor during the manufacture of low-$T_g$ drug formulations.

Amorphous solid dispersions are generally produced by solvent,[10,11] hot-melt[12,13] or other methods. Most extruded or spray dried blends are subjected to an intensive manufacturing process that impacts surface area, such as pulverization, dry granulation or compression prior to final production. Such intensive manufacturing processes may lead to recrystallization of amorphous solid dispersions, particularly for low-$T_g$ drugs. Several recent studies have reported that, even at temperatures below the $T_g$, crystal growth rates at the surface of amorphous materials can be much faster than those in the bulk structure. For example, crystal growth at the surface of amorphous indomethacin[14] and nifedipine[15] progressed at least one order of magnitude faster than in the bulk structure.

These findings indicate that manufacturing factors may have significant influence on the quality and stability of solid dispersions, which in turn emphasizes the importance of investigating the effect of manufacturing process on the quality and stability of solid dispersions. It has been reported that manufacturing methods (hot-melt extrusion and spray drying) influences the mixing capacity and phase behavior of solid dispersions.[16] To our best knowledge, however, the influence of these processes on the solubility or stability of solid dispersions containing a low $T_g$ drug has not been reported.

We previously reported that polymer combinations can be used to increase both the solubility and stability of solid dispersions of poorly water-soluble low-$T_g$ drugs.[17] In polymer combinations, hydroxypropylmethylcellulose (HPMC) improves solubilization, and polyvinylpyrrolidone (PVP) improves stability. Although we were able to optimize the solid dispersion formulation of low-$T_g$ drugs, the effect of manufacturing process on the stability and solubility remains unknown.

Here, we investigated the influence of manufacturing factors on the stability and solubility of a solid dispersion of a low-$T_g$ drug. We focused on the influence of water content,

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particle size and manufacturing method on the physical stability and solubility properties of solid dispersions with the same drug and polymer composition.

## Experimental

**Preparation of Materials. Material Sources** Two water-soluble polymers were used, hydroxypropylmethylcellulose (HPMC, TC-5R), purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan), and polyvinylpyrrolidone (PVP, PVP-K30), purchased from BASF Japan, Ltd. (Tokyo, Japan). The test drug 3-methoxy-1,5-bis(4-methoxyphenyl)-1*H*-1,2,4-triazole (BCS class II drug) was provided by Astellas Pharma Inc. (Tokyo, Japan). The principal physical characteristics of this drug are summarized in Table 1. The $T_g$ of the pure drug is 4°C, which is much lower than that of indomethacin (42°C) used as a low $T_g$ model drug,[18] and its solubility in water was 10.7 $\mu$g/mL. All other materials were of analytical reagent grade.

**Preparation of the Hot-Melt Sample** The drug and polymers were mixed at a drug : HPMC : PVP ratio of 1 : 1 : 1 for 10 min using a V-type mixer (LM-20; Kotobuki Industries Co., Ltd., Tokyo, Japan). The blend was extruded using a KEX-25 twin-screw melt extruder (Kurimoto, Osaka, Japan) with four heating zones. The four heaters were maintained at 30°C (2nd segment), 80°C (3rd segment), 120–150°C (4th segment), and 120–150°C (die part). After extrusion, the extrudates were pulverized in a fine impact mill (Contraplex, Hosokawa Micron Corporation, Osaka, Japan), and the resulting particles were sieved through three stainless steel sieves to yield three diameter fractions: $<75\,\mu$m, 75–250 $\mu$m, and $>250\,\mu$m. Particles of the small fraction ($<75\,\mu$m) were pulverized again, and the resulting particles were sieved through stainless steel sieves to yield the diameter fraction: $<32\,\mu$m. All four fractions were used to study the effect of particle size on dynamic moisture sorption and dissolution and for differential scanning calorimetry and inverse gas chromatography.

**Preparation of the Spray Dried Sample** The drug, HPMC, and PVP were dissolved in 250 mL of acetone–water at a weight ratio of 7 : 3. The drug and polymers were mixed at a drug : HPMC : PVP ratio of 1 : 1 : 1, and then 15 g were dissolved in 250 mL 7 : 3 acetone–water and spray dried using a Büchi B-295/290 spray-dryer (Büchi, Flawil, Switzerland). The inlet temperature was maintained at 110°C, and the spray-dried products were dried in a vacuum oven at 40°C for 18 h.

**Measurement of Physical Characteristics. Particle Size Distributions** Particle size distribution was evaluated by sieve analysis and laser diffraction analysis. Sieve analysis was conducted using a vibratory sieve shaker (Seisin, Tokyo, Japan) and a set of standard sieves in the range of 75–710 $\mu$m. Sieve analyses were performed on samples of 10 g and with a sieving time of 10 min. Median particle diameter ($d_{50}$) was calculated by linear interpolation of the cumulative percentage frequency curve. In the laser diffraction technique, samples were tested twice using the Rodos/Helos system (Sympatec, NJ, U.S.A.) to characterize their dispersibility.

Table 1. Physical Properties of the Study Drug

| | BCS class II drug |
|---|---|
| Molecular weight | 311.34 |
| Melting point | 128°C |
| $T_g$ | 4°C |
| Solubility (pH 1.2 buffer, 37°C) | 19.7 $\mu$g/mL |
| Solubility (water, 37°C) | 10.7 $\mu$g/mL |
| Solubility (pH 6.8 buffer, 37°C) | 9.6 $\mu$g/mL |
| Permeability (Caco-2 cells, pH 7.4) | $34.4\times10^{-6}$ cm/s |
| Hygroscopicity | None |

$T_g$, glass-transition-temperature; BCS, biopharmaceutical classification system.

**Dynamic Moisture Sorption Measurement** Vapor sorption isotherms of each sample were generated using a Symmetrical Gravimetric Analyzer (SGA-100) (VTI Corporation, Hialeah, FL, U.S.A.) at 25°C. Samples of 15–20 mg were dried at 60°C under a stream of dry nitrogen to an equilibrium criterion of 0.01% (w/w) in 2 min, for a maximum drying time of 60 min, and then exposed to increasing relative humidity (at 5% intervals) at 25°C. The step isotherm equilibrium criterion was 0.01% (w/w) in 5 min with a maximum step time of 180 min.

**Moisture Loss** The water content of each sample was determined by measuring weight loss on drying with an HR83 halogen moisture analyzer (Mettler Toledo, Tokyo, Japan). The temperature was set to 105°C, and the weight of each sample was measured over 2 h.

**X-Ray Diffraction** The crystal structure of each sample was analyzed *via* X-ray diffraction (XRD) using a powder X-ray diffractometer (RINT-TTR III; Rigaku, Tokyo, Japan). Radiation was derived from a Cu$K\alpha$ source at 50 kV and a current of 300 mA. The scanning rate was 10°/min over a $2\theta$ range of 5–40°, at a sampling interval of 0.02°.

**Differential Scanning Calorimetry** The $T_g$ value of each sample was measured by differential scanning calorimetry (DSC) with an EXSTAR DSC6000 (Seiko Instruments, Chiba, Japan). Approximately 10 mg of each drug–polymer sample was placed in an aluminum pan and heated at a rate of 5°C/min from 0–150°C. The onset $T_g$ values were recorded.

**Dissolution Studies** Dissolution was assessed following the Japanese Pharmacopoeia (JP) 15 paddle method. Each solid dispersion corresponding to 100 mg of the drug was added to 900 mL of water, at 37±0.5°C. Paddle rotation speed was 50 rpm. The concentration of dissolved drug was then measured using high-performance liquid chromatography (HPLC).

**Inverse Gas Chromatography** Inverse gas chromatography (IGC) utilizes the adsorption of a probe molecule by a sample material. IGC has widespread application in the characterization of surface properties (surface free energy, heat of adsorption, and acid-base properties of the surface) of a wide range of materials.

Dispersive surface energy of each sample was estimated with an inverse gas chromatograph (Surface Measurement System Ltd., London, U.K.). Each sample (700–900 mg) was packed into a silanised glass column (Surface Measurement System Ltd., London, U.K.) with a 3-mm inside diameter and 300 cm lengths. The column was tapped vertically for 15 min until no visible cracks, hollows, or channels were observed in the body of the powder. Both ends of the column were then loosely stopped with silanised glass wool. The packed columns were conditioned at 303 K, and methane was used for the inert reference. *n*-Decane, *n*-nonane, *n*-octane, *n*-heptane, and *n*-hexane at a gas flow rate of 10 mL/min were used to determine the dispersive surface energies. Three measurements were made for each sample.

Table 2. Mean Particle Diameter for Solid Dispersions Prepared by Hot-Melt Extrusion or Spray Drying at a Drug : HPMC : PVP Ratio of 1 : 1 : 1

| Sample | Mean diameter ($\mu$m) | |
|---|---|---|
| | Sieve analysis | Laser diffraction analysis |
| Hot melt extrusion | | |
| Large, >250 $\mu$m | 317 | — |
| Medium, 75–250 $\mu$m | 134 | 135 |
| Small, <75 $\mu$m | — | 55.9 |
| Smallest, <32 $\mu$m | — | 25.5 |
| Spray drying | — | 17.4 |

Mean particle diameters are the means of duplicate measurements.

**Storage Stability** Approximately 1 g of solid dispersion sample was packed into an aluminum pouch and stored at 40°C, 75% relative humidity for one month. Stability of the solid dispersion sample was assessed by XRD measurement, with crystallization indicated by diffraction peaks in the XRD measurement.

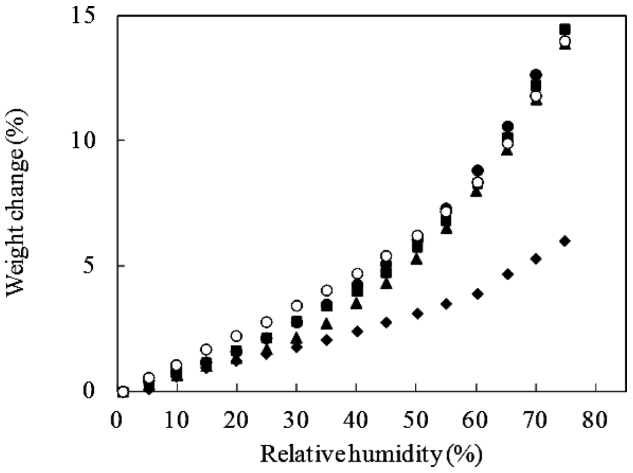


Fig. 1. Moisture Sorption Profiles for Solid Dispersions of Different Particle Sizes Obtained at 25°C

Symbols represent values of the solid dispersions prepared with hot-melt extrusions with large (◆, 317 $\mu$m), medium (▲, 134 $\mu$m), small (■, 56 $\mu$m) and smallest (●) particle sizes. Symbols also represent values of the solid dispersions prepared with spray drying (○, 17 $\mu$m).

## Results and Discussion

**Particle Size of Solid Dispersions Containing a Low $T_g$ Drug** Most extruded or spray dried blends are subjected to an intensive manufacturing process prior to final production that impacts surface area, such as pulverization, dry granulation, or compression. Such intensive manufacturing processes may lead surface crystallization and affect the absorption profile of the contained drug formulation, particularly for low-$T_g$ drugs. As surface area is directly related to particle size, it is important to examine the effect of particle size on the stability and solubility of solid dispersions containing a low $T_g$ drug. We prepared amorphous solid dispersions at a drug : HPMC : PVP ratio of 1 : 1 : 1, which was identified as an optimized formulation in a previous study.[17] In the present study, we tested particles of a drug–polymer blend prepared by hot melt extrusion with four diameter ranges, namely large, >250 $\mu$m; medium, 75–250 $\mu$m; small, <75 $\mu$m; and smallest, <32 $\mu$m. Mean particle sizes were 317 $\mu$m for large, around 130 $\mu$m for medium, 55.9 $\mu$m for small, and 25.5 $\mu$m for smallest. We also prepared spray dried samples to investigate the influence of manufacturing method on the solubility or stability of solid dispersions containing a low $T_g$ drug. Mean particle size for these spray dried samples was 17.4 $\mu$m (Table 2).

**Effect of Water Content, Particle Size and Manufacturing Method of Solid Dispersions on Physical Stability. Solid State Characterization** Initial water content of solid dispersions prepared by hot melt extrusion was 0.8% and that of solid dispersions prepared by spray drying was 3.5% (Table 3). The XRD patterns of both samples after processing were similar to those of each polymer alone, suggesting that solid dispersions of the drug existed initially in an amorphous state.

**Isothermal Water Vapor Absorption** In solid dispersions of different particle sizes prepared by hot melt extrusion, water absorption increased with relative humidity; solid dispersions with smaller particles absorbed more water than those with larger particles (Fig. 1). Given that water sorption increases the risk of crystallization, drug formulations of small particle amorphous solid dispersions may be less stable than those with larger particles. This result suggested that solid dispersions prepared with smaller particles by hot melt extrusion are more hygroscopic at any relative humidity than those with larger particles. Many amorphous materials are more hygroscopic than their crystalline counterparts due to water absorption directly into the interior of the bulk structure in addition to that by surface adsorption.

Moreover, at 25°C, 60% relative humidity which is the general storage condition of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) long-term study, only solid dispersions with large particle sizes (317 $\mu$m) prepared by hot melt extrusion absorbed less water content. Therefore, the water content of solid dispersions did not increase with decreasing particle sizes, but rather increased drastically below a certain level of particle size. These results indicate that control of the water content of solid dispersions containing a low $T_g$ drug prepared by hot melt extrusion during stability study is

Table 3. Storage Stability from XRD Patterns for Solid Dispersions with Lower and Higher Water Content at a Drug : HPMC : PVP Ratio of 1 : 1 : 1

| Solid dispersions | Loss on drying (%) | | XRD pattern | |
|---|---|---|---|---|
| | Initial | Stored sample (40°C 75% RH for 1 month) | Initial | Stored sample (40°C 75% RH for 1 month) |
| Lower water content | 0.8 | 0.8 | —[a)] | —[a)] |
| Higher water content | 3.5 | 3.4 | —[a)] | + |

Loss on drying shown is the mean of duplicate measurements. No diffraction peaks (−) or some diffraction peaks (+) from the drug observed. Solid dispersions with lower water content were prepared by hot melt extrusion and those with higher water content were prepared by spray drying. *a*) XRD patterns were similar to those of each polymer alone. XRD, X-ray diffraction; HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone; RH, relative humidity.

difficult from the point of particle size, and it should be highly optimized to ensure physical stability. No significant difference in water absorption property was seen between solid dispersions prepared by spray drying (17.4 $\mu$m) and hot melt extrusion (25.5 $\mu$m) with the similar particle sizes. These findings suggest that the manufacturing methods influenced initial water content of solid dispersions but did not influence the water absorption property.

**Glass Transition Temperature of the Solid Dispersions** The $T_g$ is a key parameter for drug design, since it delineates the temperature range between high and low molecular mobility.[4,5] Hancock *et al.* stated that the $T_g$ of amorphous solid dispersions of drugs should be at least 50°C above the expected storage temperature to ensure that the product remains stable over its shelf life.[19]

The distinctive single $T_g$ of the solid dispersions was obtained. The $T_g$ values of the solid dispersions prepared by hot-melt extrusion were 67°C for large, 66°C for medium, 65°C for small and 64°C for smallest samples (Fig. 2). These findings suggest that a drug–polymer blend prepared by the hot-melt process would have the similar molecular mobility at normal storage temperatures irrespective of particle size. These findings also suggest that the pulverizing process did not affect greatly the $T_g$ values of the solid dispersions. In contrast, the $T_g$ value of the solid dispersion prepared by spray drying with a higher water content was decreased to 42°C compared with that by hot melt extrusion (smallest, 64°C). Water uptake decreases the $T_g$ of amorphous dispersions; indeed, in one study, the decrease in $T_g$ of amorphous indomethacin with 1% water content was observed, and the decreased $T_g$ value, 10°C, corresponded closely with values predicted using the Gordon–Taylor equation.[19] In this study, the same tendency was also observed in spray drying samples.

**Storage Stability** Solid dispersion formulations, particularly those containing a low $T_g$ drug, are physically unstable and are apt to crystallize during storage, which may alter drug absorption properties. For a marketed product, this would represent a fatal quality failure. After storage for 1 month at 40°C and 75% relative humidity, diffraction peaks were observed in the XRD patterns of solid dispersions with higher water content, which indicated that some amorphous drug content crystallized during the storage period (Table 3). No such peaks were observed in solid dispersions with lower water content.

These results from the experiments on the effect of initial water content indicate that a tiny difference in water content (2.7%) had a critical impact on the stability of solid dispersions containing a low $T_g$ drug. Water may facilitate the recrystallization of solid dispersions by plasticization and competition with polymer for hydrogen binding sites.[6–8]

In this storage stability study, samples were packed into an aluminum pouch in which there were no changes in water content during storage (Table 3). Even in such a water-resistant packaging form, initial water content had a significant effect on the stability of solid dispersions containing a low $T_g$ drug. Therefore, considering the results of isothermal water vapor absorption on packaging in a non-water-resistant packaging form, solid dispersions will absorb water and the $T_g$ values will decrease during storage, thereby leading to crystallization. For solid dispersions containing a low $T_g$ drug, it is therefore critical to control the initial water content or particle size as well as the formulation itself to ensure stability during storage.

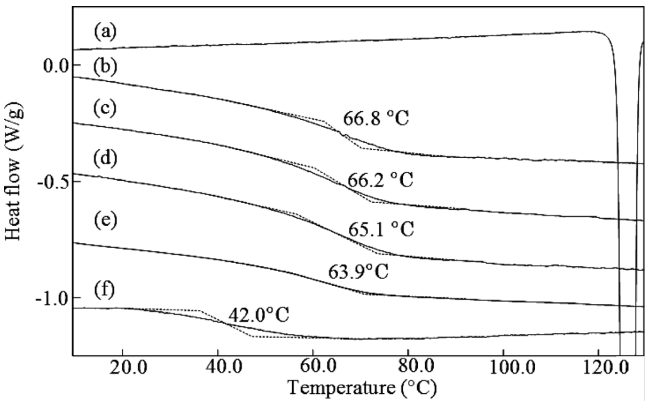


Fig. 2. Glass Transition Temperature of the Drug without Polymer (a), Solid Dispersions of Different Particle Sizes Prepared by Hot-Melt Extrusions: Large (317 $\mu$m, b), Medium (134 $\mu$m, c), Small (56 $\mu$m, d) and Smallest (26 $\mu$m, e), and Solid Dispersions Prepared by Spray Drying (17 $\mu$m, f) as Determined by DSC

Both spray drying and hot melt extrusion can be used to manufacture poorly water-soluble drugs. In this study, manufacturing conditions for spray drying were not optimized, and accordingly additional room is available to decrease the water content of the solid dispersion. Nevertheless, water content after processing must also be strictly controlled, particularly for low $T_g$ drugs. In this regard, hot melt extrusion is solvent-free, which may present significant benefits for the manufacture of solid dispersions containing low-$T_g$ drugs. And particle size of solid dispersions prepared by hot melt extrusion can be controlled to decrease water content during stability study. The hot melt extrusion process produces a blend with lower water content, a higher $T_g$ and controlled particle size, thus reducing the potential for drug crystallization and improving the stability of solid dispersions.

**Effect of Particle Size on Solubility in Solid Dispersions Prepared by Hot Melt Extrusion** As the absorption rate of poorly water-soluble drugs is limited by the rate of dissolution, the bioavailability of poorly water-soluble drugs may be enhanced by increasing a drug's solubility in the gastrointestinal tract. In our previous study, we found that HPMC increased drug solubility more effectively than PVP-VA or PVP, and drug concentration at 30 min in dissolution test was correlated with bioavailability after oral administration in dogs.[17]

Here, we examined the effects of particle size on dissolution of solid dispersions prepared by hot melt extrusion containing a low $T_g$ drug. Figure 3 shows the dissolution profiles of the drug from solid dispersions. The dissolution profiles of all solid dispersions were higher than solubility of the crystalline drug alone (10.7 $\mu$g/mL). Particle size reduction leads to an increase in surface area and consequently in the rate of dissolution, as described by the Noyes–Whitney equation.[20] Based on this theory, solid dispersions with the smallest particle size were expected to show the maximum concentration of the drug. This theory might not be applied to solid dispersions prepared by hot melt extrusion. Solid dispersions with the smallest particle size prepared by hot melt extrusion showed a dramatically decreased concentration of drug at 15 min or 30 min.

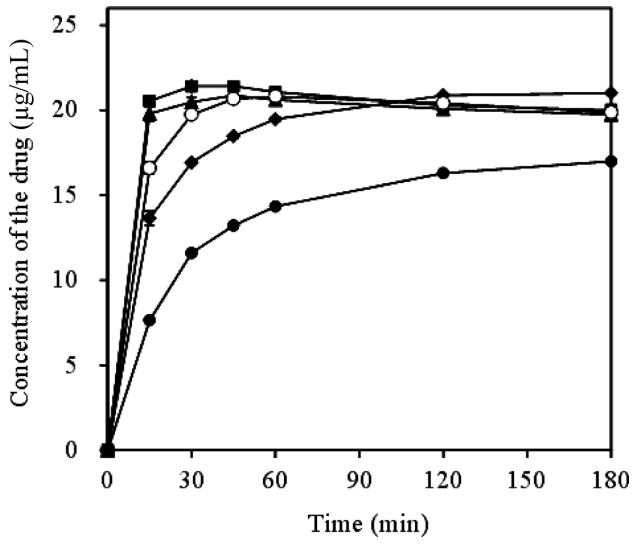


Fig. 3. Dissolution Profiles of the Drug from Solid Dispersions of Different Particle Sizes

Symbols represent values of the solid dispersions prepared by hot-melt extrusion with a large (◆), medium (▲), small (■) and smallest particle size (●). Symbols also represent values of the solid dispersions prepared by spray drying (○). Each solid dispersion corresponds to 100 mg of the drug dissolved in water. Values shown are the means of triplicate measurements±S.E.

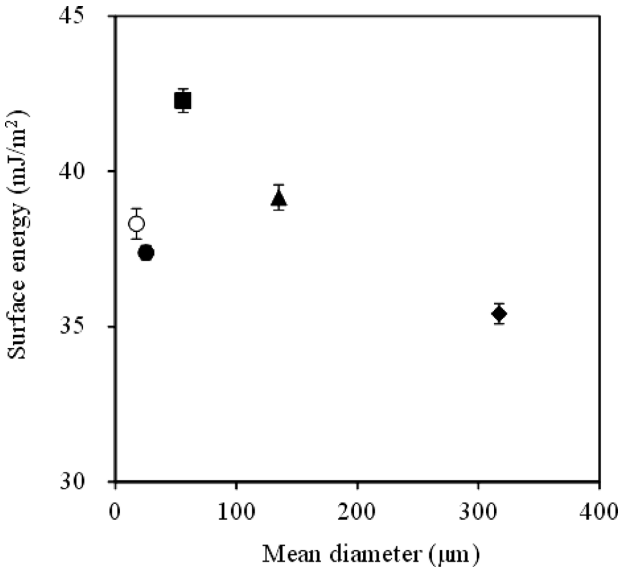


Fig. 4. Surface Energy Values for Solid Dispersions Prepared by Hot Melt Extrusion or Spray Drying *versus* Particle Size

Symbols represent values of the solid dispersions prepared by hot-melt extrusion with a large (◆), medium (▲), small (■) and smallest (●) particle size, and prepared by spray drying (○). Values shown are the means of triplicate measurements±S.E.

Table 4. Surface Energies Determined by Inverse Gas Chromatography of Solid Dispersions Prepared by Hot-Melt Extrusion or Spray Drying at a Drug : HPMC : PVP Ratio of 1 : 1 : 1

| Sample | Surface energies ($mJ/m^2$) |
|---|---|
| Hot melt extrusion | |
| Large, >250 μm | 35.4±0.3 |
| Medium, 75–250 μm | 39.2±0.4 |
| Small, <75 μm | 42.3±0.4 |
| Smallest, <32 μm | 37.4±0.2 |
| Spray drying | 38.3±0.5 |

Values shown are the means of triplicate measurements±S.E.

It is well known that surface tension is positively correlated with the wettability of particles. Surface tension has the dimension of force per unit length or of energy per unit area—the two are equivalent. When referring to energy per unit of area, surface tension is the same value as surface energy. Surface energies determined by IGC of solid dispersions prepared by hot melt extrusion or spray drying at a drug : HPMC : PVP ratio of 1 : 1 : 1 are summarized in Table 4.

Figure 4 shows the relationship between surface energy values in Table 4 and particle sizes of solid dispersions. Linear regression analysis of the values for solid dispersions prepared by hot-melt extrusion was done. The good correlation between higher wettability and smaller particle size is well known, but this was not the case with our data (the correlation coefficient, $R^2$=0.415). From this, one possible reason for the decreased concentration of drug with solid dispersions with smallest particle size in the dissolution test is decreased surface energy (wettability) of the sample.

A second possible reason is aggregation from quite a small particle size of solid dispersions. Solid dispersions with the smallest particle size showed a similar dissolution profile and surface energy value to those with large particle size (Figs. 3, 4). It was reported that in itraconazole solid dispersions prepared with HPMC, increasing particle surface area results in increased aggregation.[21] Powders of fine particles are likely to aggregate as the force of detachment is dependent on particle mass which is very small in the case of fine particles.[22] The forces of cohesion between individual fine particles are therefore greater than the forces of detachment, and thus particle aggregates form. Aggregation causes an increase in apparent particle size and a corresponding decrease in free surface area. Hence, drug dissolution rate decreases with increasing particle aggregation. On this basis, this particle aggregation may contribute to the decreased dissolution rate of solid dispersions with the smallest particle size. Solid dispersion with the smallest particle size was obtained with additional pulverizing process. In many cases solid dispersions by extrusion are not in a spherical shape and have a coarse surface caused by pulverization process after extrusion. This additional pulverizing process may have an influence on surface condition of the solid dispersions with smallest particle size to increase aggregation.

A third possible reason is that the rapid dissolution of PVP causes the amorphous drug leaving behind in the absence of the polymer, resulted in rapid recrystallization of the drug and reduced the wetting property and solubility of the drug. In this formulation, PVP was added to improve the solid state stability by increasing $T_g$ values. PVP is reportedly far less effective than HPMC or hydroxypropylmethylcellulose acetate succinate at inhibiting crystallization from a supersaturated solution.[8] The PVP-dispersion containing the smallest particle size with increased surface area may have resulted in rapid dissolution of the highly water soluble PVP.

**Effect of Manufacturing Methods on Solubility** We also investigated the effect of manufacturing methods (hot melt extrusion and spray drying) on dissolution of solid dispersions containing a low $T_g$ drug with similar particle sizes. Solid dispersions prepared by spray drying (17.4 μm) showed a higher

concentration of drug at 15 min or 30 min than those by hot melt extrusion (25.5 $\mu$m) (Fig. 3). There was no difference in surface energy (wettability) between the two solid dispersions (Fig. 4, Table 4), suggesting that manufacturing methods did not influence the surface energy of solid dispersions with the similar particle sizes. It also suggested that wettability might not be main cause of the higher dissolution of drug with solid dispersions prepared by spray drying. Particles prepared by spray drying might less aggregate compared with those by hot melt extrusion as described in 'Effect of Particle Size on Solubility in Solid Dispersions Prepared by Hot Melt Extrusion.' In the spray drying process, a solution of drug and polymer is atomized to droplets in the micrometer range which are eventually transformed into solid particles. The resulting solid dispersions are therefore in a spherical shape and have a relatively smooth and porous surface, which may decrease interparticle cohesive forces. In contrast, in many cases solid dispersions by extrusion are not in a spherical shape and have a coarse surface caused by the pulverization process after extrusion. This difference in surface properties might contribute to the difference in particle aggregation. If water content after processing could be strictly controlled to improve physical stability particularly for low $T_g$ drugs, spray drying might be superior to hot melt extrusion with smallest particles from the dissolution property perspective.

These results indicate that the particle size of solid dispersions has a significant effect on dissolution rate. For solid dispersions containing a low $T_g$ drug, it is useful to add PVP to improve the solid state stability; in contrast, PVP may decrease the solubility of solid dispersions, particularly with quite a small particle size. It is of critical importance to control the particle size of solid dispersions to enhance their bioavailability and dissolution properties.

## Conclusion

Manufacturing factors such as water content, particle size and manufacturing method, have a significant influence on the stability or solubility of amorphous solid dispersions, particularly for those containing low-$T_g$ drugs. Hot melt extrusion may benefit the manufacture of amorphous solid dispersions containing a low-$T_g$ drug by increasing the physical stability and solubility of the formulation, provided particle size is controlled.

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