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Antisolvent Crystallization of Sulfa Drugs and the Effect of Process Parameters

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Abstract: Three sulfa drugs (sulfathiazole, sulfamethizole, and sulfabenzamide) were crystallized using carbon dioxide and water as antisolvents, and the effects of the type of solvent, the crystallization temperature, and the antisolvent injection rate were investigated. Sulfathiazole crystallized in granulate form from acetone, but it was crystallized in acicular form from methanol. Sulfamethizole was crystallized in tabulate form from acetone and as plates from DMF. Sulfabenzamide was precipitated in the form of prisms from acetone and of aciculates from ethyl acetate. As the crystallization temperature increased from 30 to 50°C, the average particle size increased from 6.5 to 10.5 μm for sulfathiazole, 29.5 to 53.1 μm for sulfamethizole, and 33.0 to 59.8 μm for sulfabenzamide. The crystal habit tended to become more needle-like as the antisolvent injection rate increased. Larger particles were produced when the antisolvent was changed from carbon dioxide to water.

Keywords: Antisolvent, carbon dioxide, crystallization, particle size, sulfa drugs

INTRODUCTION

Antisolvent crystallization is an energy-saving technology that can be substituted for the classical evaporative crystallization process. The principle of antisolvent crystallization is based on the concept of using an antisolvent as a separation medium that can induce the precipitation of a dissolved solute from its solution upon the addition of a large amount of antisolvent

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(1, 2). The role of the antisolvent is to reduce the solubility of a solvent towards the solute without causing any effect on the precipitating substance. Therefore, antisolvent crystallization is considered as a promising technique to process heat sensitive materials such as proteins and pharmaceutical compounds. The crystallization of pharmaceutical compounds not only focuses on the micronization of particles but also on the change of solid-state properties of drug crystals because these two factors both strongly influence the bioavailability of drug substances (3).

Recently, gaseous or supercritical carbon dioxide has been used as an antisolvent for various drug compounds (4, 5). The substantial temperature- and pressure-dependency in the density and the solubility of carbon dioxide are its main advantage as an antisolvent to change various crystal properties such as particle size distributions, crystal habits, and thermal stability. These characteristics of drug particles obviously govern the drug release rate and biological activity upon inhalation or injection. For example, drug particles with a diameter less than 5 μm are required for the application in inhalation therapy. In an antisolvent crystallization system, nucleation is induced by the supersaturation of the solution which is governed by the miscibility between the antisolvent and solution (6, 7). When a gas antisolvent (carbon dioxide) is used, the miscibility between the antisolvent and solution largely depends on pressure and temperature. In other words, when gas (antisolvent) and liquid (solution) are mixed, the solubility of gas in the liquid greatly increases with pressure and decreases with temperature. The supersaturation of the solution is directly related to the solubility of gas in a liquid, and therefore the degree of supersaturation of the solution can be controlled to a large extent, by manipulating pressure and temperature. The degree of supersaturation affects the rate of nucleation and the kinetics of crystal growth. Hence, it may influence the characteristics of the resulting particles (8). Therefore, in gas antisolvent crystallization, the properties of the produced crystals can be easily modified by changing process parameters such as temperature, pressure, type of solvent, and the flow configurations of the antisolvent and other solutions (5). The impacts of this technology are the use of nontoxic, inexpensive, and highly flexible antisolvents such as carbon dioxide and high versatility to produce crystals with a wide variety of solid state properties.

Sulfa drugs are a group of synthetic antibacterial drugs that contain the sulfanilamide molecular structure (9). Sulfa drugs are normally used to treat bacterial infections, and some are also used in the treatment of diabetes. Although more than 5,000 sulfa drugs have been prepared and tested, fewer than 20 continue to have therapeutic value. It has been known that sulfa drugs exhibit diverse polymorphic transformations and modifications in thermodynamic stability during physical processes such as crystallization, compression, and grinding. Therefore, it would be worthwhile to process these sulfa drugs by using antisolvent methods because the process parameters would provide variable crystallizing conditions and could generate changeable characteristics for the resulting crystals.

In this study, we investigated the effects of process parameters of antisolvent crystallization methods on the solid-state properties of sulfa drug crystals. Here, two types of antisolvents were used to precipitate the drug compounds from their solutions. Carbon dioxide was used as a gas antisolvent, and water was used as a liquid antisolvent. These two antisolvents were selected in order to show how the type of antisolvent (gas or liquid) can influence the properties of resulting crystals. Sulfathiazole, sulfamethizole, and sulfabenzamide were selected as model sulfa drugs. These drug compounds were dissolved in various organic solvents, and the solutions were mixed with carbon dioxide and water, separately. The changes of crystal habit, particle size distribution, thermal stability, and crystallinity were examined by using analytical instruments.

EXPERIMENTAL METHODS

Materials

Sulfathiazole (Cat. No. S9876), sulfamethizole (Cat. No. S5632), and sulfabenzamide (Cat. No. S9757) were purchased from the Sigma Chemical Co. Acetone (99.5%), methanol (99.8%), ethyl acetate (99.5%), and N,N-dimethyl formamide (DMF, 99.8%) were used to dissolve these sulfa drugs. Carbon dioxide and distilled water were used as the gas and liquid antisolvents. All the chemicals were used as received.

Apparatus and Procedure

Antisolvent crystallization experiments were performed using two separate experimental units depending on the type of antisolvent. Gas antisolvent experiments were conducted using an apparatus shown in Fig. 1. The equipment consisted of three parts: the supply of carbon dioxide, a crystallizing chamber, and a depressurizing section. The crystallizing chamber had dual windows that enabled us to observe the phenomena of nucleation and crystal growth occurring inside the chamber. The crystallizing chamber was located in an air bath in order to maintain a constant temperature during crystallization. The first step of the crystallization experiment was the preparation of the drug solutions. Each of the three sulfa drugs was dissolved in a selected solvent with a known concentration. Sulfathiazole was dissolved in acetone and methanol with a concentration of 2.0 wt%. Sulfamethizole was dissolved in acetone with a concentration of 3.0 wt% and in DMF with a concentration of 30.0 wt%. Sulfabenzamide was dissolved in acetone, methanol, and ethyl acetate with a concentration of 2.0 wt%.

For the gas antisolvent experiment, 10 ml of the prepared solution was loaded into the crystallizing chamber and the system was sealed. This

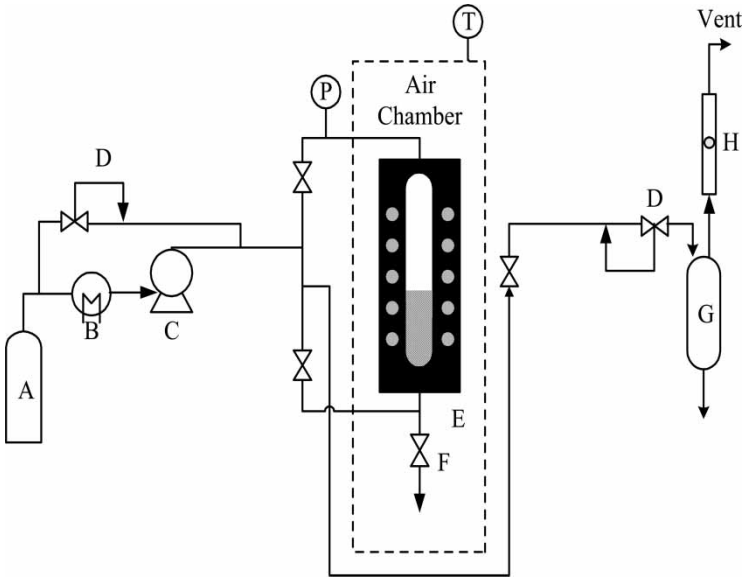


Figure 1. Experimental apparatus for the gas antisolvent experiment. (A) carbon dioxide cylinder, (B) cooler, (C) high pressure pump, (D) back pressure regulator, (E) crystallizing chamber, (F) ventilation valve, (G) solvent trap, (H) rotameter.

amount of solution loaded in the crystallizing chamber filled only one-third of the entire volume of the chamber. The temperature of the air bath was increased as desired. Typical experiments were performed at temperatures of 20, 30, 40, and 50°C. Next, carbon dioxide was introduced from the bottom of the chamber so as to achieve the mixing between the solution and antisolvent. Carbon dioxide was introduced using two different injection rates, slow injection and rapid injection. The rate of carbon dioxide injection was regulated so that the pressure of the crystallizing chamber could increase at a rate of 20.0 bar/min for the rapid injection and 0.5 bar/min for the slow injection. The temperature effect due to the carbon dioxide injection was ignored in this study. The injection of carbon dioxide and the subsequent pressure increase caused an increase in the volume of the solution and the precipitation of the dissolved drug. The volume increase of the solution caused the increase in the intermolecular distance of liquid molecules and hence caused the decrease in the solvent power towards the drug compound. During the injection, nucleation took place, and continuous precipitation and crystal growth were observed. The precipitated crystals gathered at the bottom of the chamber and collected in a filter. Carbon dioxide was continuously injected up to 95 bar at which the crystallization process was considered to be completed. The mixture of carbon dioxide and the depleted solution was discharged from the chamber by a

ventilation valve. The residual solvent on the crystal surface was removed by a continuous flow of pure carbon dioxide through the chamber for 30 min. The crystallizing chamber was depressurized and the crystals were collected for analysis. It was found that the 30 min of drying time was enough to remove the residual solvent completely, and the flow of pure carbon dioxide used in the drying step did not show any significant influence on the crystal properties. Moreover, the depressurization of the crystallizing chamber was conducted very slowly in order to prevent the surface cooling effect of precipitated crystals.

The liquid antisolvent experiments were conducted in a glass flask. A known amount of the prepared drug solution was injected into 60 ml of distilled water at a constant temperature. Injections were made using a pipette at a feed rate of ca. 10 ml/min. During the injections, the mixture was agitated to accelerate precipitation. Upon mixing the solution and water, the instantaneous precipitation of drug crystals was observed. When the mixing process of the drug solution and water was completed, the precipitated crystals were filtered and dried.

Crystal Analysis

The external shape of the crystal particles was examined by a scanning electron microscope (SEM, Hitachi). The internal structure of the crystals was analyzed by a powder X-ray diffractometer (XRD, Philips). The thermal stability of the crystals was examined by a differential scanning calorimetry (DSC, Rhometric). In DSC analysis, the heat rate of 10°C/min was used for all drug samples. Particle size distribution was measured by a particle size analyzer (PSA, Ankersmid).

RESULTS AND DISCUSSION

Effect of Type of Solvent

The modification of the crystal habit was consistently observed when the three sulfa drugs were crystallized from different solvents. Figure 2 shows the variation of crystal habits of sulfathiazole, sulfamethizole, and sulfabenzamide, depending on the solvents from which the drugs were crystallized. In these experiments, two different solvents were used for each drug compound, and carbon dioxide was used as an antisolvent. Sulfathiazole was obtained in the form of granulates (Fig. 2(a)) when precipitated from acetone, but it crystallized in acicular form (Fig. 2(b)) from methanol. Sulfamethizole was crystallized in tabulate form (Fig. 2(c)) from acetone and as plates (Fig. 2(d)) from DMF. Sulfabenzamide was precipitated in the form

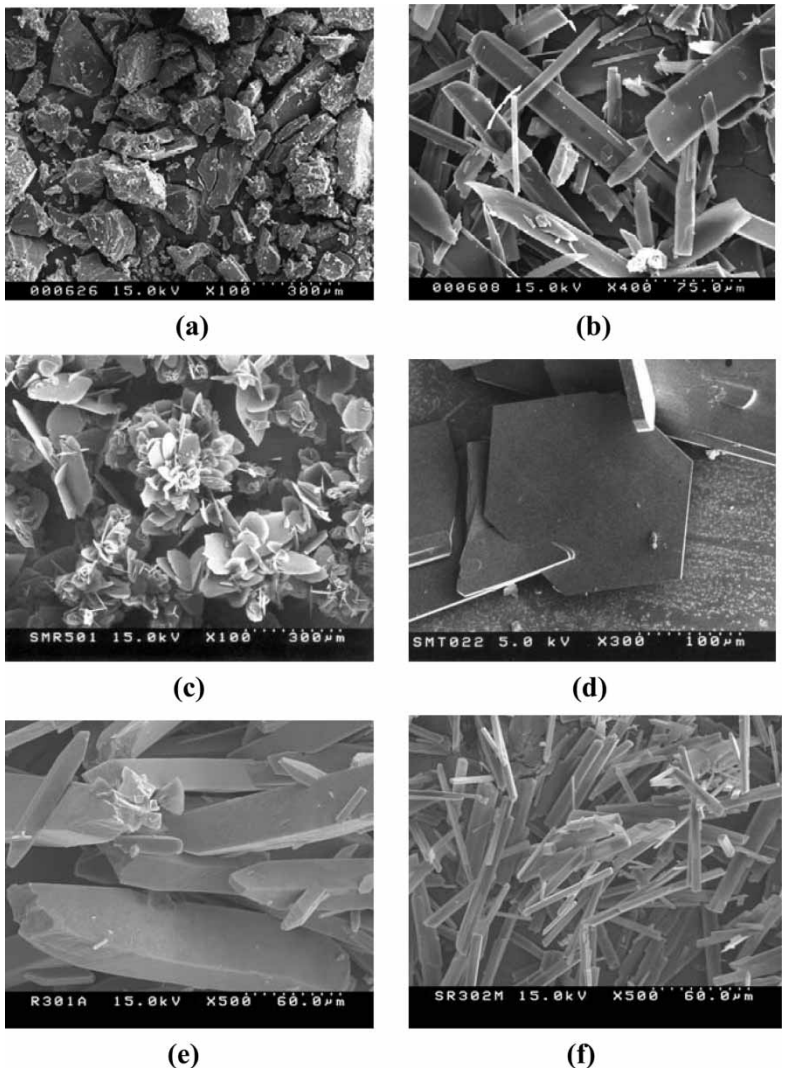
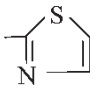
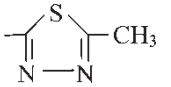
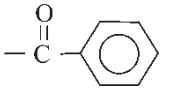


Figure 2. Crystal habits of three sulfa drugs. Sulfathiazole precipitated from acetone (a) and from methanol (b). Sulfamethizole precipitated from acetone (c) and from DMF (d). Sulfabenzamide precipitated from acetone (e) and from ethyl acetate (f).

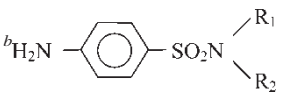
of prisms (Fig. 2(e)) from acetone and of aciculates (Fig. 2(f)) from ethyl acetate. The description of each crystal habit is summarized in Table 1.

Crystal habits are not exclusively governed by the internal crystal lattice, in that environmental factors involved in the processes of nucleation and crystal growth can affect crystal habits. The most important factor is the physico-chemical properties of the solvent from which the solute is

Table 1. The properties and crystal habits of sulfathiazole, sulfamethizole, and sulfabenzamide precipitated from different solvents using carbon dioxide as an antisolvent[a]

Drug	M_w	T_m(°C)	Solubility (mg/ml) (Solvent)	R_1^b	R_2^b	Solvent	Antisolvent	Habit
Sulfathiazole	255.3	204.1	5.25 (Ethanol)	H		Acetone	CO_2	Granulate
						Methanol	CO_2	Aciculate
Sulfamethizole	270.3	210.5	78.12 (Acetone)	H		Acetone	CO_2	Tabulate
						DMF	CO_2	Plate
Sulfabenzamide	276.3	183.2	111.1 (Acetone)	H		Acetone	CO_2	Prism
						Ethyl acetate	CO_2	Aciculate

[a] The crystal habits shown in Table 1 are the habits of crystals that were obtained in this study.



precipitated. Solvent properties such as dipole moment, dielectric constant, and the presence of hydrogen bonding may influence the crystal growth mechanism. The variation of these properties may alter the direction of structurally-dominant periodic bond chains of molecules during crystal growth. For example, the granular habit of sulfathiazole that crystallized from the acetone solvent indicates the build up of periodic bond chains in all directions, while the acicular habit obtained from methanol indicates a structurally-dominant periodic bond chain parallel to the needle axis (10).

The degree of supersaturation is another factor that influences crystal habits. Individual crystal growth kinetics usually depends, to some different extent, on supersaturation. In antisolvent crystallization, the degree of supersaturation is a strong function of the miscibility between a solvent and antisolvent, that may be related to the solubility parameters of the two media. It has been known that the miscibility between two different fluids is in proportion to the similarity of the solubility parameters of the fluids (11). In this study, the solubility parameter of the antisolvent (carbon dioxide) is 6.0 $(cal/cm^3)^{1/2}$ (12) and those of the solvents (methanol, acetone, DMF, and ethyl acetate) are in the range of 10.0–15.0 $(cal/cm^3)^{1/2}$ (13). The difference in the solubility parameter between the solvent and antisolvent, therefore, is in the range of 4.0–9.0 $(cal/cm^3)^{1/2}$, which is not significant enough to show any noticeable effect on the degree of miscibility and hence, on the degree of supersaturation or changes in the crystal habits. Therefore, it can be concluded that the modification of crystal habits observed in this study, mainly resulted from differences in the physico-chemical properties of each solvent, rather than from differences in miscibility between the solvents and antisolvent.

Crystal habits do not reflect the internal structure of crystals. Crystal habits, however, may determine the degree of agglomeration and flow characteristics of drug particles that affect the efficiency of bulk transportation and the storage of drugs. Crystal habits may also relate to the surface texture of particles that can alter the surface free energy and the release rate of a drug compound. Therefore, observing the habit modification of drug particles is meaningful in that it can provide clues to the potential of the bioavailability of sulfa drugs.

Effect of Temperature

The changes in the crystallization temperature did not show any significant effects on the crystal habit in the temperature range investigated. Crystallization temperature, however, influenced the particle size and the thermal stability of crystals. Observation revealed that larger crystals were produced when crystallization took place at higher temperatures. Figure 3 shows the variation of the average particle size of sulfathiazole, sulfamethizole, and sulfabenzamide as a function of the crystallization temperature. These particles were obtained using acetone as a solvent and carbon dioxide as an antisolvent.

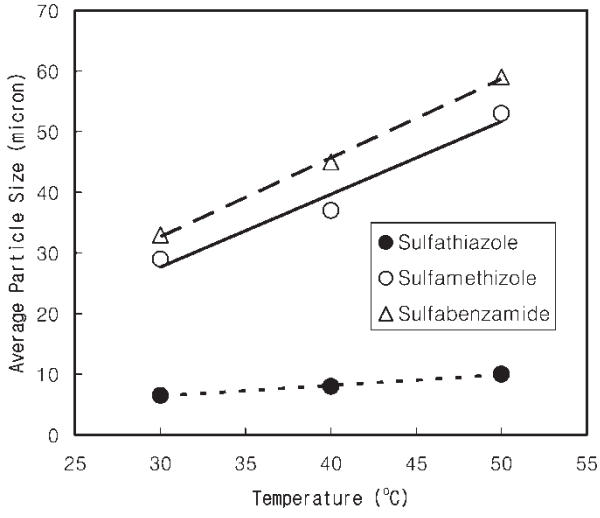


Figure 3. Variations of the average particle size of sulfathiazole, sulfamethizole, and sulfabenzamide crystals as a function of crystallization temperature when crystallized using an acetone solvent and a carbon dioxide antisolvent.

It was found that when crystallization occurred at the same temperature, the crystals of sulfabenzamide were the largest, followed by those of sulfamethizole and sulfathiazole. The average particle size of the three drugs consistently increased with an increase in the crystallizing temperature. As the crystallization temperature increased from 30 to 50°C, the average particle size increased from 6.5 to 10.5 μm for sulfathiazole, 29.5 to 53.1 μm for sulfamethizole, and 33.0 to 59.8 μm for sulfabenzamide. These results imply that higher temperatures enhance crystal growth. It is known that the rate of nucleation (the number of nuclei formed per unit volume and unit time) is inversely proportional to temperature. Moreover, as temperature increases, the solvent power of acetone toward drug compounds may increase, and it becomes harder to precipitate drugs from solutions. Therefore, at higher temperatures, the overall rate of nucleation decreases and the number of nuclei formed will be reduced. These factors may lead to the production of fewer crystals and hence have an effect on the further growth of each crystal. It was also observed that the crystals produced at higher temperatures showed a broader distribution in particle size.

Figure 4 shows the typical DSC scans for three drug samples prepared through carbon dioxide antisolvent experiments at 30°C. A DSC analysis revealed that the average fusion temperatures of sulfathiazole, sulfamethizole, and sulfabenzamide were 204.1, 210.5, and 183.2°C, respectively. These fusion temperatures of the precipitated particles were not affected by the crystallization temperatures. Also, the fusion temperatures were not significantly

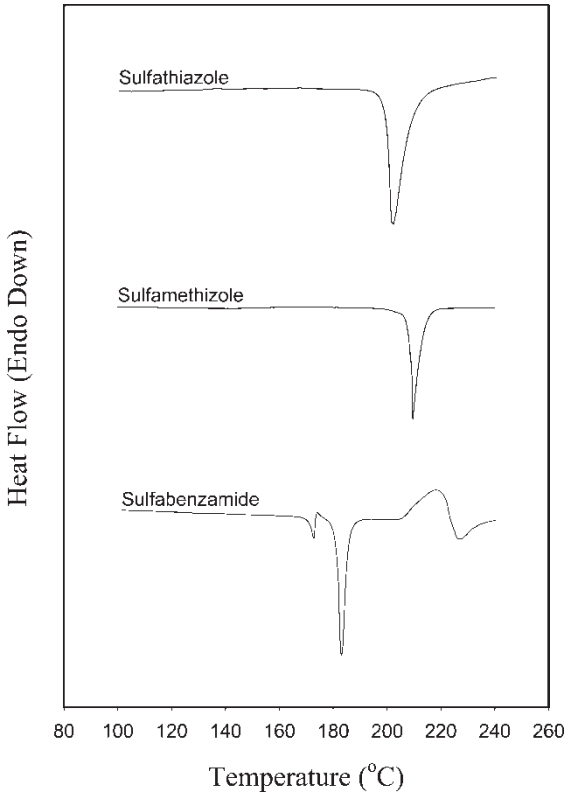


Figure 4. Typical DSC scans for sulfathiazole, sulfamethizole, and sulfabenzamide crystals obtained from carbon dioxide antisolvent experiments conducted at 30°C. Sulfathiazole and sulfamethizole were crystallized from acetone, and sulfabenzamide was crystallized from methanol.

different from those of the unprocessed material, which was prepared by the solvent evaporation method. The heat of fusion of the three drug compounds, however, was influenced by the crystallizing temperatures. When melting transition occurred, the endothermic heat flow was observed in all three drugs. The individual heat of fusion for sulfathiazole, sulfamethizole, and sulfabenzamide were in the range of 44.4–39.2, 32.5–30.0, and 136.0–126.0 cal/g, respectively when the crystallizing temperature changed from 30 to 50°C. The results show that the particles crystallized at higher temperatures exhibited less fusion heat. For drug compounds, the heat of fusion is often used to estimate the degree of crystallinity (14). Crystals with higher crystallinity require greater heat of fusion when melting takes place. These results imply that the crystallinity of the three sulfa drugs may decrease when particles are precipitated at higher temperatures. In general, the drug particles with lower crystallinity show high solubility and

enhanced dissolution rate in solutions. In this respect, the bioavailability of the drug compounds can be controlled by changing the crystallization temperature. In the DSC analysis of particles, no substantial peaks for an occluded solvent were observed, so we concluded that the amount of occluded solvent in crystals was beyond the detection limit of DSC.

Effect of Antisolvent Injection Rate

Carbon dioxide was injected into the drug solutions using two different injection rates (20.0 bar/min for rapid injection and 0.5 bar/min for slow injection). The carbon dioxide injection rate governs the supersaturation rate of the solutions and hence influences the rate of nucleation and crystal growth. In this study, the effect of the carbon dioxide injection rate was investigated by crystallizing sulfamethizole at 30°C with acetone as a solvent. It was found that crystals precipitated by using different carbon dioxide injection rates exhibited different crystal habits, particle sizes, and crystallinity. The crystal habits appeared to vary with the carbon dioxide injection rate in that they tended to become more needle-like as the injection rate increased. This behavior was a result of the enhanced relative growth rate of a particular crystal surface, which may have been caused by the high rate of addition of carbon dioxide. The rapid injection of carbon dioxide provided an environment for the high degree of supersaturation and the faster growth of a particular crystal face. Therefore, more elongated crystals would be produced. In general, it has been known that as supersaturation increases, the external shape of crystals tends to change from granular to acicular (15).

The carbon dioxide injection rate also affected the particle size of the crystals. Figures 5 and 6 show the particle size range and particle size distribution of sulfamethizole as a function of the carbon dioxide injection rate. Figure 5 illustrates the size range of crystals, but it does not include the particles whose sizes are in the upper 20% and lower 20% of the particles counted. For example, the figure shows the crystals that were generated by the slow injection of carbon dioxide ranged from 70 (D(20)) to 220 (D(80)) μm. This means that 20% of the particles that were produced from the slow injection experiments were larger than 220 μm and another 20% were smaller than 70 μm. It was found that the particles were significantly smaller when carbon dioxide was rapidly injected into the solution. In addition, the crystals with a narrower size distribution were produced by a rapid injection mode. The particles produced from the slow injection experiments were larger than the unprocessed material that was purchased from the manufacturer, while the crystals from the rapid injection experiments were an order of magnitude smaller than the others. These results imply that the carbon dioxide injection rate, i.e., the mixing rate of the solution and the antisolvent,

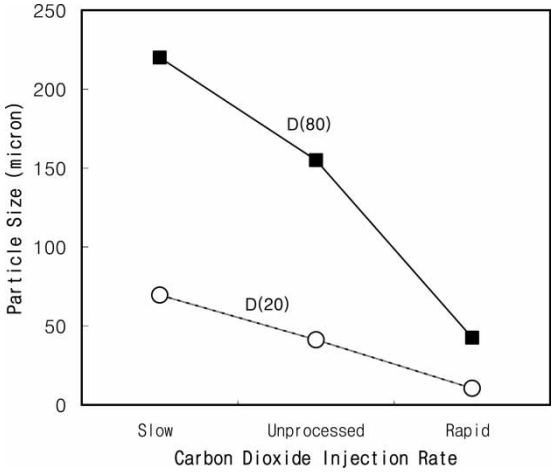


Figure 5. The variation of particle size range of sulfamethizole crystals obtained using two different carbon dioxide injection rates and these were compared with unprocessed material.

is directly related to the degree of supersaturation and crystal growth and it has a great impact on the size of the drug particles.

The X-ray diffraction pattern reflects the degree of crystallinity and molecular orientation of the crystal structures. Here, we measured the XRD patterns for three sulfamethizole samples: unprocessed particles and crystals obtained from experiments that used two different injection rates. Since the carbon dioxide injection rate governs the rate of nucleation and crystal

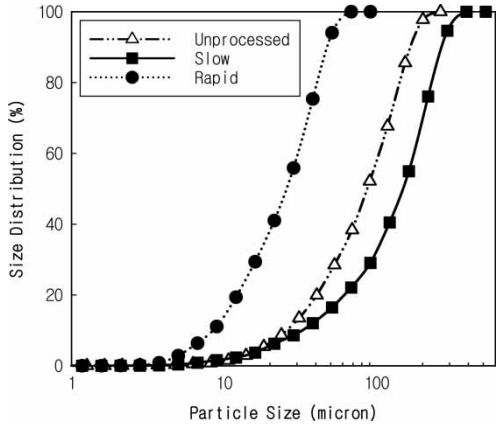


Figure 6. Size distribution of sulfamethizole crystals obtained using two different carbon dioxide injection rates.

growth, the variation of the injection rate may result in different internal crystalline arrangements. Figure 7 shows the XRD patterns of the unprocessed and processed sulfamethizole particles that were obtained from the experiments at 30°C. As labeled in Fig. 7, the interplanar spacing, *d* values of characteristic major peaks were 10.5, 7.3, 4.5, and 3.3 Å. In these experiments, acetone was employed as a solvent, and both slow and rapid injection modes were used. It was found that the XRD patterns changed depending on the carbon dioxide injection rate. The differences in the three XRD patterns in Fig. 7 can be explained by a preferred orientation in the crystalline structures. Preferred orientation is a condition in which the distribution of crystal orientations is nonrandom, and a specific crystalline frame may tend to cluster to a greater or lesser degree about some particular orientations (16). In general, the preferred orientation is indicated by the peak intensity of the XRD patterns. Comparing the three patterns in Fig. 7, the locations (2θ angle) of every peak are identical, while the relative integrated intensity of the peaks varies.

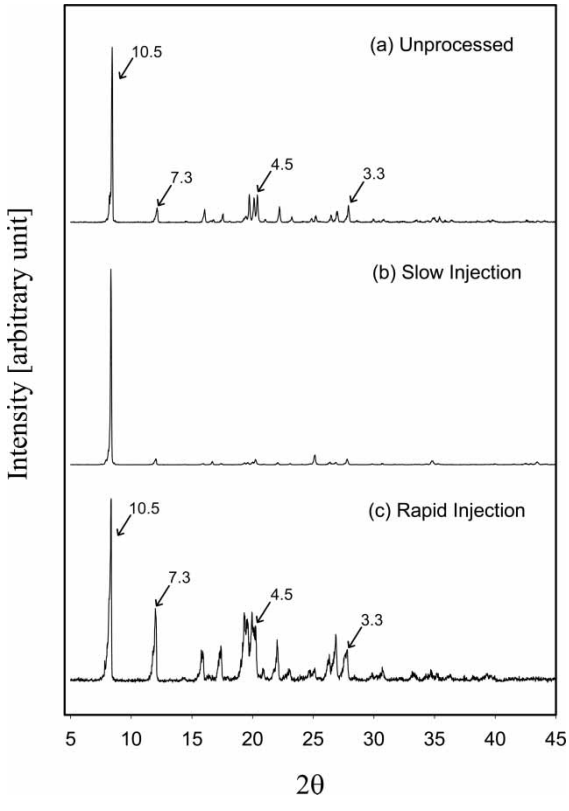


Figure 7. XRD patterns of three sulfamethizole samples: unprocessed material and crystals obtained using two different carbon dioxide injection rates.

These patterns show that the orientation of one particular molecular arrangement becomes preferred in the crystals produced by the slow injection experiment (Fig. 7(b)) when compared to the others (Figs. 6(a) and 6(c)). These results indicate that the slow rate of nucleation and crystal growth, which is due to the slow antisolvent injection, may facilitate the arrangement of molecules in a particular orientation during packing inside the crystalline lattice. This implies that the rate of carbon dioxide injection may control crystalline texture due to the change in crystallinity and preferred orientation.

Effect of Type of Antisolvent

In this study, most experiments were performed by using carbon dioxide as an antisolvent, and the effects of the solvent type, crystallization temperature, and antisolvent injection rate were investigated. In addition to these process parameters, it is worth noting how the type of antisolvent can influence the resulting particles. It has been shown that the antisolvent injection rate governed the physical properties of crystals, indicating that the rate of mixing the solution and antisolvent is an important process variable that controls the crystalline properties. When carbon dioxide was used as an antisolvent, the rate of mixing could be changed by varying the injection rate of carbon dioxide. The variation of the mixing rate between the solution and antisolvent can also be achieved by changing the type of antisolvent because the miscibility between two different fluids is a strong function of the physical and chemical properties of the fluids. Therefore, if a given drug solution is mixed with two different antisolvents, the rate of mixing and hence the nucleation and crystal growth of the crystallizing material may change. In this respect, we selected water as the other antisolvent for the drug solutions. Water can act as an antisolvent because it is miscible with organic solvents such as acetone and methanol and it has nearly zero solubility toward sulfa drugs.

In this study, we crystallized sulfamethizole using water as an antisolvent because sulfamethizole was easiest to handle when water was employed. Typical experiments were performed at 30°C using acetone as a solvent. The produced crystals were examined by SEM and PSA. It was observed that crystal habit and particle size changed compared to the carbon dioxide antisolvent experiments. When water was used as an antisolvent, the crystal habit became more acicular, while the carbon dioxide antisolvent produced tabular habit (Table 1). The average particle size of the crystals obtained from the water antisolvent experiments were ca. 90 μm, while the carbon dioxide antisolvent generated crystals with an average size of 30 μm (Fig. 3). The production of the larger crystals in the water antisolvent experiment can be explained by using the concept of the solubility parameter. The solubility parameter has been used to predict the miscibility of two different fluids. It has been known that it is easier to mix substances that have similar solubility parameters than to mix substances that have substantially different

parameters. The similarity in the solubility parameters of the solvent and antisolvent may govern the mixing rate of the two media and hence it may determine the degree of supersaturation and nucleation. Therefore, as the difference in solubility parameters of the solvent and antisolvent becomes smaller, the rate of nucleation may increase and the resulting crystal size will be reduced (4). In this study, the solubility parameters of the carbon dioxide, acetone, and water were 6.0, 9.8, and 23.5 $(cal/cm^3)^{1/2}$, respectively. Here, the difference in solubility parameters between acetone and carbon dioxide was 3.8 $(cal/cm^3)^{1/2}$ and the difference between acetone and water was 13.7 $(cal/cm^3)^{1/2}$. In other words, the difference in the solubility parameter between acetone and carbon dioxide was much smaller than the difference between acetone and water. This means that it was easier to mix the acetone solutions with carbon dioxide than to mix the acetone solution with water. The rapid mixing of acetone solution with carbon dioxide may induce the high rate of nucleation. The high rate of nucleation will generate a greater number of nuclei and therefore the size of each grown-up crystal will be reduced. This is the reason why the carbon dioxide antisolvent process produced smaller crystals compared to the water antisolvent process.

CONCLUSIONS

Modification of the crystal properties of sulfa drugs was achieved using antisolvent crystallization processes. The effects of operational variables such as the type of solvent, crystallization temperature, antisolvent injection rate, and type of antisolvent were investigated. When drugs were crystallized from different solvents, crystals with different habits were produced. The crystallizing temperature influenced the particle size and crystallinity of the drug crystals. At higher temperatures, the size of the crystals increased, and their crystallinity was reduced. The injection rate of the gas antisolvent affected the crystal habits, the particle size distribution, and the degree of crystallinity. When water was used as an antisolvent the overall crystal size increased.

ACKNOWLEDGEMENTS

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