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Habit modification of tamoxifen crystals using antisolvent crystallizations

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Abstract−The crystal habit of tamoxifen was modified using antisolvent crystallization techniques. Tamoxifen was crystallized from organic solvents using two different antisolvents (water and carbon dioxide). The habit of the precipitated crystals was modified by changing the process conditions, such as the solution and antisolvent mixing rate, the organic solvent, the presence of ultrasonic waves, and the addition of external additives. Particle size, crystal habit, particle aspect ratio and powder XRD patterns of the precipitated tamoxifen crystals were measured. With water as the antisolvent, the particle size of tamoxifen was significantly reduced compared to that of the raw material. When the antisolvent was carbon dioxide, the particle size was an order of magnitude greater than that of the raw material. The average aspect ratio of the tamoxifen crystals ranged from 1.8 to 16.2. The presence of ultrasonic waves caused a significant reduction in the aspect ratio, as well as the particle size. Furthermore, the addition of external additives was found to influence the crystal habit of tamoxifen.

Keywords: Antisolvent, Aspect Ratio, Crystallization, Crystal Habit, Tamoxifen

INTRODUCTION

Antisolvent crystallization is widely used to crystallize various organic compounds such as explosives, proteins, polymers, and pharmaceuticals [1,2]. Among these, pharmaceutical compounds are most frequently crystallized by the antisolvent technique because heating and cooling steps are not involved, and hence, concerns over thermal degradation of the drug compound can be eliminated. Water and carbon dioxide have been popularly used as antisolvents for the pharmaceuticals because most drug compounds are poorly water-soluble and are sparingly soluble in carbon dioxide. In addition, these two antisolvents are inexpensive, nontoxic to humans, and can be easily removed from crystallized pharmaceutical products.

In antisolvent crystallization, a drug dissolved in an organic solution is mixed with an antisolvent, which causes prompt precipitation of the drug compound. In this process, a high supersaturation of the organic solution takes place, leading to a fast nucleation and the formation of a large number of nuclei. These effects can induce the production of submicron-sized particles of drug compounds, which can cause an enhanced drug release rate and fast absorption of an ingredient. Because of these features of antisolvent crystallization, the technique has been used to micronize particles of polymers and biologically active ingredients [3,4]. In addition to the purpose of micronization, the antisolvent technique can be used to modify the crystal morphology or crystal habit of drug particles.

Crystal morphology and crystal habit are terms that describe the external shape of a drug particle. Crystal morphology refers to the faces of a crystal and the interfacial angles. Therefore, morphology is the most obvious characteristic of a crystal for the reliable identification of polymorphs. On the other hand, crystal habit is a qualitative descriptor and describes the shape (i.e., prism, needle, or plate). It is based on the relative lengths of the major dimensions of the crystal. Fig. 1 shows how two crystals can have the same morphology but different habits. Fig. 1(a) illustrates two particles with the same morphology but different habits, and Fig. 1(b) shows two crystals with different morphologies but similar habits. Indeed, morphology and habit are important for processing in the pharmaceutical industry. Filtering, drying, and free flowing ability depend on the external shape and the size distribution of the drug particles [5]. Therefore, it is necessary to manipulate the external shape and size of pharmaceutical compounds during their production.

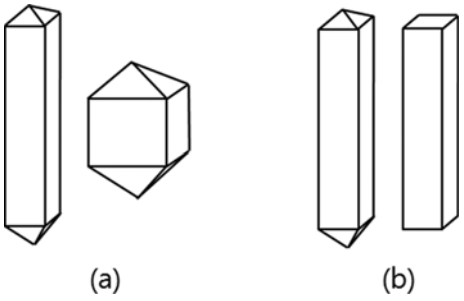

Fig. 1. Two crystals that have (a) the same morphology but different habits, and (b) the same habit but different morphologies.

In the antisolvent crystallization process, it is possible to change the morphology or habit of the resulting crystals by altering the process conditions, such as temperature, solvent, and mixing configuration [6,7]. However, it may be difficult to "control" the crystal morphology (polymorph) of drug particles since drugs mostly have a large molecular weight and may have a complex molecular packing mechanism. Instead, it may be relatively easy to manipu-

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‡This article is dedicated to Prof. Ki-Pung Yoo on the occasion of his retirement from Sogang University.

late the crystal habit because the habit can be modified by retarding the abnormal growth of a particular crystal face using an external disturbance or additive. Indeed, under ideal conditions, a growing crystal maintains geometric consistency during its growth, usually giving rise to a low aspect ratio (ratio of a particle's length to width).

In general, when a drug compound is crystallized from solution, it is desirable to obtain drug particles with a low aspect ratio (spherical or cubical habit) because it is easier to overcome the problems related to downstream processing and storage. Most crystallization processes (especially antisolvent crystallization), however, are likely to produce particles with a high aspect ratio (needle-like habit) because of the fast growth of a particular face of a crystal, which is due to the high rate of supersaturation. Therefore, control over the aspect ratio of the obtained crystals may be necessary during crystallization.

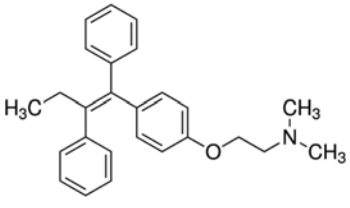
In this study, the crystal habit of a pharmaceutical compound was modified when antisolvent crystallization was performed. Tamoxifen [8], an anti-estrogen agent, was selected as a model compound. Tamoxifen was dissolved in organic solvents and the drug solutions were then mixed with water or carbon dioxide leading to particle precipitation. We investigated the effect of experimental conditions on the crystal habit of the resulting tamoxifen particles. The variation of particle size and aspect ratio of tamoxifen crystals are reported as functions of solution and antisolvent mixing rate, sonication intensity, solvent and antisolvent type, and the presence of external additives. Findings regarding the change in properties of tamoxifen particles are also presented.

EXPERIMENTAL METHODS

1. Materials

Tamoxifen (CAS 10540-29-1) was purchased from Sigma Co. Acetone, ethanol, ethyl acetate and dimethyl formamide (DMF) were selected as organic solvents to dissolve tamoxifen. Distilled water and carbon dioxide were used as the liquid and supercritical antisolvents, respectively. As external additives, α-D(+)-glucose penta acetate (CAS 604-68-2), Triton X-100 (CAS 9002-93-1), and urea (CAS 57-13-6) were employed. These chemicals were purchased from Sigma Co. and were used as received. Table 1 shows the physico-chemical properties of tamoxifen.

Table 1. Physico-chemical properties of tamoxifen

Properties	
Chemical formula	$C_{26}H_{29}NO$
Chemical structure	
Molecular weight	371.52 g/mol
CAS No.	10540-29-1
Solubility	Soluble in ethanol, methanol, acetone
Melting point	96-98 °C
Usage	Non-steroidal estrogen antagonist

2. Apparatus and Experimental Procedure

For the crystallization experiments, tamoxifen solutions were prepared using various organic solvents. Tamoxifen was dissolved in acetone, ethanol, ethyl acetate, or DMF at a concentration of 0.03 g/ml. At this concentration, tamoxifen was completely dissolved in each solvent. When external additives were used in the crystallization experiments, the selected additive was dissolved in the tamoxifen solution at concentrations of 0.001 (α-D(+)-glucose penta acetate), 0.003 (Triton X-100), and 0.001 (urea) g/ml. At these concentrations, the mixture of tamoxifen+additive formed a clear single phase in all the organic solutions.

Fig. 2 shows the experimental apparatus used in this study [9]. Two different pieces of apparatus were used for the crystallization

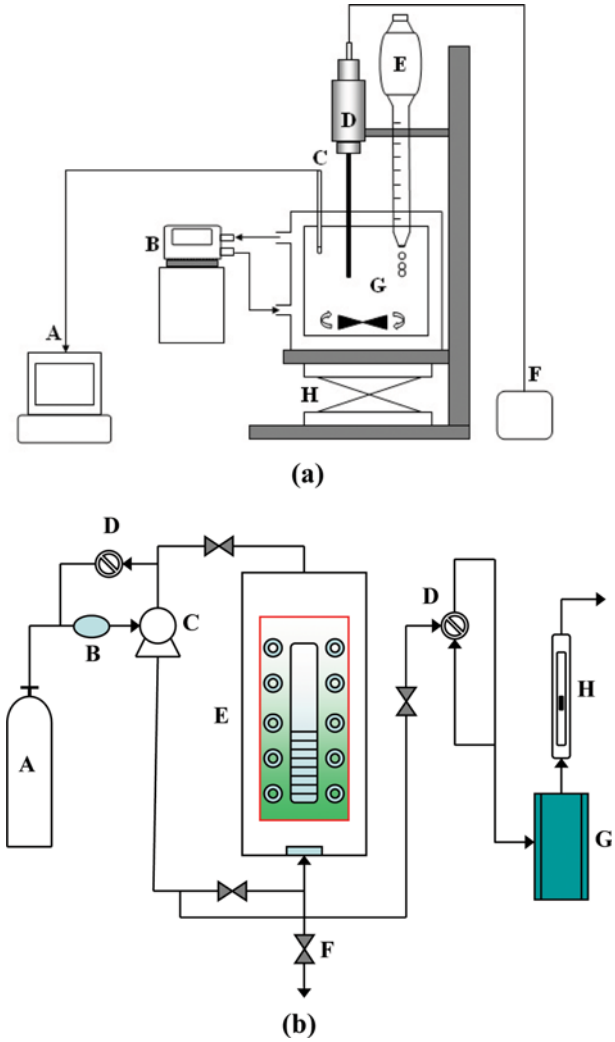


Fig. 2. (a) Apparatus for water-antisolvent experiment: (A) particle size analyzer, (B) constant temperature bath, (C) sample collector, (D) sonication probe, (E) drug solution injector, (F) ultrasonic generator, (G) crystallizing vessel, (H) magnetic stirrer. (b) Apparatus for the carbon dioxide-antisolvent 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.

experiments using two different antisolvents (water and carbon dioxide). Figs. 2(a) and 2(b) show the experimental apparatus used in the water- and carbon dioxide-antisolvent experiments, respectively. The water-antisolvent apparatus (Fig. 2(a)) consists of a crystallizing vessel, drug solution injector, and ultrasonic generator. The drug solution injector is equipped with an injection valve to control the injection rate of the drug solution into the antisolvent. The ultrasonic generator is connected to a sonication probe that is immersed in the mixture of solution and antisolvent. When necessary, ultrasonic waves were applied to the system at a frequency of 22.5 kHz. For the water-antisolvent experiment, 10 ml of the tamoxifen solution was injected into the crystallizing vessel in which 60 ml of the antisolvent (water) was already loaded. The drug solution was injected at three different injection rates: slow, medium and rapid. At these three injection rates, the tamoxifen solution was introduced to water at rates of 0.02, 0.05, and 1.0 ml/sec, respectively. As the solution was injected, the mixture of solution and antisolvent was vigorously agitated, and after the solution injection step was complete, the system was continuously agitated to allow sufficient crystal growth. In each experiment, the total time allowed for solution injection and crystal growth (crystal residence time in the system) in the mixture of the solution and antisolvent was typically 10 min. To investigate the effect of ultrasound in the water-antisolvent experiments, ultrasonic waves were applied to the system during the solution injection steps. When ultrasonic waves were applied, three power outputs (5, 10, and 15 W) were used, and the system was sonicated for a certain period (10 sec).

The carbon dioxide-antisolvent apparatus (Fig. 2(b)) consists of a carbon dioxide supply, a crystallizing chamber (Jerguson Gauge, Model 19-T-40), and a depressurizing section. The crystallizing chamber is placed in an air bath to maintain a constant temperature during the experiments. The crystallizing chamber has dual windows through which one can observe the phenomenon of particle precipitation and crystal growth. For the carbon dioxide-antisolvent experiments, 10 ml of a prepared tamoxifen solution was loaded into the crystallizing chamber. The experiments were conducted at 25 °C. After the solution was loaded, carbon dioxide was injected into the crystallizing chamber at a controlled rate and the drug solution and antisolvent were mixed. During the carbon dioxide injection, the pressure of the crystallizing chamber increased at a

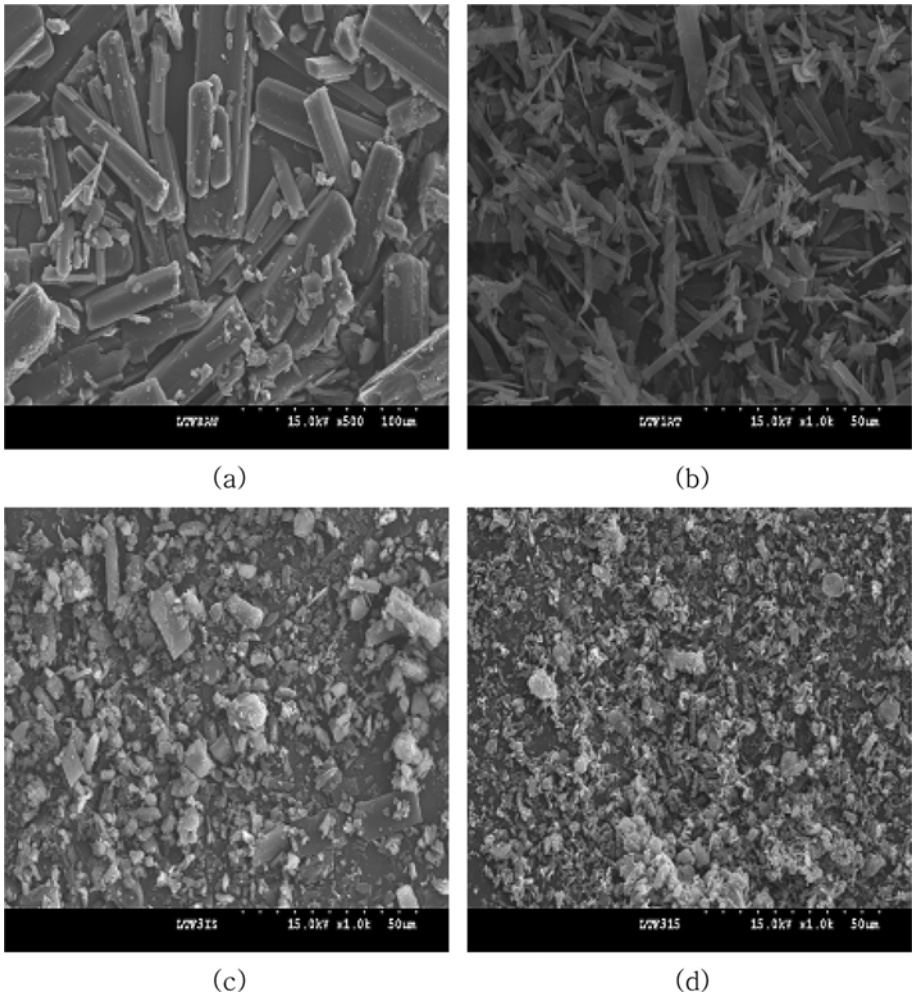


Fig. 3. SEM photomicrographs of tamoxifen crystals obtained from the water-antisolvent experiments, (a) raw material, (b) obtained by rapid injection of drug solution into antisolvent, (c) obtained by slow injection of drug solution into antisolvent, (d) obtained by rapid injection of drug solution into antisolvent in the presence of ultrasonic waves.

rate of 10.3 bar/min. The injection of carbon dioxide and the subsequent pressure increase caused an expansion of the solution and the nucleation of tamoxifen. After nucleation, the system was further pressurized to 95 bar until the carbon dioxide and solution phases were nearly merged. At this stage, the crystallization process was assumed to be complete. The precipitated crystals fell to the bottom of the chamber and were collected with a metal filter. The carbon dioxide and solution mixture was removed from the chamber using the ventilation valve. Finally, the crystallizing chamber was depressurized and the crystals were collected for analysis. The external shape of the crystals was examined by field emission scanning electron microscopy (FE-SEM, Hitachi S-4300&EDX-350). The crystal size was measured by using a particle size analyzer (PSA, Ankersmid CIS-50). The crystallinity was analyzed by powder X-ray diffractometer (XRD, Rigaku D/Max-2500) at a scanning 2θ range of 5 to 45°. The thermal stability of the crystals was analyzed by differential scanning calorimetry (DSC, TA Instruments TA-400). The samples were heated from 50 to 200 °C at a heating rate of 10 °C/min.

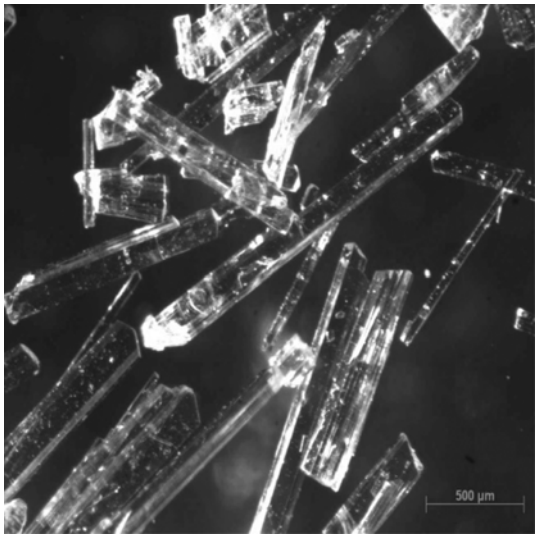


Fig. 4. Photomicrograph of tamoxifen crystals obtained from the carbon dioxide-antisolvent experiments.

RESULTS AND DISCUSSION

1. Variation of Crystal Habit

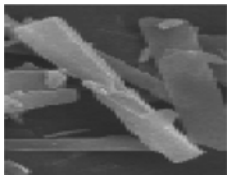
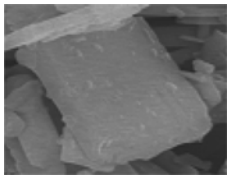
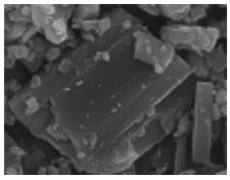
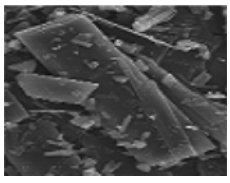
Fig. 3 shows the SEM photomicrograph of various tamoxifen crystals produced in the water-antisolvent experiments. The figure also includes an image of the as-received (raw material) tamoxifen particles. As shown, the habit of the tamoxifen crystals is modified depending on the process conditions. The raw tamoxifen crystals exhibit a large columnar habit (Fig. 3(a)). Note that the magnification of Fig. 3(a) is x500. On the other hand, the processed tamoxifen crystals show significantly reduced size and different crystal habits (Figs. 3(b)-(d), magnification is x1000). Fig. 3(b) shows the crystals after the tamoxifen solution is rapidly injected (1.0 ml/sec) into the antisolvent. Here, acetone was used as the solvent. The crystals exhibit a small acicular habit. However, after the solution is slowly injected (0.02 ml/sec) into the antisolvent, the habit changes to an irregular particulate shape, as shown in Fig. 3(c). The modification of crystal habit from acicular to particulate resulting from the change in the injection rate of the drug solution, can be explained by considering the change in the rate of supersaturation and crystal growth. When the drug solution is rapidly released into the antisolvent (rapid injection), dilution of the drug solution is prompt causing supersaturation to occur quickly. In this case, the high rate of supersaturation results in the formation of a large number of nuclei and the rapid growth of a given crystal face, which may result in the elongated acicular habit of the crystals. On the other hand, when the drug solution is slowly added to the antisolvent (slow injection), the drug solution becomes supersaturated after a sufficient amount is added. In this case, nucleation and the subsequent crystal growth are delayed, which in turn results in the relatively even growth of each crystal surface and produces particulated crystals. Fig. 3(d) shows the typical crystal habit when the drug solution is rapidly injected into the antisolvent in the presence of ultrasonic waves. Figs. 3(b) and 3(d) illustrate that the presence of ultrasonic waves induces a modification of the crystal habit from acicular to particulate. At the same time, it appears that the overall particle size of tamoxifen is reduced when ultrasonic waves are applied. The effect of ultrasonic waves on the particle size and habit will be discussed in a later section.

Fig. 4 shows the typical image of tamoxifen crystals produced from the carbon dioxide-antisolvent experiment. The magnification of Fig. 4 is x100, which is an order of magnitude greater than the images shown in Fig. 3. In this experiment, acetone was used as the solvent. Comparison of Fig. 4 and Fig. 3(b) illustrates that the change of antisolvent from water to carbon dioxide greatly modifies the crystal shape. First, the crystal size is orders of magnitude larger than the crystals produced from the water-antisolvent experiments. Secondly, the appearance of the crystals becomes translucent (Fig. 4) and the particles have a different surface texture. These results might be partly explained by considering the difference in the mixing method in the two different antisolvent experiments. In the water-antisolvent experiment, a small amount of drug solution is injected into an excess of antisolvent. Therefore, a high rate of supersaturation and nucleation is achieved; thus, small particles are produced. In the carbon dioxide-antisolvent experiment, however, antisolvent is added to the drug solution, which might delay the nucleation and crystal growth. This may allow sufficient time for the crystal growth and hence, larger particles. It is presumed that there must be other reasons for the production of such large particles with very different characteristics. One of the reasons might be the relatively high interaction between tamoxifen and antisolvent (carbon dioxide). If tamoxifen has a relatively high affinity to carbon dioxide, carbon dioxide would become a poor antisolvent towards tamoxifen. In this case, the nucleation rate of tamoxifen would decrease and a smaller number of nuclei would form. Therefore, the size of each crystal will increase.

2. Effects of Solvent and External Additives

Two most important experimental factors that influence the external habit of crystals are the type of solvent and the presence of external additives [10]. Tables 2 and 3 summarize the effects of solvents and external additives on the crystal habit of tamoxifen,

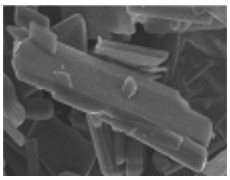
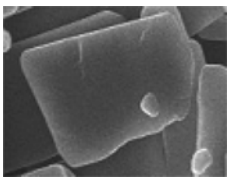
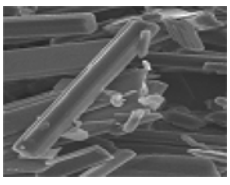
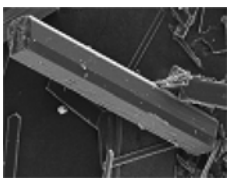
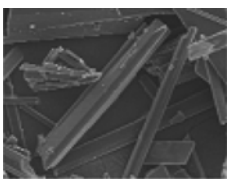
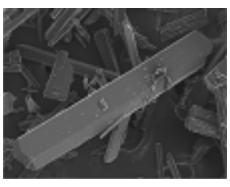
Table 2. Crystal habit, aspect ratio and particle size of tamoxifen when different solvents and antisolvents were used

Antisolvent	Solvent	Habit	Aspect ratio	Particle size (μm)
Water	Acetone		8.9	11.9
	Ethanol		2.6	9.6
	Ethyl Acetate		2.0	12.9
	DMF		2.1	14.8
CO_2	Acetone		8.2	1,090

respectively. In these tables, the typical image of tamoxifen crystals, particle aspect ratio, and particle size are presented as functions of solvents, external additives, and type of antisolvent. Here, the aspect ratio of a particle is defined by the ratio of its length and width. The aspect ratio was determined by measuring the dimensions of 100 sample particles shown in the SEM images, and by averaging their ratios. Table 2 shows the variation of crystal habit, aspect ratio, and particle size of tamoxifen when water- and carbon dioxide-antisolvent experiments were conducted. In the water-antisolvent experiments, four solvents (acetone, ethanol, ethyl acetate, and DMF) were used, and in the carbon dioxide-antisolvent experiments, only acetone was used as the solvent. As seen in the images, different habits are observed when the solvent is changed. The particle aspect ratio ranged from 2.0 to 8.9, depending on the solvent used. The particle size of tamoxifen produced from the water-antisolvent experiments was in the range of 9.6 to 14.8 μm. In contrast, the average particle size of tamoxifen obtained from the carbon dioxide-antisolvent experiment was 1,090 μm, which is two orders of magnitude greater.

Table 3 shows the effect of external additives on the crystal habit, aspect ratio, and particle size when the water- and carbon dioxide-antisolvent experiments were conducted. As shown in the table, α-D(+)-glucose penta acetate, Triton X-100, and urea are used as external additives in both sets of experiments. Acetone is used as the solvent in all the experiments. In the case of the water-antisolvent experiments, the aspect ratio ranged from 1.8 to 4.7 and the average particle size was between 2.2 and 13.2 μm. In the case of the carbon dioxide-antisolvent experiments, the aspect ratio ranged from 7.4 to 16.2 and the average particle size was between 237 and 303 μm. In the case of the water-antisolvent experiments, the presence of external additives was found to reduce the aspect ratio of tamoxifen (please see the first line of Table 2). Among the three additives, Triton X-100 was the most effective for reducing the aspect ratio and particle size. As shown in the table, Triton X-100 produced tamoxifen crystals with a square-like habit. The reduction of the aspect ratio in the presence of external additives can be explained by considering the growth retardation of a particular fast-growing crystal face because of the action of the additives. An additive that adsorbs or interacts with the crystal face in such a way that slows down the growth rate can further increase the relative area of the crystal face [11]. In the case of the carbon dioxide experiments, the external additives have little effect on the aspect

Table 3. Crystal habit, aspect ratio and particle size of tamoxifen when different external additives were used

Antisolvent	Additives	Habit	Aspect ratio	Particle size (μm)
Water	α-D(+)-Glucose penta acetate		4.0	3.8
	Triton X-100		1.8	2.2
	Urea		4.7	13.2
CO_2	α-D(+)-Glucose penta acetate		16.2	303
	Triton X-100		9.9	264
	Urea		7.4	237

ratio. On the other hand, the particle size is significantly reduced compared to the crystals produced without external additives (please see the last line of Table 2). These results imply that the role of the external additives can be influenced by the type of antisolvent. Indeed, the action of the additives (adsorption and interaction with the growing crystal surface) occurs in the environment of the solvent+antisolvent mixture. If the type of antisolvent changes from water to carbon dioxide, properties such as polarity and dielectric constant of the solvent+antisolvent mixture vary accordingly. This variation might affect the role of the external additives, so that their influence on the aspect ratio of tamoxifen is different when water and carbon dioxide are used as antisolvents.

3. Aspect Ratio as a Function of Mixing Rate

The effect of the mixing rate of the drug solution and antisolvent on the aspect ratio of tamoxifen crystals was investigated during the water-antisolvent experiments. As previously explained, the mixing rate is changed by regulating the injection rate of the tamoxifen solution into the antisolvent (water) at three different injection rates (slow, medium, and rapid). As the injection rate increases, the rate of mixing also increases. Acetone was used as the solvent and the experiments were performed at 25 °C. Fig. 5 shows the variation of the aspect ratio of tamoxifen crystals that were obtained when the three injection rates were used. The figure also includes the aspect ratio when ultrasonic waves are applied to the system during crystallization (The effect of ultrasonic waves will be discussed in next section). The aspect ratio of tamoxifen crystals tends to increase as the solution injection rate (rate of mixing) increases. Indeed, the rate of mixing is directly related to the degree of supersaturation of the drug solution and can affect the rate of nuclei formed per unit volume. Moreover, the rate of mixing could affect

the growth rate of each nucleus. In fact, the crystal growth rate reflects the mass transfer rate of the drug molecules from the solution phase to the crystal surface, which in turn may depend on the mixing rate. When the drug solution is added slowly, the rate of mass transfer decreases and induces the delayed growth of each crystal face, eventually producing particles with a low aspect ratio. In contrast, when the drug solution is added rapidly, the rapid growth of a particular crystal face produces crystals with a high aspect ratio. These results suggest that if production of crystals with a low aspect ratio is required, mixing of the drug solution and antisolvent should occur slowly during antisolvent crystallization.

4. Effect of Ultrasonic Waves

The effect of ultrasonic waves on the modification of tamoxifen crystals was investigated by sonicating the system during the water-antisolvent experiments. The experiments were conducted at 25 °C using acetone as the solvent with a solution injection rate of 1.0 ml/sec. The ultrasonic waves were supplied with three power outputs (5, 10, and 15 W) at a constant frequency (22.5 kHz). Sonication was applied for 10 sec as soon as the drug solution and antisolvent began mixing. Fig. 6 shows the average particle size of tamoxifen crystals produced using ultrasonic waves with different power outputs. The figure includes the data when no sonication is applied. The average particle size of tamoxifen is significantly reduced when the solution is sonicated during crystallization. Increasing the sonication power from 5 to 15 W does not contribute to a further reduction of particle size. In addition to the particle size, the particle aspect ratio decreases when the solution is sonicated (see Figs. 3(d) and 5).

The effect of ultrasonic waves on the reduction of particle size can be explained by considering the induction time of crystallization [12,13]. Induction time is the time elapsed between the supersaturation and the advent of crystals. It is generally known that introducing ultrasonic waves in the solution decreases the induction time between the phases of nucleation and crystallization. As the induction time decreases, the degree of supersaturation of the solution increases; therefore, a larger number of nuclei form, which in turn leads to a smaller particle size [14,15]. In addition, ultrasonic waves reduce the agglomeration of crystals, which can also

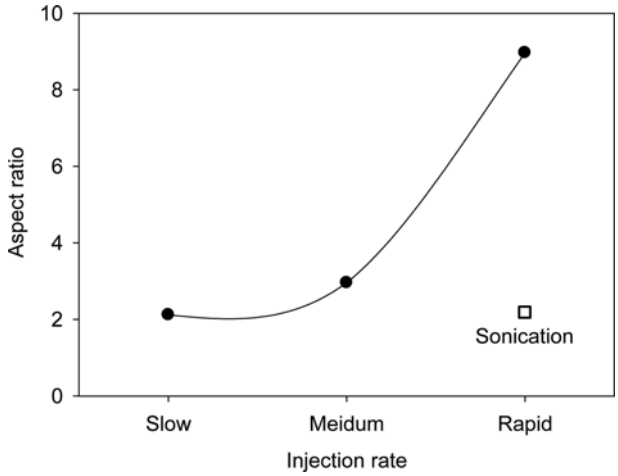


Fig. 5. Variation of aspect ratio of tamoxifen crystals that were obtained using three injection rates.

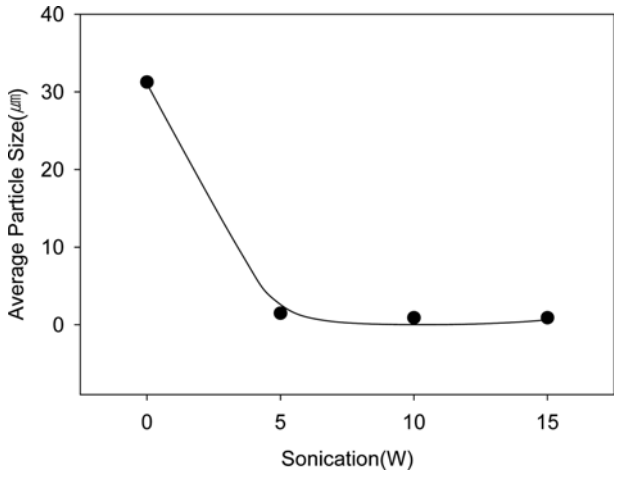


Fig. 6. Average particle size of tamoxifen crystals when the ultrasonic waves were applied to the system with different power outputs.

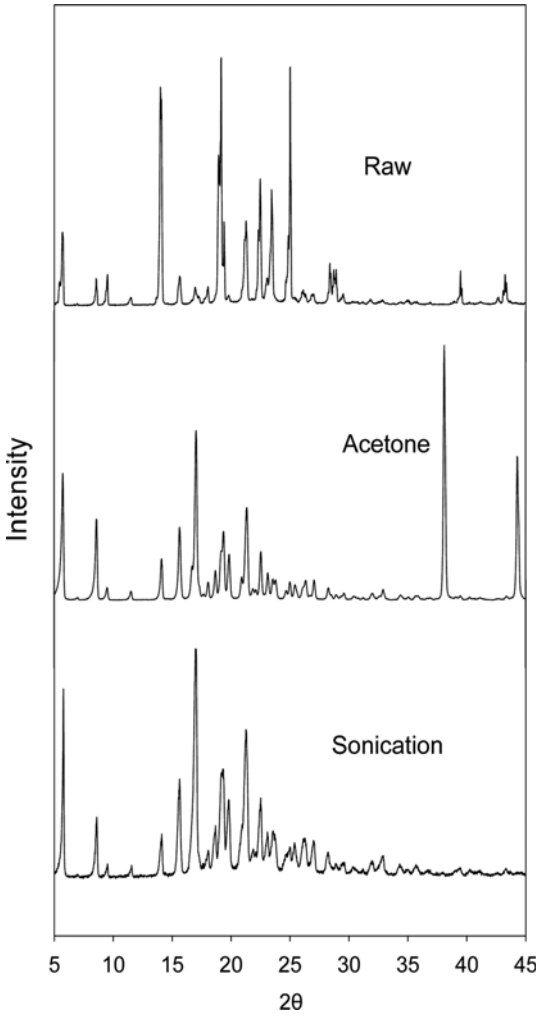


Fig. 7. X-ray diffraction patterns of three tamoxifen crystal samples: raw material tamoxifen (raw), crystals obtained from acetone solutions (acetone), and crystals obtained from acetone in the presence of ultrasonic waves (sonication).

lead to an increase in the number of product crystals, thereby leading to the reduction of particle size. The decrease of particle aspect ratio in the presence of ultrasonic waves is not surprising. In fact, the main action of ultrasonic waves is the consecutive formation and the bursting of cavitation bubbles that cause severe disturbances inside the solution. During the crystal growth step, it is likely that the disturbance caused by the ultrasonic waves may prevent any uneven growth of a particular crystal face and could generate crystals with a low aspect ratio.

Fig. 7 shows the X-ray diffraction patterns of three tamoxifen crystal samples, which are raw material tamoxifen (raw), crystals obtained from acetone solution (acetone), and crystals obtained from acetone in the presence of ultrasonic waves (sonication). The diffraction pattern of the processed tamoxifen (acetone) is quite different from that of unprocessed crystals (raw). Two strong diffraction peaks appear at 2θ=37.5° and 44.1°. The relative intensities of a diffraction peaks represent the degree of ordered arrangement of molecules in a particular orientation. Therefore, the strong intensities of these two peaks imply that the ordered molecular arrangements that correspond to those diffraction angles are dominant compared to other molecular orientations. However, when ultrasonic waves are applied, the two strong peaks disappear as shown in the third diffraction pattern in Fig. 7 (sonication). As mentioned above, the appearance of a diffraction peak indicates the presence of an ordered molecular packing, and the disappearance of this peak implies that the ultrasonic waves have interrupted the regular molecular packing of the particular orientation inside the crystal lattice.

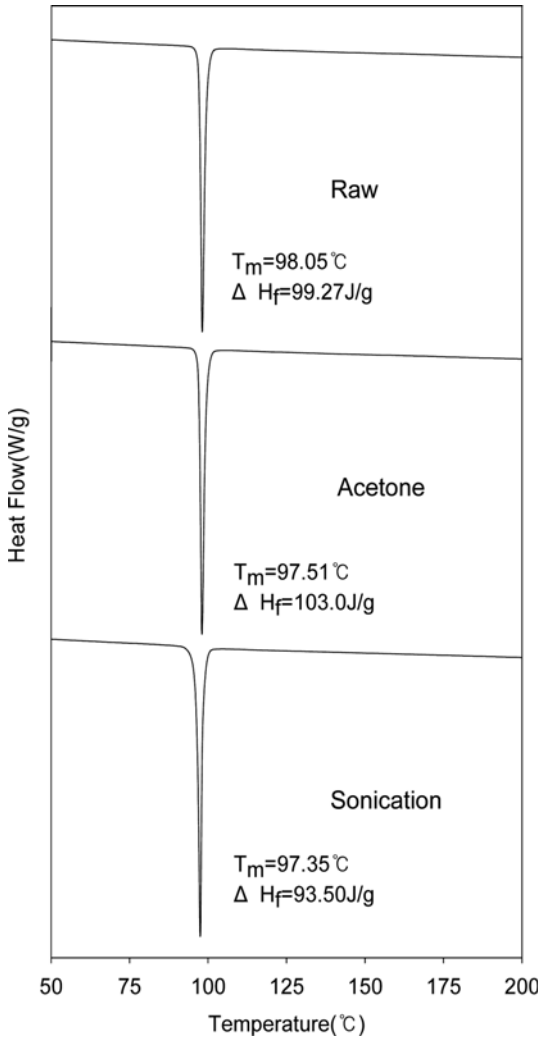


Fig. 8. DSC curves of three tamoxifen crystal samples: raw material tamoxifen (raw), crystals obtained from acetone solutions (acetone), and crystals obtained from acetone in the presence of ultrasonic waves (sonication).

Fig. 8 shows the DSC curves of the same tamoxifen crystal samples (raw, acetone, and sonication). The melting points of the three samples are essentially the same. The heat of fusion accompanying each curve, however, is different depending on the type of sample. The heat of fusion of the tamoxifen crystal obtained from acetone solution is 103.0 J/g and that of the crystal obtained in the presence of ultrasonic waves is 93.5 J/g. There is a reduction of 10% in the heat of fusion when the solution is sonicated during the crystallization. In fact, the amount of heat involved in the phase transition has been used as a standard to estimate the degree of crystallinity [16]. Therefore, this result indicates that the ultrasonic waves might lower the crystallinity of tamoxifen crystals. This result is consistent with those of the XRD patterns (Fig. 7) that show the disappearance of a specific ordered molecular packing (decrease in crystallinity) due to the presence of ultrasonic waves.

CONCLUSIONS

The crystal habit of tamoxifen was altered using antisolvent crystallization techniques. Water and carbon dioxide were used as the antisolvents. The effects of various process parameters, such as the solution and antisolvent mixing rates, the type of organic solvent, the presence of ultrasonic waves, and the addition of external additives, were investigated. The average particle size of tamoxifen produced from the water-antisolvent experiments was in the range of 9.6-14.8 μm, whereas that of tamoxifen obtained from the carbon dioxide-antisolvent experiment was ~1,090 μm. Tamoxifen crystals exhibited an acicular habit when the mixing rate of the drug solution and antisolvent was high. The aspect ratio of the tamoxifen crystals ranged from 1.8 to 16.2, depending on the process conditions. The addition of external additives reduced the aspect ratio of tamoxifen crystals. The particle size as well as the aspect ratio was significantly reduced when the solution was sonicated during the crystallization.

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