Relationship between Particle Size and Impurity Incorporation during Crystallization of (+)-Pseudoephedrine Hydrochloride, Acetaminophen, and Adipic Acid from Aqueous Solution

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Received December 20, 2001; accepted March 26, 2002

KEY WORDS: acetaminophen; adipic acid; crystallization from solution; impurity incorporation; particle size; (+)-pseudoephedrine hydrochloride.

INTRODUCTION

Crystallization from solution is a technique widely used in various fields for separation and purification (1). During this process, structurally related impurities may be incorporated into the crystal lattice of the host crystals to form solid solutions (2,3). In addition, the solvent may also be incorporated into the host crystals as liquid inclusions containing dissolved impurities (1). The incorporated impurities and solvents may possess toxicological effects and may change the physicochemical properties, such as thermodynamic properties and dissolution rate of the crystallized products, (4). These changes may lead to batch-to-batch variations, which present serious problems of quality control in the pharmaceutical industry (5). It is therefore important to control the extent of impurity incorporation during the crystallization process. In a single batch, different kinetic parameters are associated with particles of different sizes. Therefore, the extent of incorporation of impurities and liquid inclusions may be size-dependent, because both processes are affected by the crystallization kinetics (6,7). This communication reports the relationship between the size of the particles crystallized in a single batch and the extent of incorporation of impurity and solvent.

MATERIALS AND METHODS

Materials

(+)-Pseudoephedrine hydrochloride (+PC), (−)-ephedrine hydrochloride (-EC), and acetaminophen (AP) were purchased from Sigma Co. (St. Louis, Missouri). Adipic acid (AA) was purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin). Succinic acid (SA) was purchased from Mallinckrodt Baker, Inc. (Paris, Kentucky). *p*-Acetoxyacetanilide (PAA) was prepared as described previously (3). All compounds were further purified by two successive crystallizations from ethanol (Aldrich Chemical Company, Milwaukee, Wisconsin). The compounds were stored in a desiccator containing anhydrous calcium sulfate (Drierite, W.A. Hammond Drierite Company, Xenia, Ohio) and activated charcoal (J.T. Baker Inc., Phillipsburg, New Jersey). All solvents, including water (EM Science, Gibbstown, New Jersey) and ethanol, were of HPLC grade.

Methods

Batch Crystallization of +PC

The impure crystals were prepared by gradually cooling aqueous solutions containing known amounts of host molecules and impurity molecules at 0.2°C/min, controlled by a programmable circulating water bath (Neslab, model RTE-110, Portsmouth, New Hampshire). The choice of the experimental conditions was based on previous studies. Details of the crystallization conditions are listed in Table I. Before further experimentation, the harvested crystals were dried overnight in a vacuum oven at 25°C and then dried over anhydrous calcium sulfate for one week. The particles in a single batch were separated manually by standard sieves (Tyler, Ontario, Canada). Particles were shaken over a series of sieves for 10 min, and static adsorption of the particles was minimized by a static guard (NCD Inc., Grand Island, New York).

Karl Fischer Titrimetry

The water content in the crystals (50 mg) was determined using a Karl Fischer titrimeter with a sensitivity of 0.1 μg of water (Moisture Meter, model CA-05, Mitsubishi Chemical Industries Ltd., Tokyo, Japan). To determine the amount of included water, the water content of intact particles, expressed as w_0, was first determined. The particles were then ground manually in a mortar with a pestle for 5 min. The resulting fine powder was dried over anhydrous calcium sulfate to a constant weight and the water content, w_1, was determined as described above. The weight fraction of included water, w_i, was calculated by the following equation:

$$w_i = w_0 - w_1 \quad (1)$$

Progressive Dissolution and High Performance Liquid Chromatography (HPLC)

The amounts of incorporated impurities were determined by progressive dissolution (3), followed by HPLC analysis of elutes, which have been reported previously (2,4,8). During the washing process, the mole fraction of the impurity in the effluent, with respect to that of the host substance, decreases with increasing washing time, as the adsorbed impurity is washed off. After a time of the order 10 min, a plateau is reached, when the only impurity remaining is that incorporated in the host crystals. The HPLC system employed to analyze the impurity and host substance in the washings was manufactured by Waters™ (Milford, Massachusetts) and included a 510 pump, a U6K manual injector, and

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Table I. Conditions of Batch Crystallization and Properties of Doped Crystals

Host crystals and (impurity)	Volume aqueous solution	Initial and final temperatures	Initial molar concentration of host	Initial molar concentrations of impurity
+PC[a] (–EC[b])	20 mL	65 ⇒ 23°C	9.916 M	0.09916–0.4958 M
AP[c] (PAA[d])	75 mL	65 ⇒ 15°C	0.3086 M	0.003086–0.01234 M
AA[e] (SA[f])	50 mL	65 ⇒ 25°C	1.232 M	0.01232–0.06160 M

[a] +PC is (+)-pseudoephedrine hydrochloride, the host crystals.
[b] –EC is (–)-ephedrine hydrochloride, the impurity.
[c] AP is acetaminophen, the host crystals.
[d] PAA is *p*-acetoxyacetanilide, the impurity.
[e] AA is adipic acid, the host crystals.
[f] SA is succinic acid, the impurity.

a 994 programmable photodiode array detector. Baseline resolution was achieved for all three systems.

RESULTS AND DISCUSSION

Impurity Incorporation

Figures 1a–c show that larger particles incorporate more impurity than smaller particles in a single batch. In the system of +PC doped with –EC (Fig. 1a), larger particles (45–75 μm) incorporate 30% more impurities than the smaller particles. In the system of AP doped PAA (Fig. 1b), larger particles of size 75–180 μm incorporate 44%, 36%, and 16% more PAA, respectively, than smaller particles (45–75 μm). The extent of impurity incorporation is determined by both the properties of the impurity molecules and the host molecules and by the kinetics of the crystallization process. The extent of impurity incorporation is quantified by the segregation coefficient, which is defined as the ratio of the concentration of the incorporated impurity to the concentration of the impurity in the crystallization medium. The equilibrium segregation coefficient is determined by the relative solubility of the host and the guest in a given solvent and by the free energy changes for the dissolution of the guest molecules into the host solid (9). However, during crystallization, the extent of impurity incorporation is determined not only by the equilibrium segregation coefficient, but by the kinetic parameters of crystallization, such as crystal growth rate (10), temperature (6), and the degree of supersaturation (11).

When the segregation coefficient is < 1, it has previously been shown that host crystals that grow faster during crystallization incorporate more guest molecules (10). The extent of impurity incorporation by the crystals also increases when they are growing under a higher degree of supersaturation (11). In a single batch, if crystals of different sizes grow from the nuclei created at the same time, larger crystals must grow faster than the smaller crystals. This phenomenon is also known as growth rate dispersion (1). In many systems, the larger crystals are found to grow faster than the smaller crystals under the same conditions (1). Another possible cause of differences in particle size in a single batch is that larger crystals grow from the nuclei created at the stage of primary nucleation, which will have more time to grow, while smaller

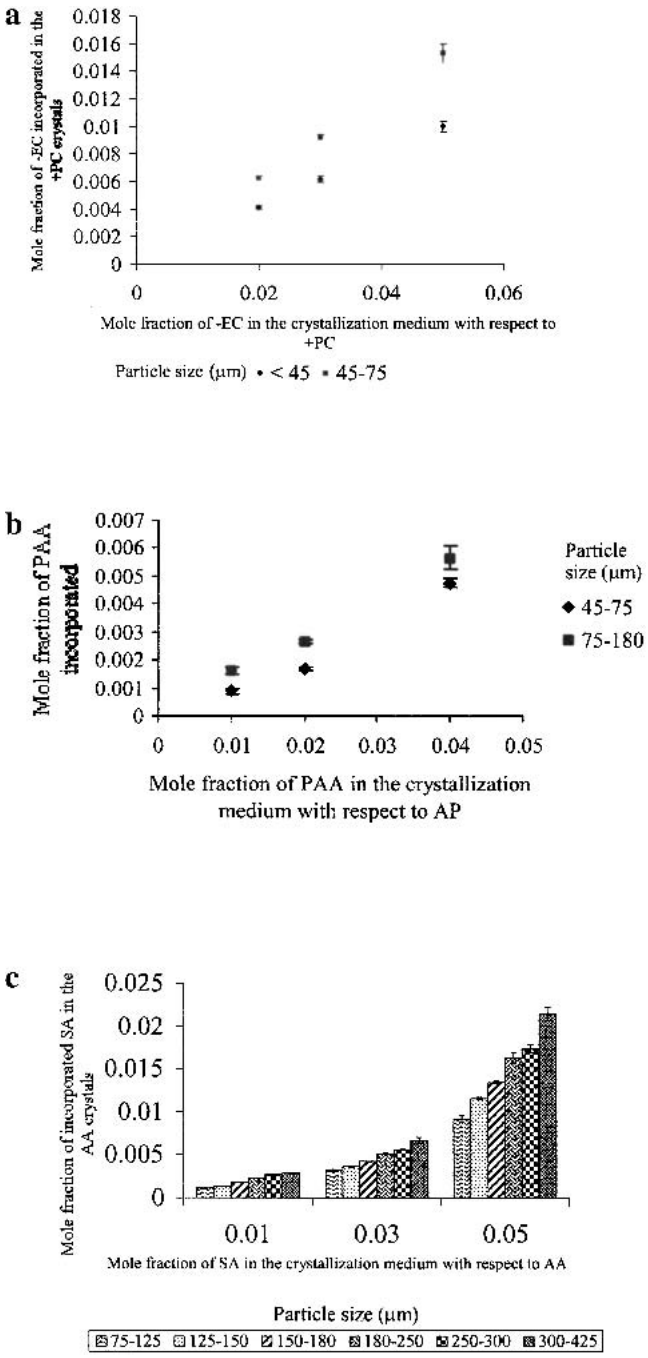

Fig. 1. Uptake of impurity by host crystals of different sizes in a single batch. The vertical bars represent the standard errors (n = 3). (a) Uptake of (–)-ephedrine hydrochloride (–EC) by (+)-pseudoephedrine hydrochloride (+PC) crystals of particle size: ◆ < 45 μm, ■ 45–75 μm. (b) Uptake of *p*-acetoxyacetanilide (PAA) by acetaminophen (AP) crystals of particle size: ◆ 45–75 μm, ■ 75–180 μm. (c) Uptake of succinic acid (SA) by adipic acid (AA) crystals of increasing particle size from left to right: 75–125 μm, 125–150 μm,. 150–180 μm, 180–250 μm, 250–300 μm, 300–425 μm.

particles may result from the growth of secondary nuclei. During crystallization by cooling, it is known that the degree of supersaturation is higher at an earlier stage of crystallization, and then gradually decreases to a plateau value (1). The larger crystals may then grow at a higher degree of supersatu-

ration. For the three model systems under study, the segregation coefficients are all less than one. Therefore, the larger crystals, which may grow faster and under a higher degree of supersaturation, incorporate more impurity molecules. Furthermore, the smaller crystals may be produced by the breakage of larger crystals at defective sites during crystallization. Because impurities tend to segregate at mechanically defective sites (12), impurities may be released when larger crystals break to become smaller crystals.

Water, the primary constituent of the crystallization medium, may be entrapped in the growing crystals to form liquid inclusions or may be sorbed on the surface and in the amorphous regions. For crystalline solids, the amount of sorbed water is usually very small (13). In the systems consisting of +PC doped with -EC and AP doped with PAA, water does not form inclusions. The water content is small (< 1%) and is independent of particle size in these two systems. However, AA is known to form aqueous inclusions (6). The relative amount of included water increases with increasing size of the particles in a single batch (Fig. 2), which is in agreement with a previous report (14). The formation of liquid inclusions has a mechanism different from the incorporation of impurity molecules. Liquid inclusion is often the result of an unstable crystal interface, which grows dendritically. It has been demonstrated that the probability of forming inclusions increases with increasing crystal size and increasing crystal growth rate (14), which explains why larger particles are more likely to form inclusions.

Impurity dissolved in the included liquid accounts for only a small part of the impurity incorporated. The maximum amount of impurity dissolved in the included liquid is calculated by the following equation:

$$P = x_w \cdot x_{SA} \quad (2)$$

where x_w is the mole fraction of included water, and x_{SA} is the mole fraction of the succinic acid, added as an impurity to the crystallization medium, with respect to the solvent. We find that impurities present in the included solvent account for less than 1% of the incorporated impurity. Therefore, most of the impurity molecules are not incorporated through the formation of a liquid inclusion, which is in agreement with the findings of a previous report (15).

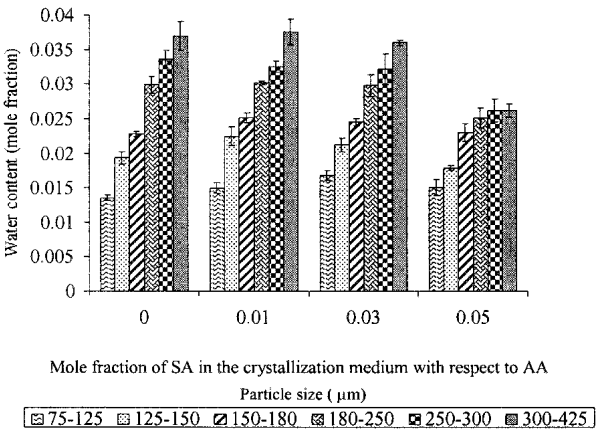

Fig. 2. Content of water included in adipic acid (AA) crystals doped with succinic acid (SA). The particle size increases from left to right: 75–125 μm, 125–150 μm, 150–180 μm, 180–250 μm, 250–300 μm, 300–425 μm. The vertical bars represent the standard errors (n = 4).

CONCLUSIONS

In three model systems, namely +PC doped with -EC, AP doped with PAA, and AA doped with SA, larger crystals incorporate more impurity molecules than smaller crystals in a single batch. This phenomenon may be general during crystallization from solution by cooling a system with a segregation coefficient less than 1. For such a system, the differences between particles of different sizes may be summarized as the follows: (1) larger crystals grow faster than smaller crystals; (2) larger crystals grow primarily at higher degrees of supersaturation; (3) larger crystals may break to become smaller crystals with the release of incorporated impurity. All these three factors explain the greater incorporation of impurities by larger particles. The amount of entrapped water in AA crystals also increases with an increase of crystal size, but the increase in the concentration of incorporated SA is not related to the increase of the amount of included water.

ACKNOWLEDGMENT

We thank Dr. Ronald A. Siegel for asking the questions that we have tried to answer in this communication.

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