Spherical Crystallization: Direct Spherical Agglomeration of Salicylic Acid Crystals During Crystallization

Abstract. *Direct spherical agglomeration of salicylic acid crystals during crystallization is described. The needle-like salicylic acid crystals simultaneously form and agglomerate in a mixture of three partially miscible liquids, such as water, ethanol, and chloroform, with agitation. The agglomerates can be made directly into tablets because of their excellent flowability. Spherical crystallization could eliminate the usual separate agglomeration step after crystallization and may be adaptable to other pharmaceutical and chemical systems.*

Fine crystals are preferred over large crystals of poorly soluble drug substances as they provide greater bioavailability (*1*). However, micronization of crystals can change micromeritic properties such as compressibility, packability, and flowability and thus prevent efficient powder processing (*2*). To overcome this problem, the micronized drug is mixed with filler and then agglomerated by a granulation technique (*3*). It would be more efficient to transform the microcrystalline drug itself into an agglomerated form during the crystallization process as the last step of the synthesis. To our knowledge, no crystallization technique that accomplishes this has been developed. We report here a novel agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process. The resulting agglomerates can have improved flowability and compressibility.

Salicylic acid was used as the model drug because of its characteristic needle-like crystal shape and poor flowability, which prevents direct compression of the crystals. First we developed a technique for the direct agglomeration of salicylic acid crystallized in ethanol. Capes and co-workers (*4*) and Kawashima and co-workers (*5*) agglomerated fine dispersed particles in liquid by adding a small amount of a second, immiscible liquid, which preferentially wetted the particles and caused them to form agglomerates. By using this method, it was possible to agglomerate salicylic acid in water with chloroform, which preferentially wetted the salicylic acid (*6*). However, it was not possible to use chloroform as the wetting liquid in ethanol, since chloroform is miscible with ethanol. We assumed that when a proper amount of water was added to a mixture of chloroform and ethanol, chloroform might be liberated from the system. A triangular diagram showing the solubility of chloroform in water-ethanol mixtures was prepared, as shown in Fig. 1 (*7*). Salicylic acid was crystallized in ethanol. The crystals were agglomerated by adding appropriate amounts of water and chloroform, the proportions being determined from the triangular diagram.

Salicylic acid (500 mg) was dissolved in ethanol (1 to 5 ml) in a stoppered test tube in a water bath at 60°C. The system was cooled to room temperature, 10 ml of water was added, and after 1 hour crystallization was complete. Chloroform (0.3 to 0.5 ml) was then added to the mixture, and the system was agitated horizontally at 200 to 400 rev/min for 10 minutes. With this procedure, the crystals formed spherical agglomerates with diameters of 1 to 8 mm. In the absence of chloroform, dispersed needle-like crystals of the drug were obtained. With increasing ethanol content in the agglomeration system, the agglomerates became irregular in shape and their hardness decreased. With 5 ml of ethanol the crystals were found to aggregate. The proportions of the three liquids which we found to yield acceptable agglomerates are shown by the shaded region in Fig. 1. The crystals produced in a mixture of the three liquids with proportions in this region were simultaneously transformed into spherical aggregates during the crystallization process. Hence we refer to this technique as spherical crystallization.

To obtain a round compacted agglomerate of crystals, we carried out another spherical crystallization in a cylindrical vessel (8.4 cm in diameter, 11.0 cm long, 500 ml in volume). Ethanol solution (58 ml) containing salicylic acid (12.5 g) at 40°C was poured into a mixture of water (250 ml) and chloroform (9.0 ml), agitated by a turbine-type agitator with six blades (4.8 cm in diameter) and thermally controlled at 5°C (*8*). When the system was agitated at 600 rev/min for 1 hour, dense spherical agglomerates were obtained, as shown in Fig. 2a. Their aver-

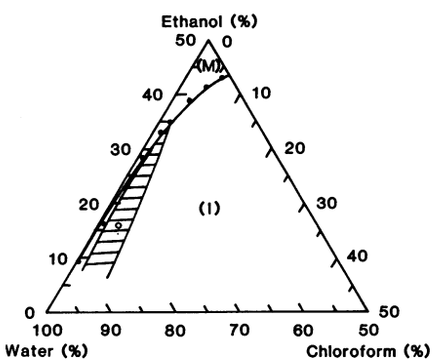
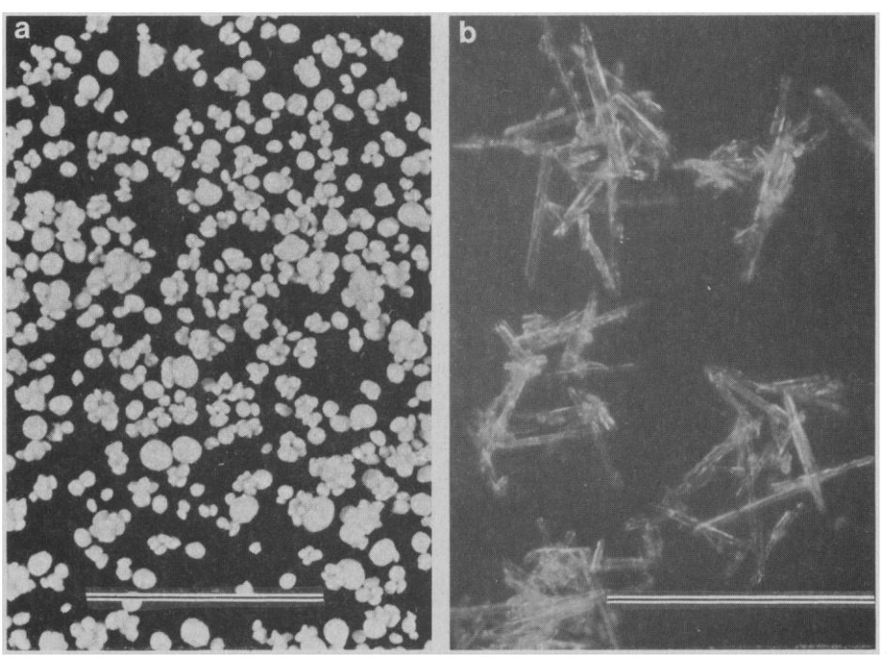


Fig. 1 (left). Diagram showing the solubility of chloroform in the ethanol-water mixture. Chloroform was miscible (*M*) in the region above the solid line and immiscible (*I*) in the region below the solid line. Acceptable spherical crystallization occurred in the shaded region. Fig. 2 (right). Micrographs of spherically agglomerated crystals (a) and primary crystals without spherical crystallization (b). Scale bars represent 10 mm in (a) and 200 μm in (b).



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age size was 930 μm, with a range from 460 to 1210 μm (*9*). For comparison, Fig. 2b shows the crystals produced in the system without chloroform, which are needles 120 μm in average length. Microscopic examination showed that the agglomerate was composed of minute needle-like crystals. We anticipated that polymorphism or solvation might occur during the agglomeration process. However, we confirmed that this was not the case in the present system by means of an x-ray and spectrophotometric inspection. The agglomerate size was easily controlled by adjusting the agitation speed, temperature of the system, chloroform content in the system, and residence time. Agglomerate size decreased with increased agitation speed and with decreased chloroform content. Increasing the temperature difference between the ethanol solution and the mixture of chloroform and water resulted in a decrease in the agglomerate size.

The micromeritic properties of the agglomerates in Fig. 2a were investigated. The angle of repose (*10*) was 36° and the density of closest packing (*11*) was 0.488 g/cm³; the corresponding values for the crystals in Fig. 2b were 51° and 0.160 g/cm³. The agglomerated crystals could be formed into tablets by direct compression (*12*). It was not possible to compress the unagglomerated crystals because of their poor flowability. The hardness (*13*) and weight (*14*) values of the tablets formed from agglomerated crystals could meet the requirements for practical use.

In preliminary studies we found that other three-component systems such as benzene-ethanol-water, carbon tetrachloride–ethanol-water, and chloroform-acetone-water could be used instead of the present water-ethanol-chloroform system. This suggests that spherical crystallization might occur generally when a suitable mixture of three partially miscible liquids is employed as the crystallization solvent. Further, we expect that spherical crystallization may be adapted to a wide variety of drugs and chemicals.

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References and Notes

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6. The contact angles of chloroform and water to salicylic acid were 0° and 105°, respectively.
7. Mixtures of ethanol, water, and chloroform in stoppered measuring cylinders (25 ml) were shaken and allowed to stand for 24 hours to determine the solubility of chloroform in ethanol-water mixtures with various proportions.
8. The proportions of the mixture of three solvents used are indicated by the open circle in Fig. 1.
9. Particle sizes were measured by sieve analysis, using the standard sieves specified in the Japanese Pharmacopeia.
10. The angle of repose was measured by pouring the powder onto a plate 10 cm in diameter.
11. The packing density was measured by tapping the powder into a measuring cylinder (50 ml).
12. Tablets were prepared with a single-punch machine (Erweka-GmbH, Frankfurt am Main, West Germany); their average weight and dimensions were 0.382 g, 10.05 mm in diameter, and 4.14 mm thick.
13. Hardness was measured diametrically by a moving plate hardness tester (Kyowa Seiko Co., Tokyo, Japan). The average value was 3.57 ± 0.63 kg.
14. The maximum difference from the mean tablet weight of 20 tablets was 2.56 percent.

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Calcium Carbonate Hexahydrate from Organic-Rich Sediments of the Antarctic Shelf: Precursors of Glendonites

Abstract. *Large euhedral crystals of calcium carbonate hexahydrate were recovered from a shelf basin of the Bransfield Strait, Antarctic Peninsula, at a water depth of 1950 meters and sub-zero bottom water temperatures. The chemistry, mineralogy, and stable isotope composition of this hydrated calcium carbonate phase, its environment of formation, and its mode of precipitation confirm the properties variously attributed to hypothetical precursors of the glendonites and thereby greatly expand their use in paleoceanographic interpretation.*

Glendonites belong to a group of unusual calcitic pseudomorphs after original minerals of unknown composition. They are associated with glacial marine deposits of Permian to Recent age and are thought to have formed syngenetically from organic-rich muds at sub-zero temperatures in polar environments (*1–3*). Therefore, they may be important indicators of the regional distribution and temperature history of polar water masses (*4*).

We report here on what we believe is the first observation of a highly hydrated calcium carbonate mineral from anoxic, organic-rich sediments of the Bransfield Strait, Antarctic Peninsula, which has all the attributes of the elusive glendonite precursor (*5*). This mineral phase is identical to synthetic $CaCO_3 \cdot 6H_2O$, known for over 100 years (*6, 6a*), and to the mineral ikaite from its single known occurrence in a carbonatite rock at the Ika Fjord, Greenland (*7*). The large euhedral single crystals from the Bransfield Strait sediments appear to be precipitated authigenically from CO_3^{2-} supplied from the early diagenetic decomposition of sedimentary organic matter and calcium from the interstitial seawater.

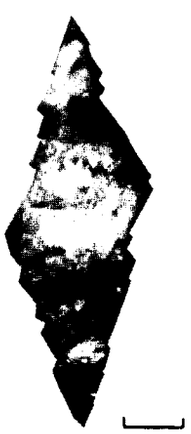

Fig. 1. Single crystal of calcium carbonate hexahydrate from Bransfield Strait sediments. This is a hydrated phase of calcite which forms at sub-zero temperatures and elevated pressures from metabolic carbonate and seawater calcium. It is the first reported occurrence of this phase forming syngenetically in organic-rich, rapidly accumulating sediments. Its crystal structure is monoclinic and identical to that of synthetic $CaCO_3 \cdot 6H_2O$, and its chemical composition is similar to that of the mineral ikaite, reported from a carbonatite rock submerged in the Ika Fjord, Greenland. Scale, 1 cm.

Crystal specimens of identical size and shape were discovered in two narrow zones at depths of 205 and 714 cm in a 12-m-long sediment core. The fresh minerals were initially amber in color and translucent; they occurred as elongate crystals with perfectly shaped bipyramidal terminations (Fig. 1). At laboratory temperature onboard ship, the interior became cloudy within hours and the mineral physically disintegrated into a mush of water and small whitish crystals, later identified as calcite. The terminations, edges of the bipyramids, and certain crystal fragments, however, remained intact for longer periods and could therefore be preserved by cold storage (*8*).

Subsamples of the hydrated crystals were analyzed for total calcium and total weight loss after ignition (*9*). With one exception, all analyses correspond to within ≤1 percent of the ideal composition of $CaCO_3 \cdot 6H_2O$ (in percentage by weight): CaO, 26.95; CO_2, 21.14; and H_2O, 51.92 (Table 1).

Prior to the analysis of hydrated specimens, dehydrated subsamples, stored at

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