

Communications to the Editor

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SPHERICAL AGGLOMERATION OF AMINOPHYLLINE CRYSTALS DURING REACTION IN LIQUID BY THE SPHERICAL CRYSTALLIZATION TECHNIQUE

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Spherically agglomerated crystals of aminophylline were prepared directly during reaction in liquid by the "spherical crystallization" technique. Agitation of a mixture of chloroform, ethanol (or methanol) and water containing ethylenediamine and theophylline yielded spherically agglomerated crystals, the size of which was determined by the agitation speed of the system and the water content in the mixture.

KEYWORDS—spherical crystallization; aminophylline; agglomeration in liquid; spherical agglomerate; phase separation; partially miscible liquid mixture

In a previous paper¹⁾ we reported development of a novel technique for the direct agglomeration of sodium theophylline crystals produced by a salting-out in liquid. The principle of the technique was developed by combining the "Wet Spherical Agglomeration"^{2,3)} technique with the phase separation phenomenon⁴⁾ in a partially miscible liquid mixture, e.g. a water - ethanol - chloroform system. By suitably changing the chloroform fraction in the mixture, the system was separated and a small amount of water liberated. This water acted as a collecting liquid or bridging liquid,¹⁻³⁾ which preferentially wetted the sodium theophylline crystals and transformed them into a spherical form. It was also found that needlelike salicylic acid crystals were spherically agglomerated during the crystallization employing this technique.⁵⁾ This technique was termed "spherical crystallization", since the resultant crystals transformed into a spherical form. Previous studies^{1,5)} suggested that spherical crystallization might occur generally when a suitable mixture of three partially miscible liquids is employed as the crystallization solvent. Further, it is expected that spherical crystallization may be adaptable to a wide variety of drugs and chemicals. The present study describes a further development of the "spherical crystallization" technique into a novel preparation method of spherically agglomerated aminophylline crystals during reaction in liquid, an extraordinary advance in the conventional preparation process.

Ethylenediamine (3.0 ml, 0.0448 mol) was added to a mixture of chloroform (60 ml), ethanol (15 ml) and distilled water (6.0 - 6.6 ml) in a round-bottom glass vessel thermally controlled at 20 °C. Then theophylline (9.3 g, 0.0516 mol) was added to the mixture. The system was agitated by a turbine-type stirrer with four blades (diam. 5 cm) at 300 to 700 rpm. An other experiment was undertaken by replacing ethanol with methanol (12 ml). In this process, some modifications in the formulation were required to obtain satisfactory results. The amounts of theophylline and water used were changed to 6.0 g (0.0333 mol) and 3.1 to 3.7 ml respectively. Agglomeration procedure followed was the same as that used in the ethanol system. After 10 to 30 minutes' agitation of the system, fine white crystals appeared, and these were immediately agglomerated into a spherical form. The size of the spherically agglomerated crystals increased gradually with residence time. After a few hours, an equilibrium state was attained. During the process, some crystals adhered to the vessel. When these adhered crystals were removed, the agglomerated crystals started to grow again, more rapidly than at the stage before removal of the adhered crystals. The representative changes in the size

distribution of the crystals with increased residence time are depicted in Fig. 1. The agglomerated crystals were separated and dried in a desiccator with sodium hydroxide.

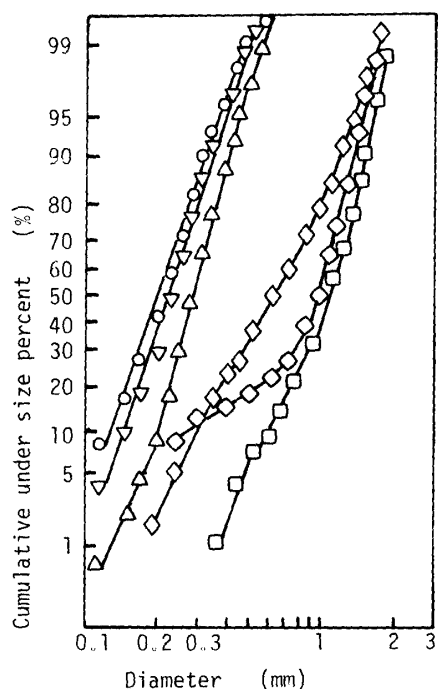


Fig. 1. Size Distributions of the Agglomerated Crystals Produced in Methanol Containing 3.5 ml of Water at 700 rpm as a Function of Residence Time

Residence time (h) from the start:

○, 1 ▽, 2 and △, 4

Residence time (min) after removal of the agglomerates adhering to the vessel: ◇, 5 ◊, 20 and □, 60.

A representative photograph of the resultant products is displayed in Fig. 2 (a). The scanning electron microscopic photographs of the surface of agglomerated crystals prepared by the present method and the aminophylline crystals prepared by a conventional method⁶⁾ in absolute ethanol solution alone are shown in Figs. 2(b) and 2(c) respectively. It was found that the agglomerate was composed of fine crystals, almost the same shape as the aminophylline crystals in Fig. 2(c). The agglomerated crystals were chemically identified as theophylline-ethylenediamine complex by IR and X-ray diffraction analyses. Theophylline⁷⁾ and ethylene-diamine⁸⁾ contents of the agglomerates converted to the anhydride form were 83.5 to 83.8 % and 15.1 to 15.2 % respectively. These values meet the theophylline and ethylenediamine contents standards for the aminophylline specified in the JP.

It was found that the average size of the agglomerated crystals could be easily controlled by changing the agitation speed and the amount of water used. The average

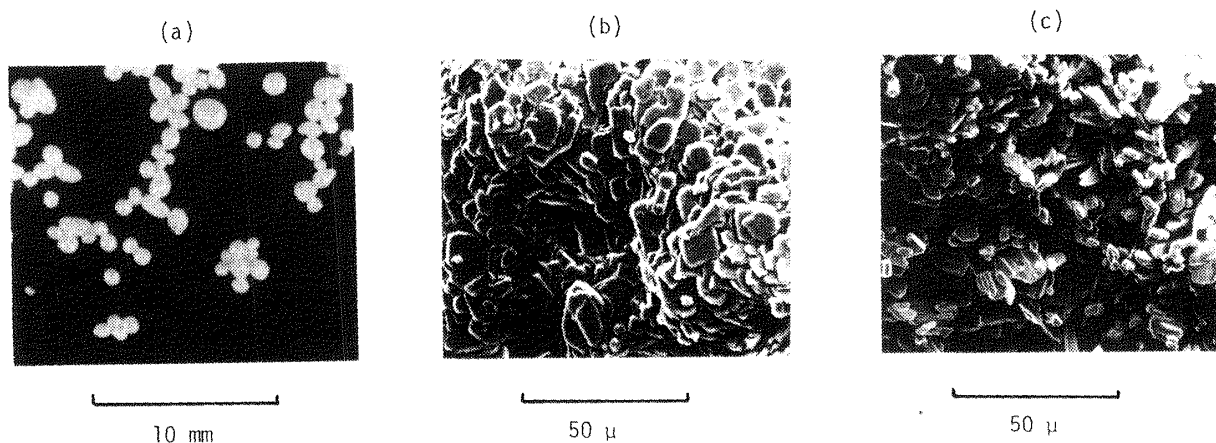


Fig. 2. Photographs of Agglomerated Crystals and Conventionally Prepared Aminophylline Crystals

- Spherical agglomerated crystals prepared in ethanol at 700 rpm and 1 h in residence time after removing the agglomerates adhering to the vessel.
- Surface topography of the agglomerated crystals prepared in ethanol at 500 rpm and 3 h in residence time after removing the agglomerates adhering to the vessel.
- Aminophylline crystals prepared by a conventional method. Theophylline (24.7 g) and ethylenediamine (9.2 ml) in 100 ml of absolute ethanol were agitated at 600 rpm for 14 h.

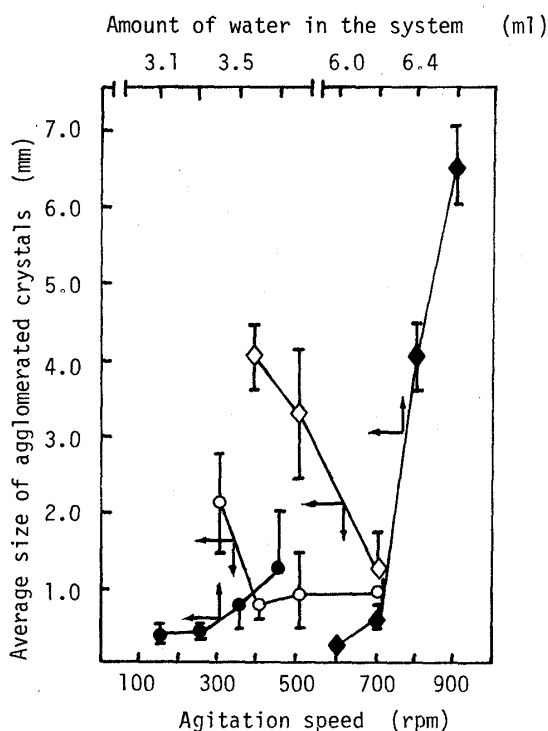


Fig. 3. Effects of Agitation Speed and Amount of Water in the System on Average Size(50 %) of Agglomerated Crystals

The size range between 16 and 84 % is described by deviation bars. The medium for agglomeration is methanol (○,●) or ethanol (◇,◆). The residence time is one hour after removal of the agglomerates adhering to the vessel.

The usual preparation process of aminophylline for compounding into a dosage form involves several steps including synthesis, crystallization and agglomeration. However, the present technique enables the above steps to be combined into only one step. The resultant aminophylline crystals were free-flowing and directly compressible due to their spherical shape. Furthermore, this technique is simple and less expensive. These may be an advantages for developing it on a commercial scale.

REFERENCES AND NOTES

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size of the agglomerate decreased with an increase in agitation speed, as seen in Fig. 3. Increased agitation speed raised the inertia force, which split the agglomerated crystals and resulted in a decrease in agglomerate size. The agglomerates increased in the size with an increase in the amount of water in the system (Fig. 3). When the water contained in the system was in excess, the system was separated clearly into a chloroform phase and an aqueous phase in which the resultant crystals were dispersed. When the water content in the system was low, the system became a single organic phase without water separating, in which agglomeration did not occur. This finding suggested that the crystals produced by the reaction were agglomerated immediately only when a suitable amount of water was separated from the system, acting as a collecting liquid for the crystals as found in previous papers.¹⁻³⁾ It was found that the agglomeration of crystals in ethanol was controlled more effectively than that in methanol by the above two factors, i.e., the agitation speed and the amount of water in the system.