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Development of Spherical Crystallization Technique and Its Application to Pharmaceutical Systems

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Abstract □ A novel agglomeration technique, termed "Spherical Crystallization Process", which can transform directly the fine crystals produced in the crystallization or the reaction process into a spherical shape was developed. By this technique, needle like crystals such as salicylic acid were transformed into free flowing and directly compressible agglomerates. Spherically agglomerated aminophylline crystals were obtained directly from the reaction system, which could reduce the preparation processes, e.g. synthesis, crystallization and agglomeration, into only one step. Sodium theophylline monohydrate agglomerates were prepared by salting out, the rate process of which was described by a first order kinetics. Agglomerated crystals of ndw complex of indomethacin-mepirizole were prepare with this technique; an improved therapeutic effect of the resultant crystals was expected.

Fine crystals are preferred over large crystals of poorly soluble pharmaceuticals as they provide greater bioavailabiliity. However. micronization of crystals frequently prevents efficient powder processing due to the poor compressibility, packability of flowability of the micronized crystals. To overcome this problem, the micronized drug is mixed with filler and then agglomerated by a granulation technique. 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.

Development of a novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during the crystallization process has been desired. In the present review, a novel agglomeration technique, termed "spherical crystallization", that accomplishes the above requirement is reported.

Development of Spherical Crystallization

Firstly spherical crystallization was developed in ethanol using salicylic acid as the model drug because of its characteristic needle-like crystal shape and poor flowability, which prevents direct compression of the crystals. It was found that finely dispersed particles in liquid were agglomerated by adding a small amount of a second, immiscible liquid, which preferentially wetted the particles and caused them to form agglomerates[1,2]. By using this method, it was possible to agglomerate salicylic acid in water with chloroform, which preferentially wetted the salicylic acid. However, it was not possible to use chloroform as the wetting liquid in ethanol, since chloroform is miscible with ethanol. It was 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[3]. Salicylic acid was crystallized in ethanol. The crystals were agglomerated by adding appropriate

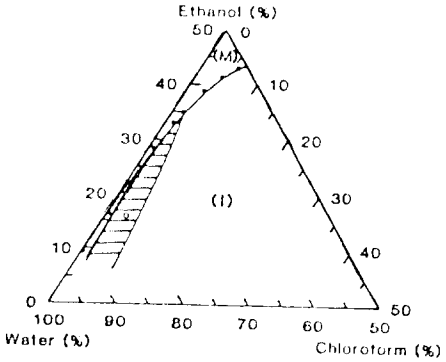

Fig. 1: Diagram showing the solubility of chloroform in the ethanol-water mixture. Chloform was miscible (*M*) in the region above the solid line and immiscible (*I*) in the region below the solid line. Acceptable spherical crystallization occurred in the shaded region.

amounts of water and chloroform. The proportions of the solvent mixture were determined from the triangular diagram.

Salicylic acid was dissolved in ethanol at 60°C. The system was cooled to room temperature, water was added to complete the crystallization. Chloroform was then added to the mixture, and the system was agitated. With this procedure, the crystals formed spherical agglomerates with diameters of 1 to 8 mm. Without chloroform, only 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. The proportions of the three liquids which the author 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 agglomerates during the crystallization process. This technique was termed spherical crystallization due to the spherical form of the resultant crystals. To obtain a round compacted agglomerate of crystals, the "spherical crystallization" in a cylindrical vessel was carried out. Ethanol solution containing salicylic acid at 40°C was poured into a mixture of water and chloroform, agitated by a turbine type agitator and thermally controlled at 5°C. When the system was agitated for 1 hour, dense spherical agglomerates were obtained, as shown in Fig. 2a[3]. For comparison, Fig 2b shows the needle-like crystals produced in the system without chloroform. Microscopic examination showed that the agglomerate was composed of minute needle-like crystals. 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. It was found that other three component systems such as benzene-ethanol-water, carbon tetra-chloride-ethanol-water and chloroform-acetone-water could be used instead of water-ethanol-chloroform system.

Application of Spherical Crystallization to Pharmaceutical Systems: Preparation of Spherically Agglomerated Crystals of Aminophylline (Theophylline ethylenediamine Complex)

The usual preparation process of aminophylline for compounding into a dosage form involves several steps including synthesis, crystallization and agglomeration. It was desirale to reduce the above steps into only one step using the spherical crystallization technique. A mixture of organic solvent, ethanol and water was used as the crystallization solvent. The organic solvents used were chloroform, 1-hexanol, isopropyl acetate, iso-butyl acetate, isoamyl acetate, ben-

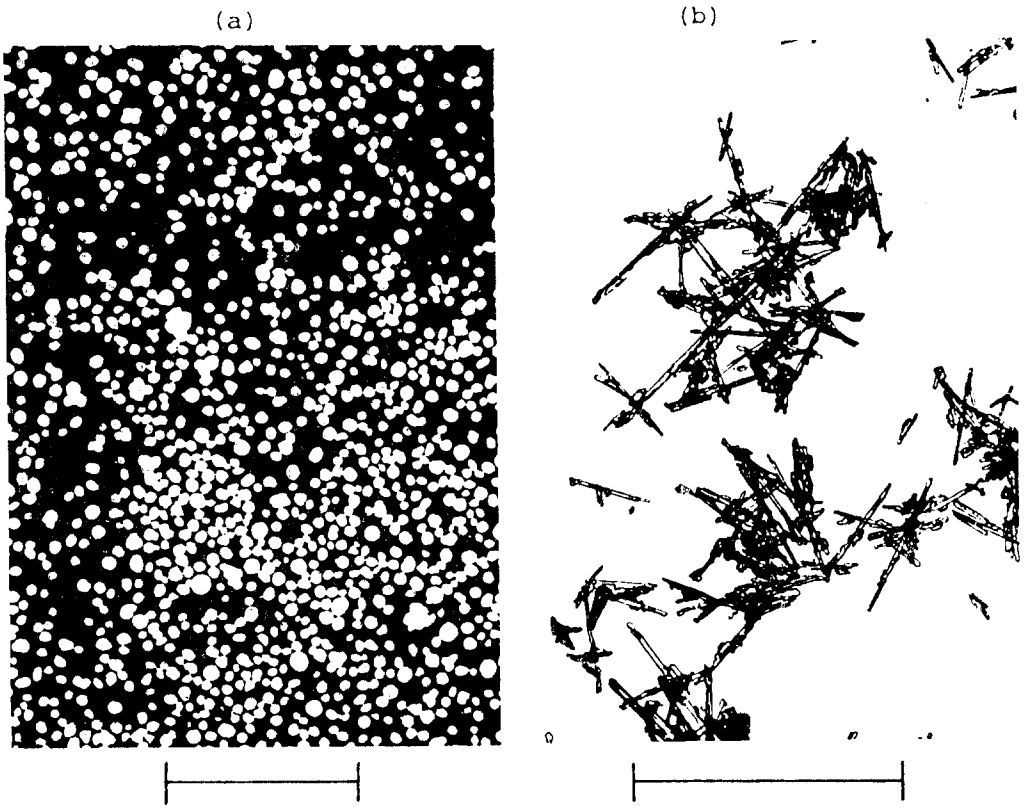

Fig. 2: Micrographs of spherically agglomerated crystals (a) and primary crystals without spherical crystallization (b). Scale bars represent 10mm in (a) and 200μm in (b).

zene, toluene, n-hexane or n-heptane. Ethylenediamine and theophylline were dissolved in the mixture and agitated for a few hours with a paddle type agitator. Fine white crystals formed and agglomerated simultaneously into spheres.

It was found that the agglomerated crystals had three different crystalline forms, described here as the α, β, and γ-forms. The β-form was identical with aminophylline specified in JP (X), while the α and γ-forms were different. Infrared spectroscopy and X-ray diffraction analyses in Fig. 3[4] suggested that the α and γ-form of the agglomerated crystals were theophylline-ethylenediamine complexes with different crystalline forms. The water content in the agglomerates was classified in the following way: $<0.5\%$, 5-6% and 8-9%. Irrespective of the water content, the ratio of theophylline and ethylenediamine remained essentially the same. The water content of 5-6% and 8-9% corresponded approximately to 1 and 2.5 moles of water of crystallization, respectively. This suggesed that the β and γ-forms of the agglomerated crystals contained 1 and 2.5 moles of water of crystallization, respectively. The ethylenediamine content in the agglomerated crystals increased with increasing the amount of ethylenediamine used. This indicated that the ethylenediamine contents in the agglomerated crys-

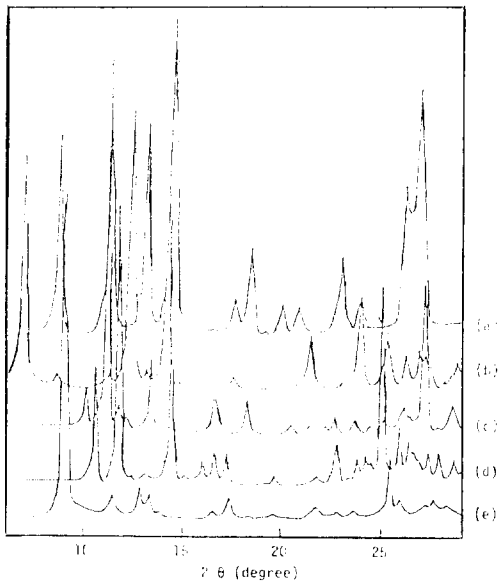

Fig. 3: X-ray powder diffraction patterns of agglomerates, anhydrous theophylline, theophylline monohydrate and aminophylline.
(a) Theophylline monohydrate
(b) Anhydrous theophylline
(c) α-form of agglomerate
(d) β-form of agglomerate, aminophylline
(e) γ-form of agglomerate

tals could be adjusted that of aminophylline specified in JP(X) by changing the amount of ethylenediamine used.

It was found that the average size of the agglomerated crystals could be easily controlled by changing the agitation speed and the amound of water used. The size of the agglomerated crystalls decreased with an increase in agitation speed. Increased agitation speed raised the inertia force, which split the agglomerated crystals and resulted in a decrease in agglomerate size. The agglomerated crystals increased in the size with an increase in the amount of water in the system. The agglomerated aminophylline crystals were free-flowing and directly compressible due to their spherical form. Furthermore, this technique is simple and less expensive. These may be an advantages for developing it on a commercial scale.

Spherical Crystallization of Sodium Theophylline Monohydrate

Direct agglomeration of sodium theophylline monohydrate crystals produced by salting out in a liquid was carried out in a stirred vessel. Mixtures of chloroform and ethanol in various mixing ratios were placed in round-bottom flask thermally controlled at 30°C. Ethylenediamine solutions of theophylline at various concentrations were prepared separately. Ethylenediamine solution of theophylline and an aqueous solution of sodium chloride were added to chloroform-ethanol mixture with stirring at a various speed using a screw-type agitator. After agitation of the system for 20~30 minutes, fine white crystals appeared and were immediately agglomerated into a spherical shape. The size of the spherical agglomerate increased gradually and attained an equilibrium state after 10~15 hours agitation. The dried products were directly compressible due to their characteristic spherical forms. The products were identified chemically as a mixture of sodium theophylline monohydrate and sodium chloride by X-ray analysis and spectrophotometry.

The spherical crystallization kinetics were described in terms of the rate of decrease in the residual concentration of theophylline in the crystallization solvent. After an induction period (t_i), the residual concentration of theophylline in the medium decreased rapidly and then gradually approached an equilibrium state. It was found that the rate of decrease in residual concentration was a function of the agitation speed of the system and of the concentration difference between the initial and the eguilibrium state. The rates of decrease in residual concentration for both spherical cry-

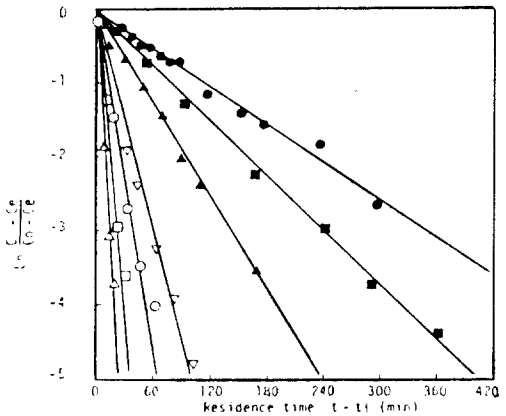

Fig. 4: Kinetic plots of crystallization. Ordinary crystallization-composition of solvent(%): aqueous fraction 16.0, ethanol fraction 84.0; agitation speed (rpm): △, 1050; □, 650; ○, 400; ▽, 250. Spherical crystallization-composition of solvent (%): aqueous fraction 16.0, ethanol fraction 55.8, chlorofrom fraction 28.2; agitation (rpm): ▲, 1050; ■, 650; ●, 400. Initial concentration of theophylline in the solvent; 0.0488 (mol/*l*).

stallization and a conventional crystallization without agglomeration increased with increase in the agitation speed and in the concentration difference between the initial and the equilibrium state. It was found that the kinetics of crystallization followed the first-order rate equation (1) as shown in Fig. 4[5], irrespective of the crystallization method, i.e. spherical crystallization or ordinary crystallization.

$$\ln \frac{C-Ce}{Co-Ce} = -K(t-t_i) \quad \cdots\cdots\cdots\cdots\cdots\cdots (1)$$

where C is the residual concentration of theophylline in the medium at residence time t, and Co and Ce are the initial and the equilibrium concentrations. K is the crystallization rate constant. The rate constant increased linearly with the agitation speed. The effect of agitation speed on the rate constant was stronger for the ordinary crystallization than for the spherical crystallization. The finding indicated that the generation of crystal nuclei in the ordinary crystallization depended more strongly on the agitation intensity of the system than in the spherical crystallization.

Preparation of Spherically Agglomerated Crystals of New Complex of Indomethacin-mepirizole

Mixtures of indomethacin (stable form γ) and mepirizole (anhydrate) in various mixing ration were dissolved in ethylacetate at 70°C. After the solution of the mixture was cooled to 10°C, it was poured into water at the same temperature, The system was agitated with a turbine type agitator for 20 minutes. Yellowish spherically agglomerated crystals yielded Identifications of the agglomerated crystal by means of X-ray diffraction analysis and infrared spectrophotometry suggested that a new complex of indomethacin-mepirizole was formed. The phase diagram of the agglomerated crystals with various compositions of indomethacin and mepirizole was prepared using a differential scanning calorimeter (DSC). When the molecular ratio of indomethacin to mepirizole=2 : 1 in the agglomerated crystels. eutectic and liquid lines coincided as shown in Fig. 5[6]. The agglomerated crystal with this molecular ratio exhibited a sharp endothermic peak at 113°C in the DSC thermogram, while the physical mixture of indomethacin and mepirizole (molecular ratio= 2 : 1) and the other agglomerated crystals revealed two peaks in Fig. 5. When selecting the proper composition of the mixture dissolved in ethylacetate, the resulting agglomerated crystal formed a new complex of indomethacin-mepirizole (molecular ratio=2 : 1). An improved therapeutic effect of the new complex might be expected, since it was reported[7] that coadministration of mepirizole reduced the reverse action of indomethacin and improved its therapeutic action.

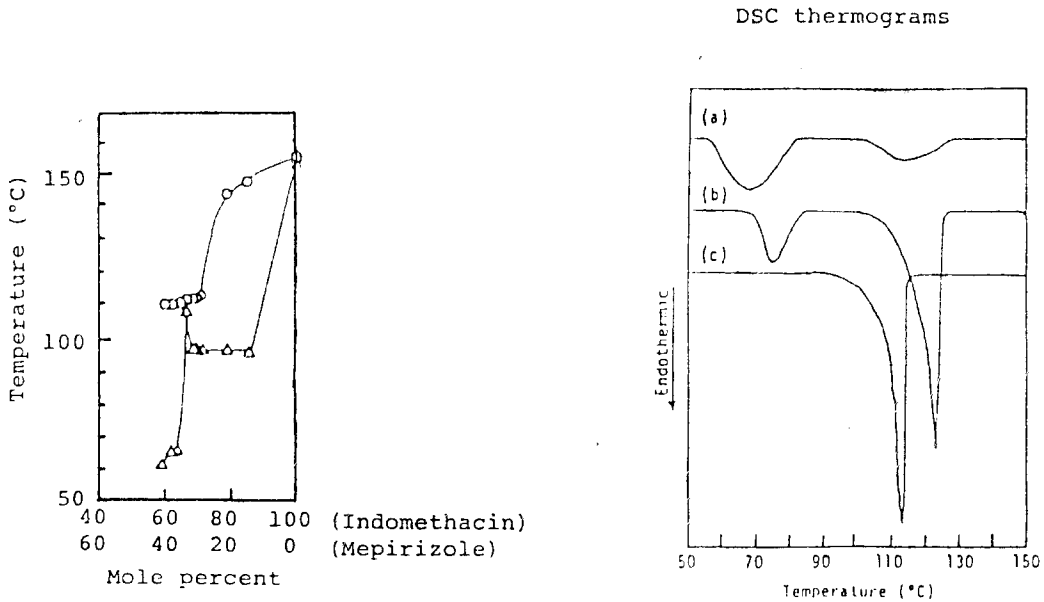

Fig. 5: Phase diagram of spherically agglomerated crystals by DSC. Molecular ratio; IMC:MEP=2:1
(a) IMC(β)/MEP physical mixture
(b) The spherical agglomerated crystals
(c) The spherical agglomerated crystals

Prospect of the Spherical Crystallization

The spherial crystallization can occur generally when a suitablle mixture of two or three partially miscible liquids is employed as the crystallization solvent. Further, this technique can be adapted to a wide variety of drugs and chemicals.

The spherical crystallization technique enables several processes including synthesis, crystallization, separation, agglomeration etc. to be combined only one process. Reducing preparation step can save time and cost. The agglomerated crystal size can be suitably controlled to compound easily the crystals into the pharmaceutical formulaton. The flowability and compressibility of the agglomerated crystals can be improved in such that they can be directly tabletted. In addition, polymorphism, solvation or complexation with another dissolved compound may occur during the agglomeration process. Using this phenomena, it is possible to convert the crystalline form of drug to a desirable polymorphic form or to prepare a new complex of drug during the crystallization for obtaining better bioavailability.

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