# Spherical crystallization and pharmaceutical systems

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*Direct spherical agglomerations of pharmaceutical crystals accompanied with and without polymorphism, solvation or complexation, during crystallization or reaction are described. The resultant agglomerated crystals can be compounded directly into pharmaceutical formulations without further processing, such as granulation.*

## Why is spherical crystallization needed?

Fine crystals are preferred to large crystals of poorly soluble pharmaceuticals as they provide greater bioavailability. However, micronization of crystals frequently prevents efficient powder processing due to the poor compressibility, packability or 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.

A novel agglomeration technique that would transform crystals directly into a compacted spherical form during the crystallization process has long been desired. In this review, a new technique termed 'spherical crystallization', which meets the above requirement, is reported.

## Development of spherical crystallization

Spherical crystallization was first developed 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 particles finely dispersed in a liquid were agglomerated by adding a small amount of a second, immiscible, liquid that preferentially wetted the particles[1,2]. By using this method, it was possible to agglomerate salicylic acid in water with chloroform, which preferentially wetted the salicyclic acid. However, it was not possible to use chloroform as the wetting liquid with ethanol, since the two liquids are miscible. It was assumed that when a certain amount of water is added to a mixture of chloroform and ethanol, chloroform is liberated from the system. A triangular diagram showing the solubility of chloroform in water–ethanol mixtures was prepared as shown in Fig. 1 (Ref. 3). Salicylic acid was crystallized from ethanol and the crystals were agglomerated by adding appropriate 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 and 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 1–8 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 these media were simultaneously transformed into spherical agglomerates during the crystallization process. This technique was termed spherical crystallization. To obtain a round compacted agglomerate of crystals, 'spherical crystallization' was carried out in a cylindrical vessel. An ethanolic 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 h, dense spherical agglomerates were obtained, as shown in Fig. 2a (Ref. 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

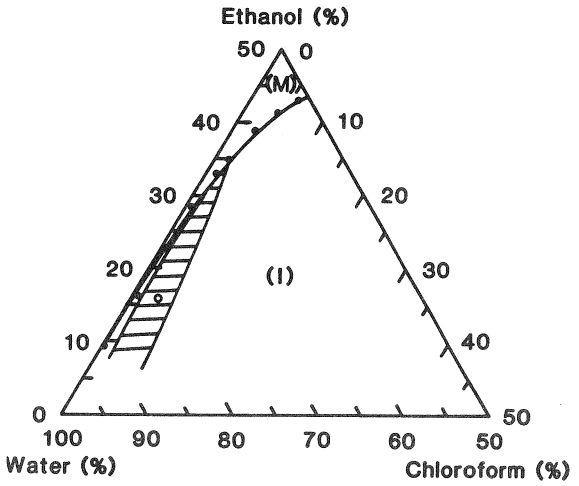


*Fig. 1. Diagram showing the solubility of chloroform in the ethanol–water mixture. Chloroform was miscible (M) in the region above the solid line and immiscible (I) in the region below the solid line. Acceptable spherical crystallization occurred in the shaded region.*

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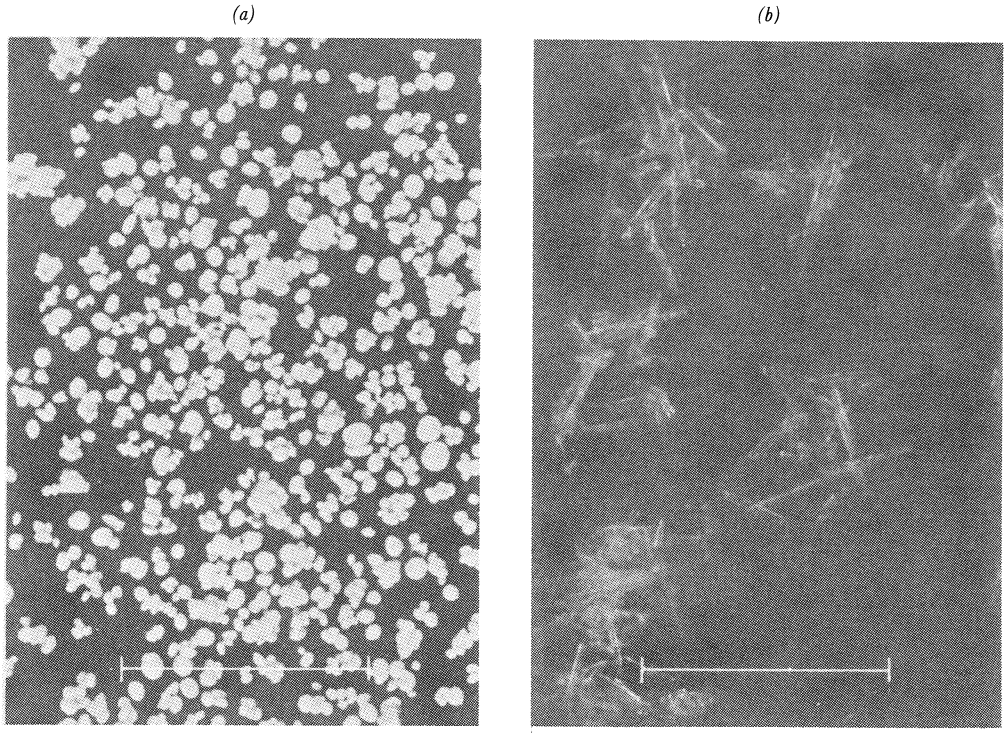


*Fig. 2. Micrographs of spherically agglomerated crystals (a) and primary crystals without spherical crystallization (b). Scale-bars represent 10 mm in (a) and 200 μm in (b).*

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 tetrachloride–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 process by which aminophylline is prepared involves several steps, including synthesis, crystallization and agglomeration. It was desirable to reduce the above steps into a single stage 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, hexan-1-ol, isopropyl acetate, isobutyl acetate, isoamyl acetate, benzene, 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 to aminophylline as specified in the Japanese Pharmacopoeia X, while the α- and γ-forms were different. Infrared spectrometry and X-ray diffraction analyses in Fig. 3 (Ref. 4) suggested that the α- and γ-forms 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. Water contents of 4–6% and 8–10% corresponded approximately to 1 and 2.5 moles of water of crystallization, respectively. This suggested that the β- and γ-forms of the agglomerated crystals contained 1 and 2.5 moles of water of crystallization, respectively. The ethylenediamine content of the agglomerated crystals increased with increase in the amount of ethylenediamine used. This indicated that the ethylenediamine content of the agglomerated crystals could be adjusted to that of aminophylline as specified in the Japanese Pharmacopoeia 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 amount of water used. The size of the agglomerated crystals 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 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, the technique of spherical crystallization is simple and inexpensive. These advantages may warrant its development on a commercial scale.

## Spherical crystallization of sodium theophylline monohydrate

Direct agglomeration of sodium theophylline monohydrate crystals was achieved by 'salting out' from a solution in a stirred vessel. Mixtures of chloroform and ethanol in various ratios were placed in round-bottomed flasks thermally controlled at 30°C. Ethylenediamine solutions of theophylline, of various concentrations, were prepared separately. A solution of theophylline in ethylenediamine and an aqueous solution of sodium chloride were added to a chloroform–ethanol mixture which was stirred at various speeds using a screw-type agitator. After agitation of the system for 20–30 min, 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 h agitation. The dried products were directly compressible due to their characteristic spherical forms. The products were identified chemically as mixtures of sodium theophylline monohydrate and sodium chloride by X-ray analysis and spectrophotometry.

The kinetics of spherical crystallization 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 equilibrium state. The rates of decrease in residual concentration for both spherical crystallization 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 (Ref. 5), irrespective of the crystallization method, i.e. spherical crystallization or ordinary crystallization.

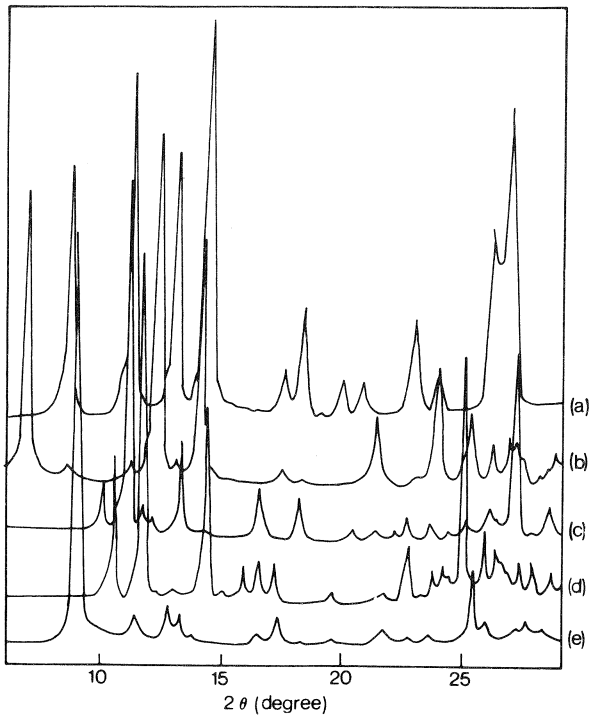


*Fig. 3. X-ray powder diffraction patterns of agglomerates, anhydrous theophylline, theophylline monohydrate and aminophylline: (a) theophylline monohydrate; (b) anhydrous theophylline; (c) α-form of agglomerate; (d) β-form of agglomerate, aminophylline; (e) γ-form of agglomerate.*

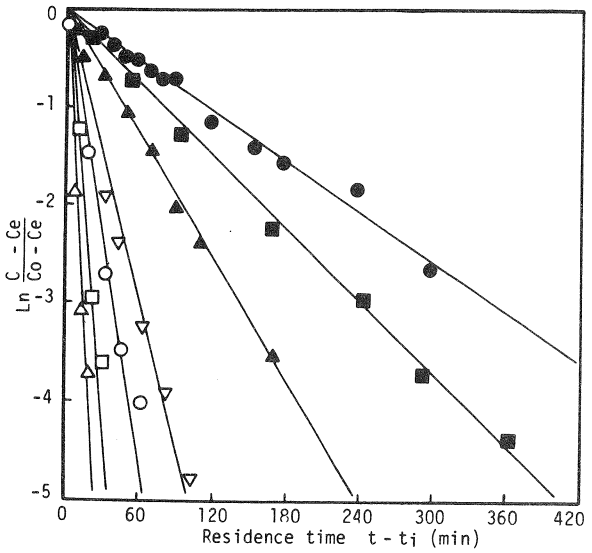


*Fig. 4. Kinetic plots of crystallization. Ordinary crystallization – composition of solvent (%) was aqueous fraction 16.0, ethanol fraction 84.0; agitation speed (r.p.m.) was △, 1050; □, 650; ○, 400; ▽, 250. Spherical crystallization – composition of solvent (%) was aqueous fraction 16.0, ethanol fraction 55.8, chloroform fraction 28.2; agitation speed (r.p.m.) was ▲, 1050; ■, 650; ●, 400. Initial concentration of theophylline in the solvent was 0.0488 (mol $l^{-1}$).*

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

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. This 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 a new complex of indometacin–epirizole

Mixtures of indometacin (stable form γ) and epirizole (mepirizole) anhydrate in various ratios were dissolved in ethyl acetate at 70°C. The solution of the mixture was cooled to 10°C and poured into water at

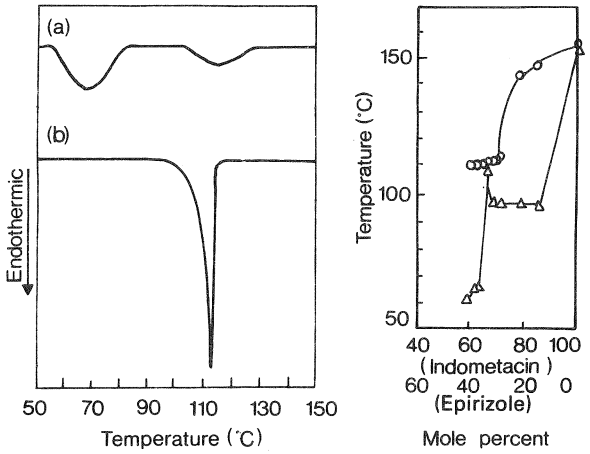


*Fig. 5. (left) Phase diagram of spherically agglomerated crystals by DSC and (right) DSC thermograms. In the thermograms the molecular ratio indometacin: epirizole was 2:1, (a) was indometacin (β-form)/epirizole physical mixture and (b) was the spherical agglomerated crystals.*

the same temperature. The system was agitated with a turbine-type agitator for 20 min. Yellowish spherically agglomerated crystals were obtained. Identification of the agglomerated crystals by means of X-ray diffraction analysis and infrared spectrometry suggested that a new complex of indometacin–epirizole was formed. The phase diagram of the agglomerated crystals with various compositions of indometacin and epirizole was prepared using a differential scanning calorimeter (DSC). When the molecular ratio of indometacin to epirizole was 2:1 in the agglomerated crystals, eutectic and liquid lines coincided as shown in Fig. 5 (Ref. 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 indometacin and epirizole (molecular ratio = 2:1) revealed two peaks, as shown in Fig. 5. When selecting the proper composition of the mixture dissolved in ethyl acetate, the resulting agglomerated crystal formed a new complex of indometacin-epirizole (molecular ratio = 2:1). An improved therapeutic effect of the new complex might be expected, since it was reported[7] that co-administration of epirizole reduced the adverse effects of indometacin and improved its therapeutic action.

## Scope of spherical crystallization

Spherical crystallization can occur generally when a suitable mixture of two or three partially miscible liquids is employed as the crystallization solvent. This technique can be adapted to a wide variety of drugs and chemicals.

The spherical crystallization technique enables several processes including synthesis, crystallization, separation and agglomeration to be combined in a single process. Reducing the number of preparation steps can save time and cost. The size of the agglomerated crystals can be suitably controlled so that the crystals can be easily compounded into the pharmaceutical formulation. The flowability and compressibility of the agglomerated crystals can be improved in such a way that they can be directly tableted. In addition, polymorphism, solvation or complexation with another dissolved compound may occur during the agglomeration process. Using these phenomena, it is possible to convert the crystalline form of drug to a desirable polymorphic form or to prepare a new complex of drug that will exhibit better bioavailability.

## References

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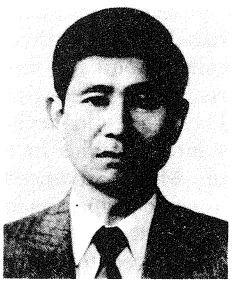

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