Spherical Crystallization as a Novel Particle Design Technique for the Development of Pharmaceutical Preparations

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1. A particle design technique for the development of pharmaceutical dosage forms

To develop highly qualified solid dosage forms to assure accurate drug delivery, highly functional powdered materials and highly elaborated (stable and reliable) powder processing are required. The functional properties of powder are classified into three groups:

1) primary function: intrinsic properties of particles (e.g. crystalline form, particle size, particle shape, etc.)
2) secondary function: assemblage properties of massed particles (e.g. flowability, packability, etc.)
3) higher level multiple function: properties responsive to environmental factors (e.g. pH, humidity, heat, light, etc.)

Particle design is done to improve the properties of particles, to impart a new function to particle preparations, and to guarantee more stable and reliable powder processing. It is difficult to simultaneously design multiple functions of particles, so particle design has been conducted in several steps. A further modification of particle properties sometimes damages the already modified properties. The development of an efficient particle design technique has long been desired to simultaneously control both primary and secondary particle properties. The microencapsulation process is assumed to be one of the methods of accomplishing this object. In this process, the predesign of the core particle to be encapsulated by modifying particle size, shape and surface property is necessary to optimize the encapsulation process. The author has been searching for a particle design technique to modify the primary and secondary functions of particles in one step during the crystallization process as a last step in the preparation of particles. The spherical crystallization technique was developed as a particle design technique to meet such requirements.

In this review, the primary design of particles to improve their micromeritic properties and multiple design to develop a new dosage form of pharmaceuticals by using this technique are described. Recent developments in research on the multiple designs of powdered materials by conventional techniques are also reviewed. Finally, the activities of the division of Particulate Preparations and Designs of the Society of Powder Technology, Japan to develop particle design technology in Japan are introduced.

2. Primary design of particles by the spherical crystallization technique

2.1 The spherical crystallization technique

The spherical crystallization technique is a novel multiple operation process including crystallization and agglomeration processes, by which the crystals produced are directly agglomerated into spherical forms. The primary and secondary functional properties of particles are controlled simultaneously by the crystallization and agglomeration operations of this technique, respectively. In this process, two or three partially miscible solvents are used as crystallization solvents. When a proper composition of the mixture is chosen, phase separation occurs and a small amount of solvent is liberated. This solvent preferentially wets the crystals produced and aggregates them into the agglomerated form. Using a three solvents system, a solvent, a non-solvent and a third solvent that is miscible with the former two solvents are chosen. For salicylic acid, water-chloroform-alcohol is a representative solvent combination. Spherical crystallization is carried out in the shaded region of the triangle phase
in Fig. 1, in which a small amount of liberated chloroform agglomerates the precipitated crystals. When the system is sheared, the aggregates of crystals transform into a spherical form. Therefore, this technique has been termed “spherical crystallization”4).

In the spherical crystallization process, the mass growth rate of particles is proportional to the difference between the supersaturated and equilibrium concentrations of solute in the solvent. However, the linear growth rate of particles is independent of the degree of supersaturation of solute in the solvent. The particles still grow even after the mass growth rate becomes null. This phenomenon indicates that the particles grow by the agglomeration of crystals themselves as well as by crystallization, and they also grow by agglomeration alone after crystallization is finished5). Spherical crystallization processes are classified into three groups, i.e. temperature decreasing, solvent change and salting out methods.

2.2 Primary designs of particles by the spherical crystallization technique

The spherical crystallization technique can improve powder processing by modifying the poor micromeritic characteristics of crystals to the desired ones. It is difficult to directly compress salicylic acid crystals due to their characteristic needle shapes, which are responsible for their poor flowability and packability. The spherical crystals designed by this technique can be directly compressed into tablets, due to their improved micromeritic properties, as shown in Table 1. The wettability of crystals can be improved by increasing the proportion of water in the mixed solvents of chloroform-ethanol-water6).

The spherical crystallization technique can

![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.](image)

![X-ray powder diffraction patterns of agglomerates, anhydrous theophylline, theophylline monohydrate, and aminophylline. Key: (a) theophylline monohydrate; (b) anhydrous theophylline; (c) α-form of agglomerates; (d) β-form of agglomerates, aminophylline; (e) γ-form of agglomerates.](image)

| Table 1 Micromeritic properties of primary crystals and agglomerates |
|---------------------------------------------------------------|
| Micromeritic properties | Agglomerates | Primary crystals |
| Angle of repose | $36^\circ$ | $51^\circ$ |
| $a^a$ | 0.0955 | 0.3397 |
| $b^a$ | 0.0466 | 0.0295 |
| $k^b$ | 0.0049 | 0.0092 |
| Closest packing density | 0.488 g/cm$^3$ | 0.160 g/cm$^3$ |
| Tablet | Compressible$^c$ | Not compressible |

$^a$ Parameter in Eq. 5. $^b$ Parameter in Eq. 6. $^c$ Tablet properties: diameter, 10.05 mm; thickness 4.14 mm; average weight, 0.382 g; weight variation, 2.56% (the maximum percentage difference from the mean weight).
be applied to the reaction system as well as to the crystallization process. Spherically designed aminophylline crystals can be produced directly during the reaction of theophylline with ethylenediamine in the mixture of ethanol-organic solvent-water. In the conventional reaction system, absolute ethanol is used as the reaction solvent. The organic solvents employed in this process are listed in Table 2. Fifteen to thirty minutes after starting the reaction, the produced fine white crystals of aminophylline were transformed into spherically agglomerated crystals. The agglomerated crystals have three different crystalline forms, i.e., α-, β- and γ-forms, depending on the type of organic solvents used. The X-ray diffraction patterns of the polymorphs are shown in Fig. 2. The β- and γ-forms have 1 and 2.5 moles of water of crystallization, respectively, but the α-form has none. Aminophylline synthesized by the conventional method corresponds to the β-form. In Table 2, the agglomerates with water contents of 0.48%, 4.21% and 8.31% are identified with the α-, β- and γ-forms, respectively. The agglomerates are directly compressible microspheres, the diameters of which can be controlled easily by changing the agitation speed of the system and the amount of water in the reaction system, as shown in Fig. 3.

This technique can be adapted to the multiple crystallization system including two pharmaceuticals to produce a new molecular complex. When indomethacin (γ-form) and epirizole (anhydride) are crystallized in the mixture of ethanol-water system, a spherically crystallized

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**Table 2** Effect of organic solvents used on spherical crystallization

| Organic solvent         | Water in the system, mL | Drug and water contents in the agglomerate, % | Average diameter of agglomerate, mm | Solubility of water a |
|-------------------------|-------------------------|---------------------------------------------|-----------------------------------|-----------------------|
| l-Hexanol               | 10.00                   | 84.86 15.15 0.48                            | 0.86 5.85                         |
| Isopropyl acetate       | 3.75                    | 82.82 16.43 5.78                            | 1.55 1.66                         |
| Isobutyl acetate        | 3.25                    | 81.38 17.19 6.32                            | 1.45 1.44                         |
| Isoamyl acetate         | 2.25                    | 84.30 15.74 5.28                            | 0.81 0.0385                       |
| Benzene                 | 1.95                    | 83.78 15.79 4.98                            | 0.90 0.0373                       |
| Toluene                 | 1.60                    | 83.65 16.27 5.31                            | 1.40 0.0073                       |
| n-Hexane                | 0.25                    | 82.04 17.46 6.19                            | 1.35 0.00897                      |
| n-Heptane               | 0.13                    | 83.17 16.77 5.57                            | 1.35 0.0118 b                     |
| Chloroform              | 4.00                    | 85.13 15.47 8.31                            | 5.52(µm)d                         |
| Aminophylline c         | —                       | 83.39 14.39                                | 0.74                              |

* a Solubility in the organic solvent (v/v%) at 20°C. b Solubility at 22°C. c Prepared by a conventional method (4). d Measured by a photographic counting method.

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**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 (o, •) or ethanol (o, □). The residence time is one hour after removal of the agglomerates adhering to the vessel.
polymorphic mixture of indomethacin (β-form) and epirizole (amorphous) is produced. In the ethylacetate-water mixture, a new molecular complex of indomethacin and epirizole with a molecular ratio of 2:1 is formed at the loading of epirizole > 65%. The process of the dissolution of indomethacin in the agglomerate of the new complex is described by zero-order dissolution kinetics. The rate of the dissolution of indomethacin of the complex is three times faster than that of the metastable β-form of indomethacin. The dissolution kinetics of epirizole in the complex is also represented by the zero-order rate process, as seen in Fig. 4.

An improved therapeutic effect of the new complex might be expected, since it was reported that co-administration of epirizole reduced the adverse effects of indomethacin and improved its therapeutic action.

3. Highly qualified designs of particles by spherical crystallization

The primarily designed particles are usually further modified to impart more sophisticated functions to them to produce highly qualified powder preparations. This process is termed the highly qualified design of particles. The spherical crystallization technique can design...
particles to be highly qualified at the same time in the primary design stage. In this paper, preparations of controlled release microspheres of ibuprofen with acrylic polymer are described. Ibuprofen is coprecipitated with acrylic polymer to be embedded in the polymer. The ethanol solution of ibuprofen and the polymer is poured into water with agitation. In the initial stage, the ethanol solutions of drug and polymer are dispersed in water in the form of fine droplets. The ethanol is diffused out of the droplets, and water enters them. During this procedure, the droplets are solidified through the coprecipitation of drug and polymer, by which matrix-like microspheres are produced. This mechanism is illustrated in Fig. 5. The diameter of microsphere is controlled by changing the agitation speed and the concentration of the surfactant added to the water. The surface topographies of the microspheres are shown in Fig. 6. When the concentration of polymer in the system is low, many micropores are produced on the surface of the microsphere. The pore diameter and the number of micro-

| Key | Formulation | Ibuprofen : Eudrast | Dissolution medium |
|-----|-------------|----------------------|-------------------|
| ○   | No. 1       | S100 (10 : 1)        | JPX No. 2 Water   |
| □   | No. 2       | L100-55 (10 : 1)     | JPX No. 2 Water   |

Size fraction: ○: -16 + 48mesh
□: -48 + 80mesh

Fig. 7 Dissolution profiles of microspheres
pores are reduced by increasing the polymer concentration. It is suggested that the drug release rate from the microsphere can be controlled by changing the polymer concentration in the system. The drug release rate is also determined by the characteristics of the polymer used, e.g. solubility depended on pH. Eudragit® RS is useful in retarding the drug release rate. Eudragit® S and L100-55 can be used as an enteric coating polymer, as shown in Fig. 710).

4. The multiple design of particles by conventional methods

To accomplish successful multiple designs of particles, highly qualified materials and elaborate equipment should be selected. With respect to materials, the development of highly functional excipients and polymers is required. From the viewpoints of safety and reliability, the modification of widely used materials is preferable. New modified materials, such as partially pregelatinized corn starch, microcrystalline cellulose and carboxymethylcellulose sodium and lactose for direct compression, have been produced11). Chitosan and purlan are expected to be used as novel biomaterials12). Biodegradable polymers have been extensively researched to develop new dosage forms which can be implanted or injected13). With regard to coating polymers, aqueous coating polymers have been developed to avoid the use of organic solvent.

The development of new equipment for multiple particle designs has been desired. New mechanics which can simultaneously design the primary properties of particles should be introduced. The application of fluidized and spouted beds to coat discrete particles may meet the requirement14). The system of coating in a vacuum may present another way15).

5. Activities of the Division of Particulate Preparations and Designs of the Society of Powder Technology, Japan and the Division of Particulate Modification Technology of the Association of Powder Process Industry and Engineering in Particle Design Technology

The Division of Particulate Preparations and Designs of the Society of Powder Technology, Japan was founded in 1985 to systematize the techniques for particle designs developed in various fields, such as pharmaceutical, chemical, agricultural and food industries, as one field of powder technologies, e.g. particle design technology. Particle design technology should be directed towards needs-oriented science to establish a new system of developing multifunctional particulate preparations. To accomplish this object, knowledge and experience in various fields, including applied chemistry, chemical engineering, electronics, material science and biopharmacy, etc., should be systematically accumulated. Such information should be open to the public so it will be available for applications in industries. The division of Particulate Preparations and Designs (Chairman: Prof. Y. Kawashima, Gifu Pharmaceutical University) sponsors a symposium on particulate preparations and designs every year co-sponsored by other academic societies and associations, such as pharmacy, chemical engineering, ceramics, material science, food, etc. October 29 and 30, 1987, the 4th symposium will be held in Atami. Prof. D. Duchène, Université de Paris-sud, and Prof. M. Okazaki, Kyoto University will be invited as special lecturers. Another activity of this division is to standardize the materials, formulations and processing of agglomeration (Chairman of the working group: Prof. H. Sunada, Meijo University).

The division of Particulate Modification Technology was founded in the Association of Powder Process Industry and Engineering in 1985 (Representative, Dr. T. Yokoyama, Hosokawa Micron Corp., Coordinator Dr. Y. Funakoshi, Kyoto Powder Research Laboratory) to stimulate and to link the academic activities of powder process industries. This division sponsors academic meetings, exhibitions and factory tours for engineers. They are usually held three times a year. It also co-sponsors the symposium on particulate preparations and designs.

Both divisions of the Particulate Preparations and Designs and the Particulate Modification Technology cooperate closely to promote the science and technology of particle design in powder technology in Japan.

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