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Parameters determining the agglomeration behaviour and the micromeritic properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems

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Abstract

The parameters determining the agglomeration behaviour and micromeritic properties of spherically agglomerated crystals of acebutolol hydrochloride prepared by the spherical crystallization technique with a two- or three-miscible-solvent system (i.e., bridging liquid, good solvent, poor solvent) were investigated. With decreasing amount of water (= bridging liquid) in the three-solvent system, the median diameter of agglomerated crystals increased, having a wider size distribution. When the composition of the system approached that of phase separation (= saturation with water), smaller sized agglomerates with a narrower size distribution were produced. The median diameter of agglomerates decreased with increasing content of ethanol (= good solvent) in the formulation. Spherically agglomerated crystals were produced evenly with the two-solvent system, i.e., water and isopropyl acetate (= poor solvent), in which the water played both the roles of bridging liquid and good solvent. The median diameter of agglomerates decreased with increasing agitation speed of the system.

Keywords: Spherical crystallization; Agglomeration behavior; Solubility phase diagram; Quasi-emulsion droplet; Agglomerated crystal; Micromeritic properties

1. Introduction

The technique of spherical crystallization was first developed by the present authors (Kawashima et al., 1982). In this system, the precipitated crystals were directly agglomerated into spherical forms without using any binder during the crystallization process. The crystallization solvent was a ternary mixture composed of a good solvent dissolving the drug, a poor solvent for precipitating the drug and a third solvent immiscible with the system, termed the bridging

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liquid. The bridging liquid preferentially wets and agglomerates the crystals produced by pouring the good solvent solution of drug into the poor solvent under agitation of the system. By using this technique, the physicochemical properties of pharmaceutical crystals were dramatically improved for pharmaceutical processes, e.g., mixing, filling, and tabletting, because of their excellent flowabilities and packabilities (Kawashima, 1990). This technique has been further developed to prepare novel drug delivery systems by coformulating a polymer in the system, such as microspheres (Kawashima et al., 1989a), microballoons (Kawashima et al., 1991) and nanospheres (Niwa et al., 1993).

In a previous paper (Kawashima et al., 1989b), it was surprisingly found that spherical crystallization phenomena occurred evenly in a two (poor and good solvents) or three (good, poor solvents and bridging liquid) miscible solvent system. In such systems, a quasi-emulsion droplet of the good solvent was formed, in which the drug was precipitated via diffusion of the good solvent to the poor solvent (= dispersing medium). In the present study, the agglomeration mechanism and the parameters governing the diameter of the agglomerate in the miscible solvent systems were further investigated by observing the process of crystallization in the quasi-emulsion droplet under an optical microscope. A solubility phase diagram of the solvent was constructed in order to explain this interesting phenomenon by the diffusion of good solvent from the emulsion droplet to the dispersing medium.

2. Materials and methods

2.1. Spherical crystallization process

As a model drug, acebutolol hydrochloride, anti-arrhythmic agent (Rhone-Poulenc Rorer Co., Ltd, France), was used. Ethanol and methanol were found to be suitable as good solvents because of their excellent solubilities for the drug (21 and 400 mg/ml for ethanol and methanol at 20°C, respectively) and miscibilities with the dispersing phase (poor solvent). As poor solvents, cyclohexane, diethyl ether, ethyl acetate, isopropyl acetate and isopropyl ether and a binary mixture thereof were found to be applicable. Ethanol and isopropyl acetate were employed in the present study as the good and poor solvents, respectively. Distilled water was chosen as a bridging liquid because of its excellent wettability with the drug and immiscibility with the dispersing medium (i.e., poor solvent). A certain quantity of water (0.5–2.5 ml) and ethanol (5–15 ml) were mixed to dissolve the drug. The poor solvent (180 ml) saturated with water used as a dispersing medium was placed in a 500 ml flask stirred with a propeller-type agitator at 400–550 rpm. Three baffles were inserted in the flask to improve the agitation of the system. When the drug solution of ethanol and water was poured into the dispersing medium at room temperature, a w/o emulsion was formed immediately in the flask. A small amount of original crystals ($\leq$ 20 mg) were introduced into the w/o emulsion system for seeding to promote the crystallization in the droplets and agglomeration, after stable emulsion droplets were produced. During the experiment, a small amount of the dispersed system was intermittently withdrawn by a pipette to be placed on a glass plate under an optical microscope for observation of spherical crystallization (Fig. 3).

A small-scale test was also carried out in a 25 ml test tube to simulate the spherical crystallization process. About 1 ml of the drug solution (composition ratio of the solution: drug, 4.5 g; ethanol, 5.0 ml; water, 1.5 ml) was dispersed into 10 ml of isopropyl acetate saturated with water in the test tube under gentle hand shaking. The emulsion produced was withdrawn from the system, and placed on a glass plate. Changes in the emulsion droplets and crystallization in the droplets on seeding were observed continuously under an optical microscope (Fig. 4). During the process, a few drops of isopropyl acetate unsaturated with water were placed on the emulsion droplets to keep water diffusing from the droplets into the dispersing medium to promote crystallization when necessary.

Spherical crystallization with the two-solvent system was carried out using water (good solvent, 4.0 ml) dissolving the drug (4.5 g) and isopropyl

acetate unsaturated with water (dispersing medium, 180 ml) in a 500 ml flask under agitation at 400–650 rpm. Other experimental conditions were the same as those of the three-solvent system. Water in the droplets of the w/o emulsion transferred gradually into the dispersing medium, since water dissolved into isopropyl acetate up to 2.3% w/w (saturated state). Residual water trapped in the crystals precipitated in the droplets acted as a bridging liquid to bind them into a spherical form.

2.2. Measurement of micromeritic properties of agglomerated crystals

Spherically agglomerated crystals were separated from the system by filtration and were dried in a desiccator with silica gel at room temperature. The particle size distribution of agglomerated crystals was evaluated via a sieve method by using the standard sieves specified in the JP XII. The surface topography of agglomerated crystal was observed under a scanning electron microscope (JSM-T330A, Nihon Denshi Co. Ltd).

2.3. Construction of solubility phase diagram of the solvents used for spherical crystallization

Poor and good solvents having the following ratios were taken in seven test tubes, i.e., isopropyl acetate-ethanol = 16:0, 15:1, 14:2, 13:3, 12:4, 11:5, 10:6. A small amount of methylene blue was added to each mixture to enable observation of the phase separation point. The water was introduced carefully into each system with a pipette or a microsyringe (50 μl) and the mixture was shaken vigorously by hand. When phase separation occurred, a small blue aqueous droplet of methylene blue was clearly observed. By connecting the phase separation point of each mixture, a phase separation line (a–h) was drawn in a triangular solubility phase diagram as shown in Fig. 2. On the upper side of the phase separation line, the three solvents were miscible, whereas they were immiscible on the lower side.

3. Results and discussion

3.1. Spherical crystallization behaviour in the miscible region of the three-solvent system described in terms of the solubility phase diagram

The spherical crystallization procedure was found to follow three stages as illustrated in Fig. 1.

First stage: When the drug solution of the mixture of good solvent (ethanol) and water was poured into the dispersing medium, i.e., isopropyl acetate saturated with water, the system immedi-

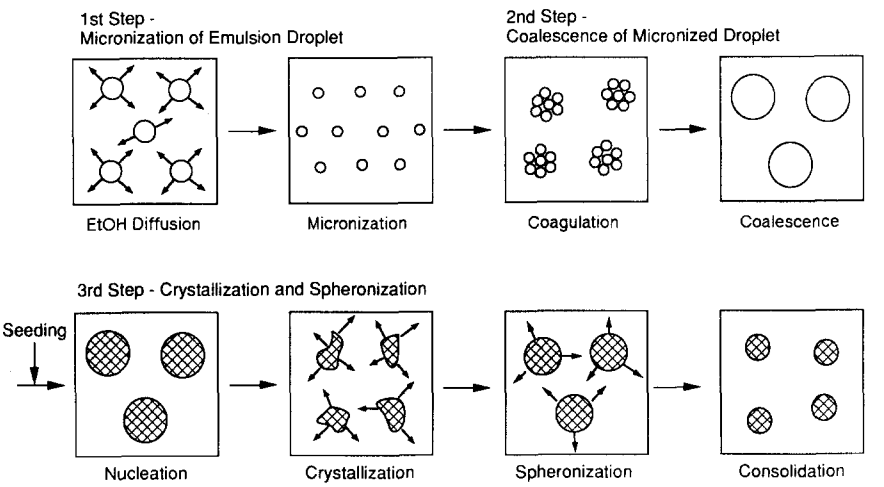

Fig. 1. Spherical crystallization process with three-solvent system. First stage, finished fast; second stage, continued for 2–3 min.

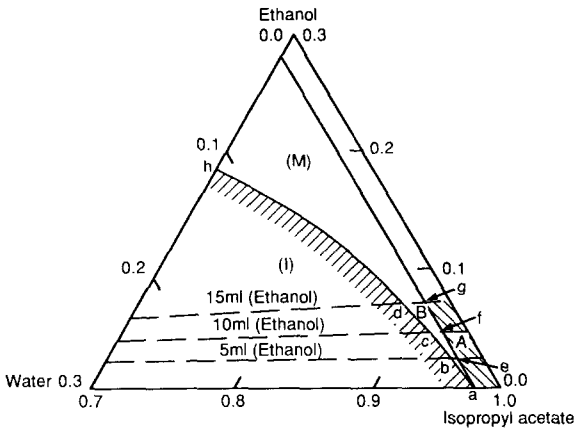

Fig. 2. Solubility phase diagram for spherical crystallization. (I) Immiscible region of solvents; (M) miscible region of solvents.

ately turned opalescent like milk, since w/o emulsion droplets were produced. The system became gradually semi-transparent. This was caused by the decrease in particle size of emulsion droplets due to the rapid diffusion of ethanol out of the droplets into the dispersing medium. The water in the droplets did not diffuse completely from the droplets because of its strong affinity with the drug, which led to formation of the emulsion droplets, although the solvent system was miscible. This phenomenon was clearly observed under the microscope. In this stage, the ethanol concentration in the droplets should be reduced rapidly along the ethanol (concentration = 1.0)-water (concentration = 1.0) side line of the triangular phase diagram. The ethanol content in the dispersing medium increased along the line connecting the top point of the good solvent (i.e., concentration of ethanol = 1.0) and point (a), which corresponds to the initial composition of dispersing medium saturated with water, up to the point of composition determined (e.g., points e, f, or g) according to the formulation (in Fig. 2). The first stage finished rapidly compared to the others.

Second stage: The small emulsion droplets yielded during the first stage coagulated under agitation and the particle size of droplets increased as observed under the microscope (Fig. 3). With decrease in the ethanol concentration in the droplet, the interfacial tension of the droplet increased leading to the coalescence of droplet. During this process, the droplets might become saturated with the drug.

Third stage: Seed crystals were introduced into the system to induce crystallization, when a stable emulsion saturated with the drug was obtained. The emulsion droplets gelled and coalesced to produce a gelatinized mass. With diffusion of water and the residual good solvent from the gelled droplets into the dispersing medium, they became solidified and consolidated to produce uniform spherical particles under the shear force with stirring.

At the initial point (a), the dispersing medium saturated with water could no longer dissolve

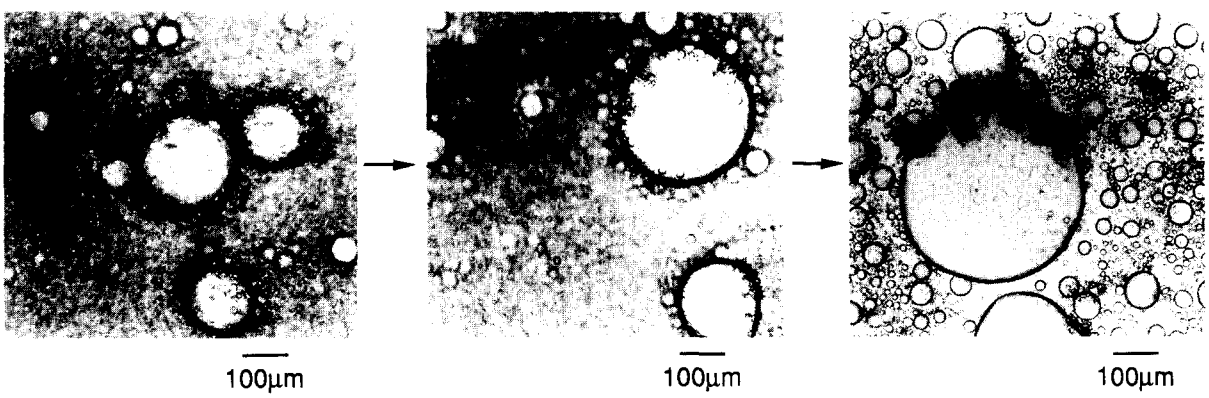

Fig. 3. Coalescence process of micronized droplets in the second stage.

Table 1
Effects of the amounts of ethanol and water on agglomeration

5 ml ethanol					10 ml ethanol				15 ml ethanol			
Water (ml)	D_{50} (μm)	Agglomerate recovery (%)	BD (g/ml)	T_p (min′, s″)	D_{50} (μm)	Agglomerate recovery (%)	BD (g/ml)	T_p (min′, s″)	D_{50} (μm)	Agglomerate recovery (%)	BD (g/ml)	T_p (min′, s″)
0.5	1000	91.1	0.37	3′40″	908	89.3	0.34	2′45″	850	81.3	0.31	1′30″
0.8	982	93.6	0.37	5′30″	941	88.9	0.32	3′10″	860	83.3	0.31	1′50″
1.2	895	90.9	0.38	10′	882	88.9	0.31	5′45′	776	82	0.29	2′
1.5	648 [a]	95.3	0.39	28′	817	91.6	0.34	5′30″	643	80	0.3	2′30″
2.0					591	91.3	0.36	11′	592	81.3	0.28	3′15″
2.5					685 [b]	89.9	0.33	8′	521	82.2	0.28	4′30″
Average		92.7	0.38			90.0	0.33			81.7	0.29	

BD, bulk density; T_p, induction period.
[a] Saturated point (b) in Fig. 2.
[b] Saturated point (c) in Fig. 2 with drug of 5.62 g.

water, but the diffusion of the ethanol from the droplets into the dispersing medium changed the composition of the dispersing medium along the phase separation line upward to e, f or g from a in Fig. 2, resulting in the further diffusion of water from the droplets to dispersing medium.

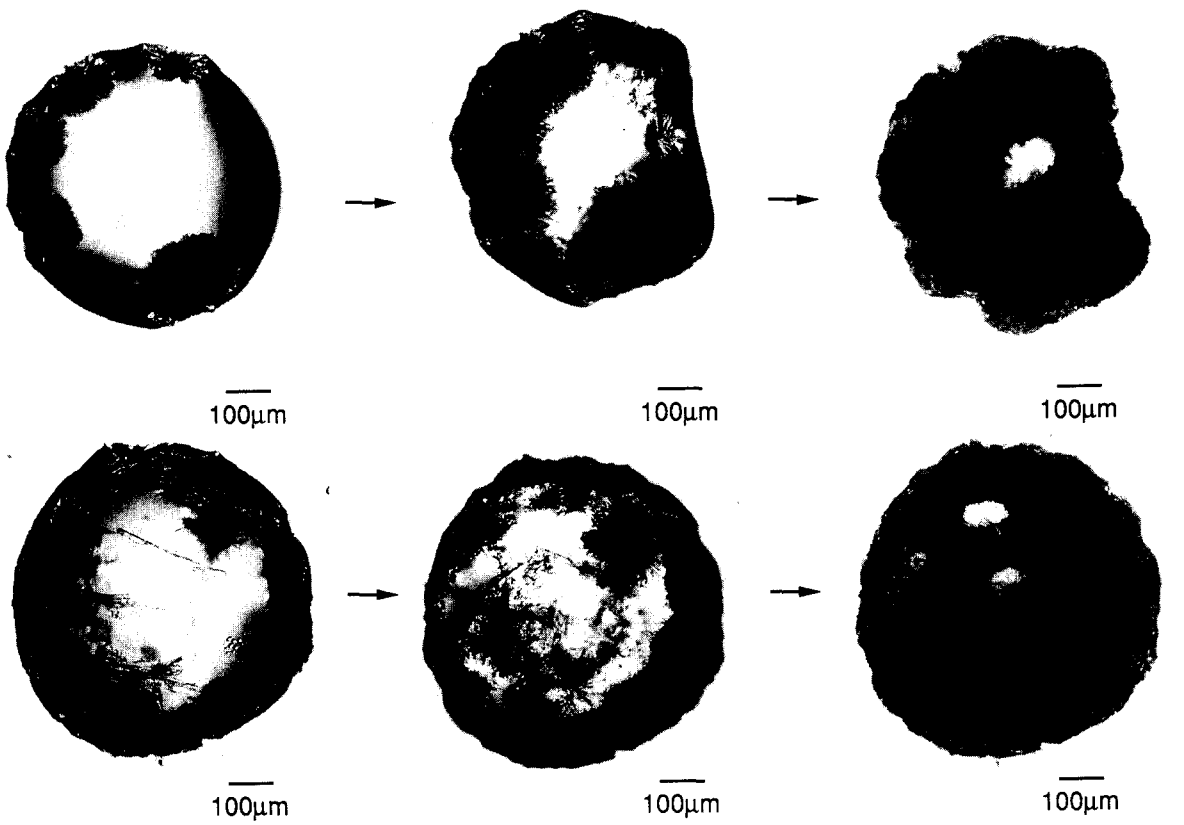

Fig. 4. Nucleation and crystallization processes in droplet after seeding (five seed crystals were sprinkled on the surface of the droplet).

The content of water in the dispersing medium increased along the dotted line connecting the points e, f or g and the top point of water in Fig. 2. The rate of diffusion of water should decrease further as the composition of the system approaches the points b, c, or d on the phase separation line in Fig. 2 and agglomeration should occur after a longer induction period (TP) as shown in Table 1.

The crystallization process in the droplets withdrawn from the small-scale system mounted on a glass plate after seeding was observed under the microscope as shown in Fig. 4. It was found that nucleation occurred at the contact points with seed crystals sprinkled on the surface of droplets. As crystallization progressed, the droplets became gradually gelatinized and solidified 10–20 min after seeding.

3.2. Effects of the amounts of good solvent and bridging liquid in the formulation on the agglomeration behaviour

The effects of the composition ratios of the good solvent (= ethanol) and the bridging liquid (= water) in the system on the particle diameter of spherically agglomerated crystals were investigated. The solvent composition of the system was varied along the dotted line as exhibited in Fig. 2 according to the amount of water in the formulation with the amount of ethanol remaining constant, e.g., 5, 10 or 15 ml as shown in Table 1. In regions having a lower water composition, such as A in Fig. 2, the rate of diffusion of water from the droplets became rapid and the droplets readily supersaturated with the drug. Crystallization in the droplets occurred quickly even at the first or second stage described in Fig. 1 without seeding. Therefore, the shape of the resultant agglomerates became non-uniform from powdery to less spherical agglomerates, and their size distribution became broad. The average diameter of agglomerated crystals increased with increasing content of water in the system due to the enhanced agglomeration of powdery crystals. Fig. 5 shows the resultant agglomerate, having a surface composed of a hard shell with fine needle-like crystals.

In regions having a higher ratio of water in the composition, such as B in Fig. 2, the rate of diffusion of water from the droplet to the dispersing medium decreased. The decrease in diffusion rate caused prolongation of the induction period before initiation of crystallization in the droplet. In order to promote crystallization, seed crystals were introduced into the system. In this region, the agglomeration of crystals progressed via three stages. As the composition of the system approached the phase separation curve (e.g., b, c and d in Fig. 2), the median diameter of the

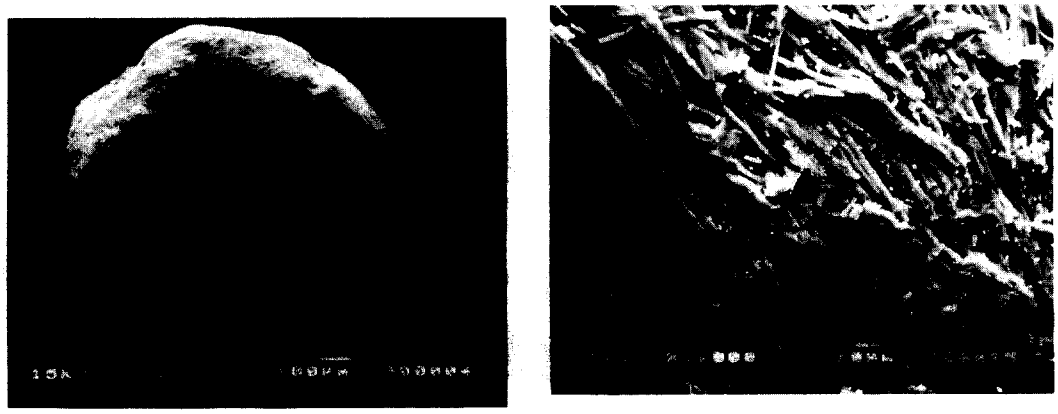

Fig. 5. Agglomerated crystals prepared in region A of the solubility phase diagram.

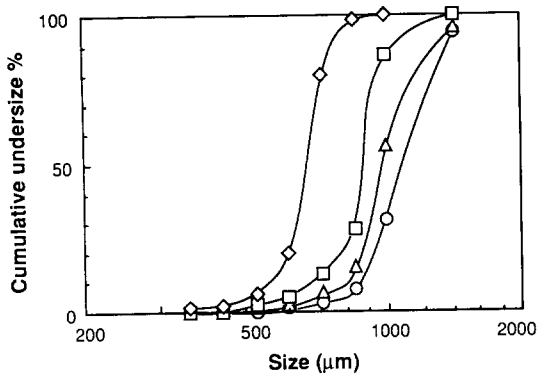

Fig. 6. Size distribution of agglomerated crystals with three-solvent system. Ethanol, 5 ml; water: 0.5 ml (○), 0.8 ml (△), 1.2 ml (□) and 1.5 ml (◇).

agglomerates (D_{50}) decreased as shown in Table 1 and the size distribution of particles became narrower as found in Fig. 6. The geometric standard deviation decreased from 1.25 to 1.22 on decrease in the amount of water from 1.5 to 0.5 ml, respectively. This was explained by the fact that the gelled droplets were under the shear force in the prolonged agglomeration process due to the reduced diffusion rates of water and ethanol from the droplets.

When the amount of ethanol in the system was increased while the amount of water remained constant, the composition of the dispersing medium changed upward along the line (aefg) in Fig. 2 corresponding to the ethanol composition of the formulation. The diffusion rates of ethanol and water from the droplets were enhanced with increasing content of ethanol in the system. The increase in the diffusion rate of water from the droplets shortened the agglomeration process of the crystals produced in the droplets. The decrease in water content of droplets reduced the agglomeration force of the crystals due to the increase in the unwetted parts of crystals with water in the agglomerate, resulting in the formation of flocks produced with a pendular bridge of

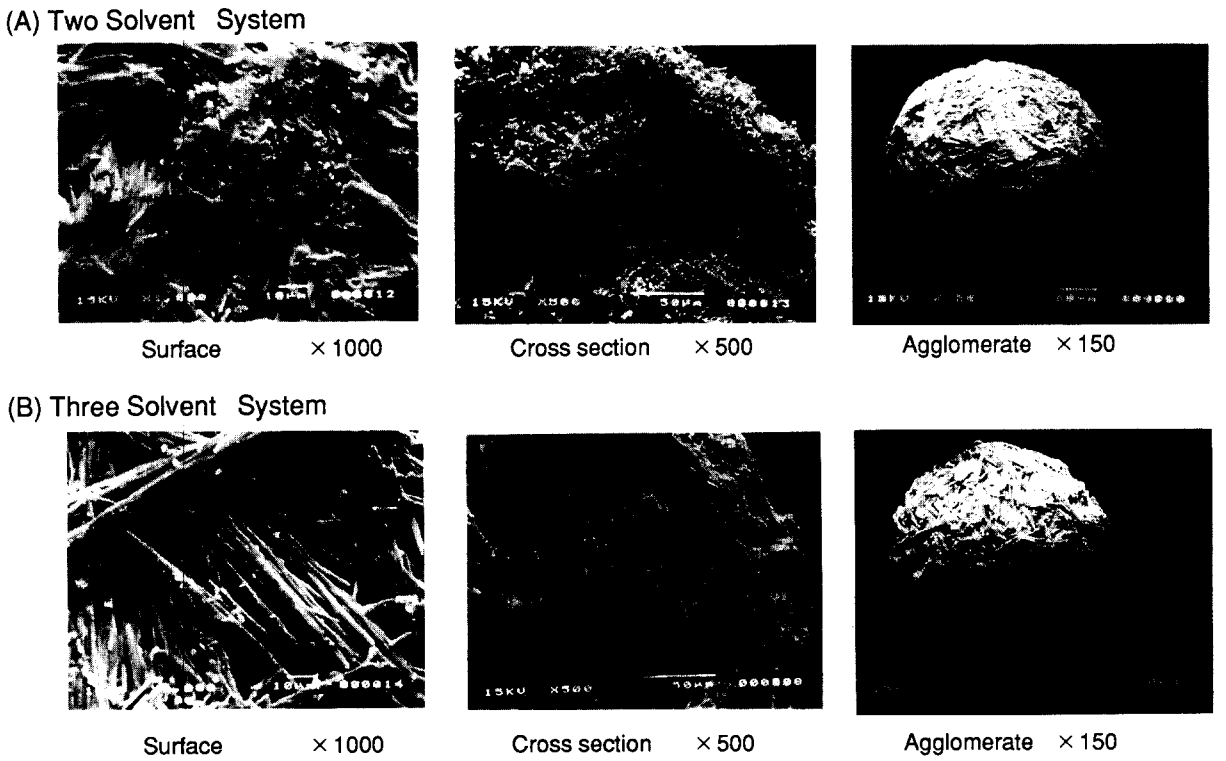

Fig. 7. Scanning electron microphotographs of agglomerated crystals prepared with two- and three-solvent system. (A) Two-solvent system; (B) three-solvent system: (water (1.5 ml)-ethanol (5 ml)-isopropyl acetate (180 ml)).

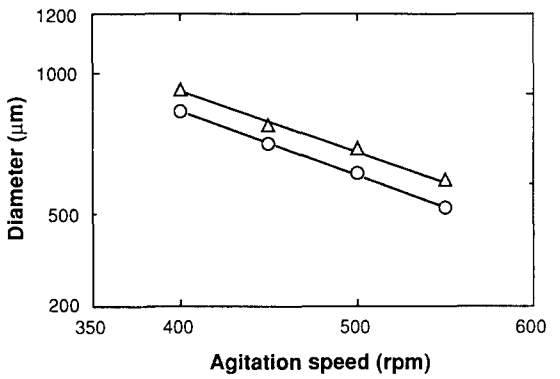

Fig. 8. Effect of agitation speed of system on average diameter of agglomerate in three-solvent system. Ethanol, 10 ml; water: 0.8 ml (△), and 1.2 ml (○).

water. Therefore, the median diameter of agglomerates decreased with increasing content of ethanol in the formulation as shown in Table 1. The formation of flocks decreased the bulk density. The recovery of agglomerates decreased with increasing ethanol content of the system as shown in Table 1 due to the increased solubility of the drug in the system.

3.3. Spherical crystallization with binary solvent system

It was found that spherically agglomerated crystals were produced even with a two-solvent system, i.e., bridging liquid (= water) and poor solvent (= dispersing medium, isopropyl acetate), without using good solvent. In this system, water played both roles of bridging liquid and good solvent dissolving the drug. With this system, the poor solvent unsaturated with water should be employed to dissolve the water diffused out of its droplet. When the aqueous solution of drug was poured into the poor solvent under agitation, an emulsion was formed, however, the system did not become milky white as found in the ternary system. After seeding, crystallization and agglomeration occurred in the droplet with the diffusion of water from the droplet to the dispersing medium. The greater interfacial tension of the aqueous bridging liquid than that of the ethanol-aqueous bridging liquid in the ternary system could strongly aggregate the crystals, producing agglomerates with a thick shell, making a densified surface as found in Fig. 7. The surface of the product was closely compacted with needle-like crystals.

3.4. Effect of agitation speed of the system on the agglomeration

The particle size of agglomerated crystals was determined during the processes of dispersing the emulsion droplet and consolidating the gelled droplet. With increasing agitation speed of the system, the shear force applied to the droplets increased, leading to more dispersed and consolidated droplets. This resulted in a reduction in the particle size of the product. The median diameter of agglomerated crystals produced in the three-solvent system decreased with increasing agitation speed and amount of water in the system as shown in Fig. 8. In the two-solvent system, the median diameter of agglomerates and the induction period for crystallization decreased and the bulk density of agglomerated crystals increased with increasing agitation speed as shown in Table 2.

Table 2
Effects of agitation speed on agglomeration

Agitation speed (rpm)	BD (g/ml)	Agglomerate recovery (%)	D_{50} (μm)	T_p (min′, s″)
400	0.36	92	764	19′
500	0.37	96	506	17′
650	0.38	93	412	13′30″

BD, bulk density; T_p, induction period.

In conclusion, the behaviour of spherical crystallization with the miscible composition of two- or three-solvent systems via a quasi-emulsion produced by pouring the good solvent solution of the drug into the poor solvent was determined from the diffusion rates of good solvent or/and bridging liquid from the emulsion droplet into the dispersing medium (= poor solvent). The agitation speed of the system is the main parameter determining the average diameter of agglomerated crystals.

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