Factors Effecting Spherical Granulation of Drugs by Tumbling Granulation Method

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Factors effecting spherical beads granulation by using centrifugal fluidizing granulator were studied. Spherical beads were prepared by feeding powdered drugs on Non-pareil-103 while spraying a binder solution containing various sugars or polymers.

Effect of binder species on the granulation was compared using nicotinamide as a model drug. Aqueous solutions of polymers commonly gave beads of high crushing strength, however, serious agglomeration of beads was observed. Aqueous sucrose solution produced beads of the highest strength with less agglomeration, while other sugars produced fairly fragile beads.

Various drugs with different solubilities were granulated using aqueous sucrose solution as a binder to examine the effect of physicochemical properties of drugs on the granulatability. Water-soluble drugs such as nicotinamide or isoniazid produced spherical beads with a smooth surface, whereas slightly water-soluble drugs such as tipepidine hibenzate or bisbentiamine produced beads of irregular shape and rough surfaces. Dusting of powders was little in the former but was serious in the latter.

The granulatability of these slightly water-soluble drugs was greatly improved by adding ethanol in the binder solution and the optimal ethanol concentration was around 30%. At this concentration, immersional wetting ($\Gamma \cdot \cos\theta$) of the solvent to these drugs took the maximum value. On the basis of these findings, the granulatability of drugs using a CF granulator was discussed in relation to the solubility and wettability of drugs to the binder solvent.

Keywords bead; granulation; binder; wettability; drug property; sugar; polymer

Introduction

In the development of controlled release dosage forms for oral administration, multiple-unit dosage forms such as granules or beads are believed to have many advantages.[1–5] Spherical granulation is one of the valuable techniques used to prepare this kind of dosage form. The preparation of spherical and smooth core beads with uniform size is especially important to control the release rate accurately by using a polymer coated membrane around them.[6] Thus, many methods of spherical granulation have been developed such as spray granulation, spray drying granulation, fluidized bed-mixing granulation, tumbling granulation and *etc.*[6,7]

Among them, the tumbling method is suitable to obtain core beads of particle sizes ranging from 500 to 3000 μm. By this method, powdered drugs and/or excipients are adhered onto tumbling core materials while spraying a binder solution. A centrifugal fluidizing (CF) granulator classified with the above kind of granulator has widely been utilized because of the ease of operation and wide applicability to various kinds of drugs with different properties. This granulator can be applied in preparing either core beads or controlled release beads in general.

However, most of the papers on the CF granulation have concerned only the coating process and there have been few studies reported on the process of the granulation,[8–10] though this often causes many problems in preparing the controlled release beads.

The present study was performed to obtain basic information for CF granulation rather than the CF coating. Effects of the binder species, the binder solvent, solubility and wettability of drugs on the granulatability were investigated using several kinds of drugs with different solubilities.

Experimental

Materials Nicotinamide (NA), isoniazid (ISA), aspirin (AP) and salicylic acid (SA) used as model drugs were of JP grade. These original sources were as follows: NA and ISA (Yuki Gosei Kogyo Co., Ltd., Japan), AP and SA (Katayama Chemical, Japan). Tipepidine hibenzate (TP) and bisbentiamine (BB) were produced in our company, Tanabe Seiyaku Co., Ltd. These model drugs were used after grinding by a hammer mill. Polyvinylpyrrolidone (PVP), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (TC-5), dextrin, sucrose, glucose, sorbitol, lactose and mannitol used as a binder were of JP grade. These binders were used without further purification. The original sources were as follows: PVP (k-30: BASF Japan Co., Ltd., Japan), HPC (Nippon Soda Co., Ltd., Japan), TC-5 (Shin-Etsu Chemical Co., Ltd., Japan), dextrin (Nichiden Chemical Co., Ltd., Japan), sucrose (Taito Co., Ltd., Japan), glucose (Katayama Chemical, Japan), sorbitol (Towa Chemical Industry Co., Ltd., Japan), lactose (DMV, Netherland), mannitol (Kyowa Hakko Kogyo Co., Ltd., Japan).

Preparation of Spherical Beads For the preparation of spherical beads, a CF granulator (CF-360S: rotor diameter 360 mm, Freund Industrial Co., Japan) was used. This apparatus is illustrated schematically in Fig. 1. A specially designed rotor is installed inside of the large stationary cylinder (stator). A bed of core materials forms a fluidizing doughnut ring along the wall of the stator with a rope like twisting motion which is created by the joint forces of centrifugal force, rotating speed, gravity and fluidization air directed through the slit. Beads are prepared by adhering powders on the core materials while spraying a binder solution. Maximum capacity of this machine is usually 5 kg of final product.

Two hundred grams of Non-pareil-103 (500—710 μm: Freund Industrial Co., Ltd., Japan) was used as a core material. This was placed on the rotor of a CF granulator. While spraying a binder solution, 400 g of drug powders were gradually fed to the driving bed which adhered to the surface of the Non-pareil-103. Under these experimental conditions, about 600 g
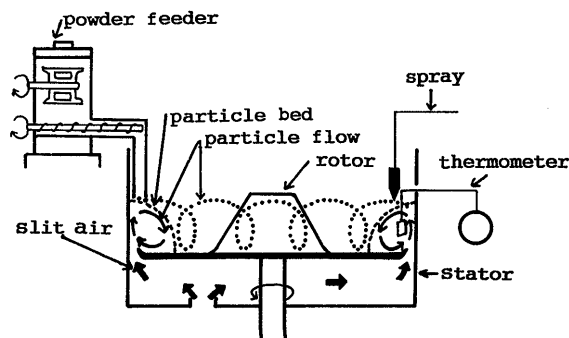

Fig. 1. Scheme of CF Granulator

of the final product was obtained which is a little smaller than the capacity of the machine. But from experience, the amount of product was known to be enough to compare the differences in the granulatability for each formulation.

The granulating condition is shown in Table I. The produced beads were dried overnight at 45 °C.

Evaluation of Beads Propeties Particle Size Distribution: Using 10 g of the beads, particle size distribution was determined by the JP sieves.

Crushing Strength of Beads: The apparatus developed for the measurement of crushing strength is schematically shown in Fig. 2. One bead (710—1000 μm) was placed on the dish of the balance (Model KO-1600, Kubota) and held between the dish and the bar which was fixed at the vertical position. Then load was gradually increased on the rod while the weight required to crush the bead was measured, this was defined as the crushing strength. Each crushing strength was obtained after more than 10 runs.

Friability: Five grams of the 500—1000 μm beads were put in a stainless vessel (diameter, 45 mm; length, 60 mm) and were planetarily vibrated with a spex mixer (spex industries) for 10 min. Friability was estimated as below:

$$\text{friability } (\%) = \frac{\text{weight of beads less than } 500\,\mu\text{m}}{\text{initial weight of beads}} \times 100 \tag{1}$$

Evaluation of Drug Properties Solubility of the Drugs: The solubilities of the six drugs (NA, ISA, AP, SA, TP and BB) were determined at 25 °C in water, ethanol or 30% ethanol solution respectively. The drugs were suspended in the solvent and these suspensions were occasionally stirred for 20 h at 25 °C, then the suspensions were filtered using a membrane filter and the filtrates were subjected to spectrophotometric assay.

Mean Particle Size of the Drugs: Laser granulometry (Granulometry model 715, Cilas Co., Ltd.) was used for slightly water-soluble AP, SA, TP or BB. The powdered drugs used for granulation were dispersed in their saturated solutions and were applied to the granulometry. The optical micrographs were used for water-soluble NA and ISA.

Bulk Density of the Drugs: To a 100 ml graduated cylinder, a drug powder was fed at a constant rate from the position of 2 cm height from the top edge of the cylinder. Then the weight of the powder was measured and bulk density was calculated.

Wettability of Drugs: The wettability of drugs was determined by a liquid penetration method at 25 °C.[11−14] A glass tube packed with drug powder (inner diameter, 3.1 mm; length, 150 mm) was prepared and the bottom was dipped in a saturated solution of the drug in 0, 10, 30 or 50% ethanol solution. The length of flow in time t was measured at a fixed interval. This mothod is based on an equaion derived by Washburn (Eq. 2).

$$h^2 = \frac{\Gamma \cdot \cos\theta \, R}{2\eta} t \tag{2}$$

where h is the length of flow in time t, η is the viscosity of the saturated solution, Γ is the surface tension of the liquid, R is the mean radius of the capillary tube and θ is the contact angle. Wettability was evaluated as immersional wetting ($\Gamma \cdot \cos\theta$). $\Gamma \cdot \cos\theta$ was calculated from the slope

TABLE I. Granulation Condition

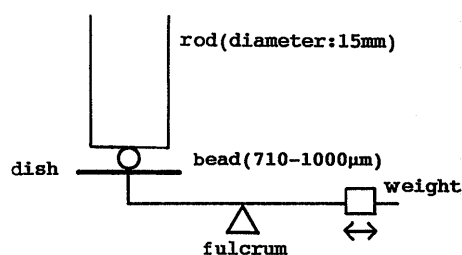| Weight of binder solution	100 g
Rotating speed	150 rpm
Blower rate	150 Nl/min
Spray air pressure	0.8 kg/cm^2
Spray velocity	5 ml/min
Blower temperature	20—30 °C

Fig. 2. Scheme of Apparatus for Measurement of Crushing Strength

of the linear plot of h^2 vs. t and the value of R was calculated by the following Eq. 3.

$$R = \frac{2\varepsilon}{(1-\varepsilon)S_W\rho} \tag{3}$$

where ε is the porosity of the powder bed and was calculated from the weight and volume of the drugs filling the capillary tube, S_W is the specific surface area and ρ is the density of drug powder. S_W and ρ were determined by the air penetration method (type SS-10, Shimadzu Co., Ltd.) and Autopycnometer model 1320, micromeritics/Shimadzu Co., Ltd., respectively.

Results and Discussion

Effect of Binder Species Using aqueous solutions of water-soluble polymers or sugars as a binder, granulation of a model drug, NA, was performed in the CF granulator according to the operating conditions shown in Table I. The concentrations of polymers were fixed to 4.5% and those of sugars were made to a nearly saturated solution. The granulatability and the properties of the resultant beads are compared (Table II).

In Table II, the weight percents of the beads whose particle size is more than 1000 μm (denote as $F > 1000$) or less than 500 μm (denote as $F < 500$) are presented. The former and the latter can be regarded as an index for granule agglomeration and unadhered powders, respectively.

In the use of sugars as a binder, agglomeration was not as large as in the case of polymers, however, comparatively large amounts of powders remained unadhered to beads. The beads produced by use of lactose or mannitol were very fragile as shown by the friability values. Only the beads produced by using sucrose gave exceptionally high crushing strength. This sugar gave the beads a higher crushing strength than did polymers. Glucose produced beads of uniform size with high yield from the small $F > 1000$ and $F < 500$ values.

All of the polymer binders produced beads of high crushing strength, however, agglomeration was very serious. Thus in the use of a polymer, antiadherents such as talc may be useful to improve the granulatability.

Effect of Binder Concentration The effects of binder concentrations on the crushing strength were examined for sucrose, sorbitol and glucose and are shown in Fig. 3.

In this experiment, the amount of the binder solution was fixed at 100 g, and the contents of the drug in a series of the beads were slightly different because of the variation

TABLE II. Effect of Binder Species on CF Granulatability for NA

Binder	Conc. in aq. soln. (w/w%)	$F > 1000^{a)}$ (%)	$F < 500^{b)}$ (%)	Crushing strength (g)	Friability (%)
Sucrose	65	4.6	6.4	413±49.0	2.3
Glucose	45	1.6	0.4	59±16.1	0.7
Sorbitol	65	9.0	3.9	115±22.1	2.7
Lactose	18	13.6	9.9	62±14.4	7.7
Mannitol	22.5	1.9	7.1	108± 7.6	9.8
Dextrin	4.5	23	0.2	343±50.5	1.0
TC-5	4.5	63	0.1	251±74.8	1.8
HPC	4.5	26	0.3	242±96.2	0.7
PVP	4.5	25	0.2	295±89.9	2.6

a) Weight fraction of granules of which diameters are more than 1000 μm.
b) Weight fraction of granules of which diameters are less than 500 μm.

of binder concentration.

By use of sucrose, the crushing strength increased as the concentration of binder increased, reflecting the high binding ability of sucrose. The increase in sucrose content could strengthen the binding force between particles.

On the other hand, by use of sorbitol or glucose, the crushing strength was decreased with the increase of binder concentration. This indicates that the binding force of these sugars were not as strong as sucrose. During the preparation, a part of NA might have dissolved in the binder solution sprayed on the beads and have acted as a binder by itself. The higher crushing strength at the lower binder concentration might reflect that the binding force of NA was stronger than that of glucose or sorbitol.

Effect of Moisture Content on Beads Strength The results shown in Fig. 3 were all obtained after drying the wet beads overnight at 45 °C. Therefore, in the case of glucose or sorbitol, remaining moisture might be the cause of the low crushing strength of these beads. In Table III, the crushing strength of the beads prepared using three sugar solutions and dried overnight or extensively at 45 °C was compared. Reduction in moisture content by drying well commonly increased crushing strength. However, the effect of moisture content on the crushing strength was the least in sucrose. This means that beads of high crushing strength could be stably produced by using sucrose as a binder. Hence, in the following section, effect of drug properties on granulation was described using sucrose as a binder.

Effect of Physicochemical Properties of Drugs We know by experience that granulatability differed greatly with active ingredients even if the preparation conditions were identical. Thus, the effect of drug properties was studied by using several model drugs with various water solubilities.
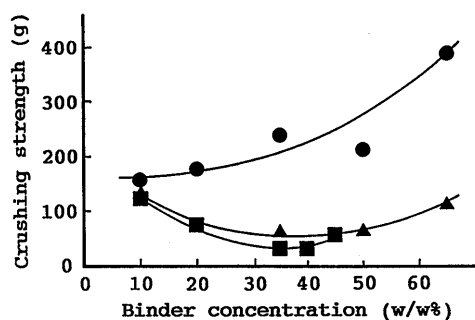

Fig. 3. Effect of Binder Concentration on Crushing Strength
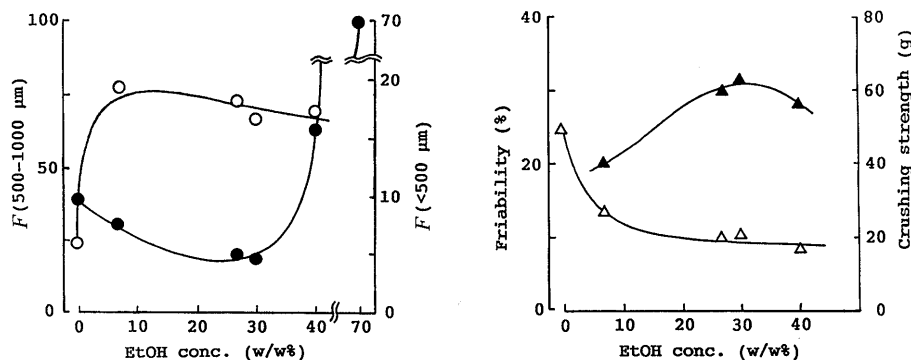
●, sucrose; ▲, sorbitol; ■, glucose.

NA, ISA, AP, SA, TP or BB were granulated with 65% sucrose in aqueous solution and the granulatability was evaluated. The results were shown in Table IV together with the representative drug properties (water solubility, particle size and bulk density).

The extent of dusting in the manufacturing process should reflect the extent of drug adherence on the beads surface. Water-soluble drugs such as NA and ISA were spherically granulated without dusting. On the other hand, in the case of slightly water-soluble drugs such as TP and BB, dusting and agglomeration occurred in the granulation process and much concavoconvexness was observed on the surface of the resultant beads.

Solubility levels of AP and SA were nearly equal, however, AP was spherically granulated while SA was not. This result may suggest that the spherical granulation by a 65% sucrose solution is difficult when solubility is less than 0.3 w/v%.

TABLE III. Relationship between Moisture Content in NA Beads and Crushing Strength

Binder solution	Well dried		45 °C overnight	
	Moisture content (%)	Crushing strength (g)	Moisture content (%)	Crushing strength (g)
65% sucrose	0.04	439±118.5	0.60	413±49.0
65% sorbitol	0.15	158± 27.3	0.56	115±22.1
45% glucose	0.40	200± 24.6	0.91	59±16.1

TABLE IV. Properties of Drugs Used and Granulatabilities in CF Granulator

Drug	Drug properties			Granulatability	
	Solubility in water (w/v%)	Particle size (μm)	Bulk density (g/cm^3)	A	B
NA	47	30—50[a]	—	—	Sphere
ISA	13	30—50[a]	0.65	—	Sphere
AP	0.33	30.9[b]	0.72	—	Sphere
SA	0.22	27.4[b]	0.75	+ + +	Rough
TP	0.017	13.1[b]	0.56	+ + +	Agglomerative
BB	0.006	5.7[b]	0.50	+ + +	Concavoconvex

In this study 65% sucrose in aqueous solution was used as a binder. A, extent of dusting in manufacturing process, + + +, violent; −, none; B, granule shape. a) Determined by microscopic observation, b) determined by CILAS method.

Fig. 4. Effect of Ethanol Concentration in Binder Solution on BB Bead Properties

●, F<500; ○, F 500—1000; ▲, crushing strength; △, friability.

Use of Mixed Solvent of Water and Ethanol for BB Beads

As binder solvents, various organic solvents are often used. Among them, ethanol is a preferable one because of its low toxicity. Thus, the effect of ethanol on granulatability was studied by adding it to binder solutions at various ratios. The granulation of BB, which was impossible by using an aqueous sucrose solution, was carried out. In this experiment, the concentration of sucrose was made at 25% since the solubility of sucrose decreases with ethanol.

As shown in Fig. 4, the $F(<500\,\mu m)$, the index of the unadhered powder portion of BB beads, decreased with the increase in the ethanol concentration, took the minimum value at a 30% ethanol solution, then increased again. The ratio of $F(500—1000\,\mu m)$, the index of normal single core beads, was comparatively low at 0% but increased remarkably with the addition of ethanol into the binder solution. Friability tended to decrease with the addition of ethanol. Crushing strength showed maximum value at 30%.

These results suggest that 30% ethanol solution is the most suitable in the manufacture and gives assurance of the BB bead quality.

Wettability of Drugs to Various Ethanol Solution

Funakoshi pointed out that wetting of drugs to binder solvent has much influence on granulation.[10] One reason for poor granulatability in the slightly water-soluble drugs may be the poor wetting of drugs to water (Table IV).

The crushing strength of beads (σ) are theoretically related with immersional wetting ($\Gamma \cdot \cos\theta$) as follows[15–17]:

$$\sigma = C\frac{\Gamma}{d}\cdot\cos\theta\frac{1-\varepsilon}{\varepsilon}\cdot\Psi\cdot F(\psi) \qquad (4)$$

where C is a constant, d is the radius of constituted particle, ψ is relative saturation of voids and $F(\psi)$ is the function of ψ. Thus immersional wetting of BB was actually determined for 0, 10, 30, 50% ethanol solutions.

Figure 5 shows a typical plot of h^2 vs. t according to the Washburn Eq. 2. As shown, a linear relationship was held between them. The immersional wetting of BB powder was calculated from the slope obtained by the least-square approximation method and R calculated by Eq. 3.

The method was also applied to other slightly water-soluble drugs and the results are shown in Fig. 6 together with BB.

AP and SA showed the maximum wettability values at 30% ethanol concentration. This ethanol concentration was also coincident to that at which BB was optimally granulated. The wettability of TP was also greatly improved by the addition of more than 10% ethanol.

Granulation of Slightly Water-Soluble Drugs with Mixed Solvent

From the wettability measurement, granulatability of AP, SA and TP was expected to improve as did BB when a 30% ethanol solution is used as the binder solvent. Thus, these drugs were granulated using 25% sucrose in a 30% ethanol solution and the results are shown in Table V.

Sphericity of AP, SA and TP beads were greatly improved and the extent of dusting decreased similarly to BB. In the case of AP and SA, the solubilities were more than 1 w/v% in 30% ethanol, therefore, the increase in the solubility might also be attributable to the improvement
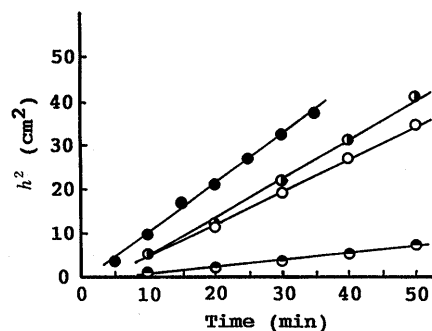
Fig. 5. Relationship between Length of Flow in BB Powder Bed and Time

Ethanol concentration of the solvent: ○, 0%; ◑, 10%; ●, 30%; ◒, 50%.
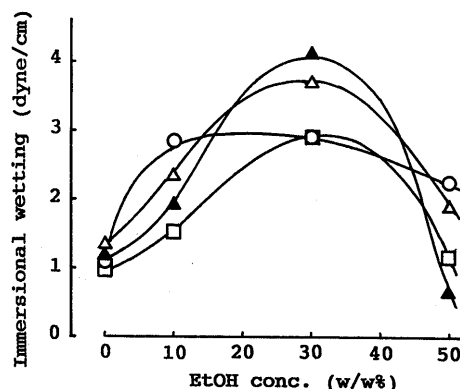
Fig. 6. Relationship between Immersional Wetting of Various Drugs and Ethanol Concentration in Binder Solutions

△, AP; □, SA; ○, TP; ▲, BB.

TABLE V. Relationship between Drug Properties and Granulatabilities

Drug	Solubility (w/v%)			Relative[a] wetting value	Granulatability	
	Water	30% EtOH	EtOH		A	B
AP	0.33	2.4	20	2.7	—	Sphere
SA	0.22	1.7	37	3.1	—	Sphere
TP	0.017	0.082	0.26	2.0	—	Sphere
BB	0.006	0.095	0.62	3.4	—	Sphere

In this study 25% sucrose in 30% EtOH solution was used as a binder. A, extent of dusting in manufacturing process, —, none; B, granule shape. a) Relative wetting value was denoted as $\Gamma\cdot\cos\theta$ in 30%EtOH/$\Gamma\cdot\cos\theta$ in water.

of granulatability. In the case of TP and BB, the solubilities were still low in 30% ethanol, whereas, the granulatabilities were improved greatly. The increase of wetting would have much effect in these two drugs.

Figure 7 shows the scanning electron micrographs of TP and BB beads prepared with 65% sucrose in aqueous solution or 25% sucrose in 30% ethanol solution. It is shown that the shape of the beads was clearly improved by use of 30% ethanol in both TP and BB.

Thus, the granulatability of the slightly water-soluble drugs could be improved by an increase in wettability to binder solution. This principle might be widely applicable to the granulation of other slightly water-soluble drugs.

In conclusion, the granulatability of the drugs by use of the CF granulator was effected by many factors. Especially, the effect of drug properties had much importance. Water-soluble drugs were granulated with 65% sucrose in
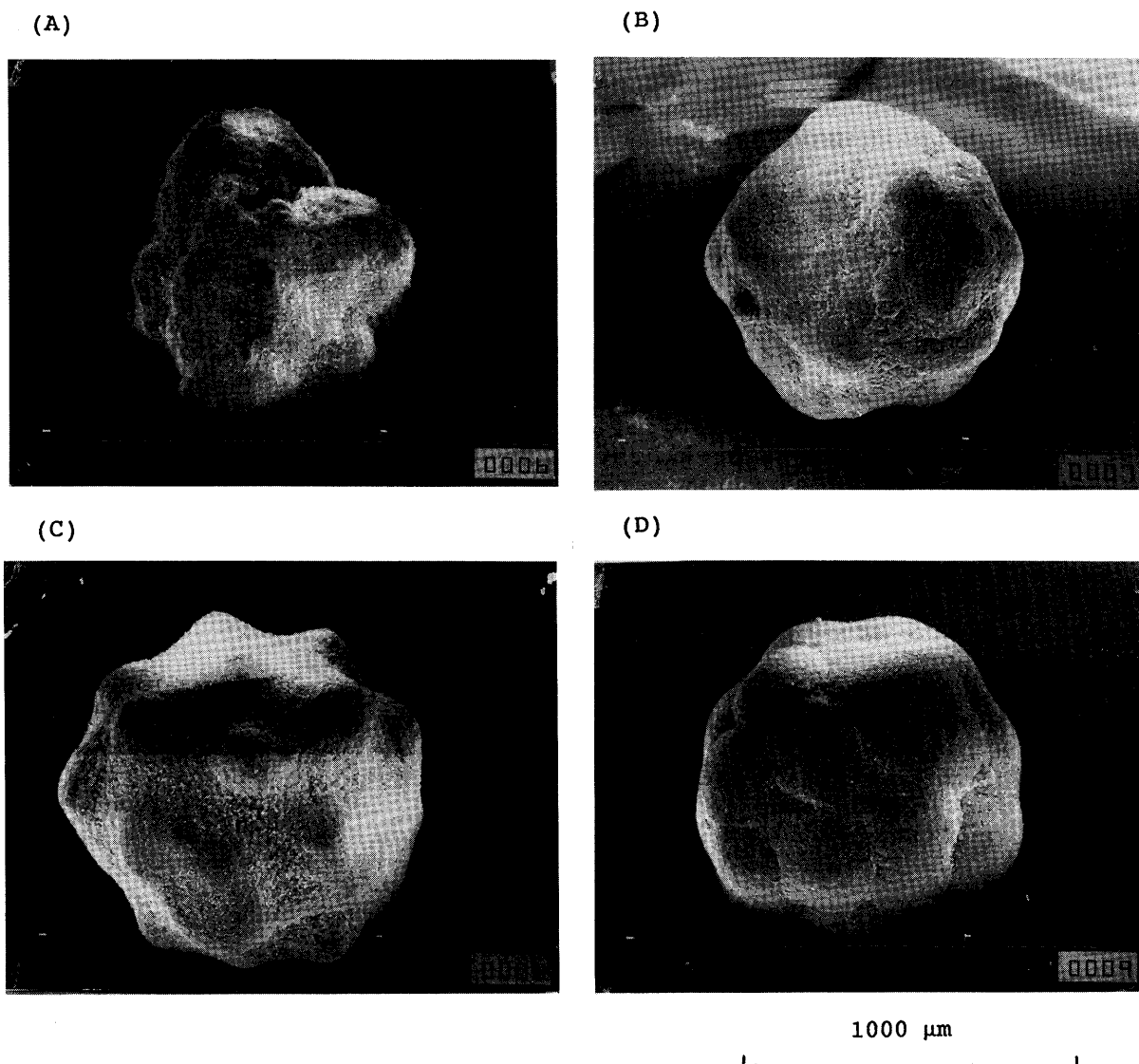
(A) (B)

(C) (D)

1000 μm

Fig. 7.   SEM of Representative Beads

A, TP bead prepared with 65% sucrose in aqueous solution; B, TP bead prepared with 25% sucrose in 30% ethanol solution; C, BB bead prepared with 65% sucrose in aqueous solution; D, BB bead prepared with 25% sucrose in 30% ethanol solution.

aqueous solution with fewer difficulties. While, slightly water-soluble drugs create problems in granulation such as dusting, agglomeration or irregular shaped beads. These problems were improved greatly by the use of 30% ethanol solution as a binder solvent. This seems to concern the improvement in wetting of binder solution to powdered drugs.

As another way to improve the wettability, the use of surfactant could be effective. However, we preferred the use of ethanol since simpler formulations seemed better in the practical pharmaceutical developments. Effects of surfactant on the granulatability as well as the use of polymeric compounds as the binder remain to be studied.

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