

Microagglomeration of pulverized pharmaceutical powders using the Wurster process I. Preparation of highly drug-incorporated, subsieve-sized core particles for subsequent microencapsulation by film-coating

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Abstract

A novel agglomeration process of pulverized pharmaceutical powders into subsieve-sized agglomerates (microagglomeration) was designed for manufacturing highly drug-incorporated core particles for subsequent microencapsulation by film-coating. The microagglomeration of pulverized phenacetin powder, whose mass median diameter was 9 μm , was performed by spraying an aqueous colloidal dispersion of acrylic polymer, Eudragit[®] RS30D, as a binding/coating agent using a spouted bed assisted with a draft tube (the Wurster process), and the effect of process variables was examined. An appropriate spray liquid flow rate made it possible to produce microagglomerates of 20–50 μm with 60% yield. However, 10% of the product still survived as particles smaller than 10 μm even at the elevated liquid flow rate. In contrast, the survived particles smaller than 10 μm tended to be predominantly reduced to 2%, while coarse agglomerates larger than 53 μm were not excessively produced, by additionally setting a fixed bed of glass beads in the spouted bed apparatus. The length of the draft tube influenced compaction of the agglomerates as well as their surface-smoothing. Equipping the fixed bed of the glass beads and the long draft tube in the spouted bed allowed us to prepare microagglomerates of 20–50 μm at yield of 55% applicable as highly drug-incorporated, free-flowing, surface-smoothed, narrowly size-distributed core particles for subsequent microencapsulation by film-coating. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Air suspension techniques assisted with spraying, including tumbling, spiral and centrifugal fluidization processes and spouted bed process, have been widely used for agglomeration and coating processes in the pharmaceutical industry (Ghebre-Sellassie, 1989; Mehta, 1989; Banks and Aulton, 1991; Jones, 1994). Current technology in agglomeration and coating by these techniques has advanced to such a level that manufacturing of conventional pharmaceutical solid dosage forms such as granules, small granules and coated beads is no longer a major point of concern. Recent progress on drug delivery systems, on the other hand, requires a high function and performance for particulate systems that manufacturers have not realized so far. Because of its easiness for producing complicated, multi-layered particle structure, the air suspension techniques again most probably provide an useful resource for designing and developing such highly functional particulate systems (Fukumori and Ichikawa, 1997).

Practically, the air suspension techniques have been applied to a processing of particles larger than 200 μm or more (Fukumori and Ichikawa, 1997). A lower critical size where the usual pharmaceutical powders can be discretely processed will be around 20 μm . This is because below this size individual particles become hard to be steadily fluidized without any retardation due to their adhesive or cohesive characteristics, as indicated by Geldart's fluidization map (Geldart, 1973) and demonstrated by the present authors (Fukumori et al., 1991a). From the practical point of view, however, it is not so easy to process even the particles of 20–200 μm in the fact that there are many operating difficulties involved with powder handling, depending on the physicochemical properties of particles employed, e.g. hygroscopicity, electrostatic charging and/or solubility to spray solvent.

In spite of these difficulties, there are some cases where a processing of fine particles smaller than 200 μm is required in a fluidized bed process. For instance, it would be a promising process if the product is to be applied to a

suspension where its particle size is better to be small, if particles are to be multi-layered by coating while their size has to be kept as small as possible, or if ready-made fine powders with an adhesive property are to be discretely coated for their surface-treatment. Recently developed novel fluidized bed process using the rapid expansion of supercritical fluid solutions (Tsutsumi et al., 1995) or equipping the opposed, pulsed air-jet assembly (Tsujimoto and Yokoyama, 1996; Tsujimoto et al., 1998) may have an advantage over conventional fluidized bed process hitherto adapted in terms of agglomeration and coating for subsieve-sized fine particles. The processing of such fine particulate systems for practically functional adaptation, however, still has some unsolved problems. One severe problem in this subject is how to prepare highly drug-incorporated, fine core particles with a free-flowability, a smoothed surface and a narrow size distribution. While preparation and evaluation of cores for subsequent film-coating have been widely performed so far (Sakamoto, 1994; Watano et al., 1997), they were mainly targeted for relatively large particles.

Generally, particles used as cores for film-coating would be classified as follows: (1) drug-layered particles; (2) crystals of drug; and (3) agglomerates composed of drug(s) and excipient(s). Although the first ones have been used in the case where high drug content is not required, it is difficult to increase drug content in the case that their size has to be small. Second, it is not easy to obtain the drug particles with a sharp size distribution in a crystallization stage of drug. In addition, drug crystals can be easily fractured in the spouted bed. Therefore, processing of fine drug powders into agglomerates smaller than 50 μm is considered to be ideal for the preparation of fine cores having high drug content. Traditionally, a fluidized bed granulation of drug powders with a less amount of excipients and binder has been attempted to produce agglomerated drugs with a high content (Patel et al., 1989; Liu et al., 1994; Vecchino et al., 1994; Radtke et al., 1998). However, the smallest product size was larger than 300 μm in their reports. The technique to prepare fine ag-

glomerates having the aforementioned properties in the range of particle size less than 50 μm , which can be applicable for subsequent microencapsulation by film-coating, is still not established.

In a previous study, the present authors proposed a novel concept of agglomeration, the so-called microagglomeration (Fukumori et al., 1991a). This technique is a process of converting finely pulverized cohesive drug powders into free-flowable, subsieve-sized agglomerates having a high drug content with the aid of a small amount of binding/coating agent. Based on this concept, microagglomeration and subsequent encapsulation of pulverized pharmaceutical powders with an organic solvent-based ethyl cellulose solution system were carried out by using a spouted bed assisted with a draft tube (the Wurster process). It was demonstrated that sustained release microcapsules, whose mass median diameter was 31 μm , could be successfully prepared by the Wurster process. The polymeric material used as a binding/coating agent showed a low agglomeration tendency for the particles around 40 μm (Fukumori et al., 1991b), but its binding strength was too high for the particles of 10 μm order. Consequently, this was responsible for the unavoidable production of the broadly size-distributed products containing coarse agglomerates. These should be unsuitable properties for the cores used for subsequent microencapsulation by film-coating.

In the present study, an attempt was made to prepare microagglomerates applicable as cores for subsequent microencapsulation by the Wurster process using Eudragit[®] RS30D, an aqueous colloidal dispersion of acrylic polymer. The reason that the aqueous polymer dispersion was selected as a binding/coating agent was in the fact that its binding strength, resulting from softening of polymer, could be lowered by changing inlet air temperature during operation (Ichikawa et al., 1993). The purpose of this study was to investigate what operating techniques were required to produce such cores through the microagglomeration process using Eudragit[®] RS30D.

2. Experimental

2.1. Materials

As a model drug powder, slightly water-soluble phenacetin (Maruishi Seiyaku, Japan) was used. Its density is 1240 kg/m^3 (Okada and Fukumori, 1975). Coarse phenacetin crystals were twice pulverized with a hammer-mill (Fuji Paudal, Osaka, Japan). Eudragit[®] RS30D, a commercially available aqueous pseudolatex, was a generous gift from Röhm GmbH (Darmstadt, Germany) and was used as a binding/coating agent. Triacetin (TA, Wako Pure Chemicals, Osaka, Japan) and anhydrous silica (Aerosil #200, Nippon Aerosil, Japan) were used as a plasticizer and an antiadherent, respectively. Three kinds of glass beads (GB06, GB08 and GB10, Top, Japan) were used after washed by distilled water and ethanol. The average diameters of the glass beads, which determined by using a micrometer for at least 200 particles, were 640 μm for GB06, 900 μm for GB08 and 1080 μm for GB10, respectively. The density of the glass beads, determined by an air comparison pycnometer (Toshiba-Beckman, Model 930, Japan), was 2500 kg/m^3 .

2.2. Equipment for microagglomeration

Microagglomeration was carried out by using a spouted bed processor with a draft tube (Grow Max (140), Fuji Paudal, Osaka, Japan) known as the Wurster configuration. A schematic diagram of the equipment is illustrated in Fig. 1. The chamber consisted of two parts: a lower cylindrical product container (0.14 m diameter, 0.20 m depth) and an upper conical expansion chamber (0.30 m diameter, 0.34 m height), both made of stainless steel with a view port of transparent acrylic resin. The product container contained an inner cylindrical draft tube (0.07 m diameter). Three types of draft tube with different length were used: 0.20 m (long), 0.17 m (middle) and 0.11 m (short). The long draft tube was employed, unless otherwise indicated. A perforated stainless plate used as an air distributor was located at the lower end

of the product container. The opening of the plate in the area beneath the draft tube was larger in diameter than that outside. The majority of air is passed through the inner draft tube, leaving sufficient airflow to just suspend particles at the outer draft tube. The plate was covered with a cotton cloth to support the horizontally moving particles at the bottom of the product container. A pneumatically atomized nozzle with a liquid outlet caliber of 0.6 mm was located in the center of the air distributor. The plate was covered with a cotton cloth to support the horizontally moving particles at the bottom of the product container. A pneumatically atomized nozzle with a liquid outlet caliber of 0.6 mm was located in the center of the air distributor. The polymeric dispersion was applied to the nozzle via a peristaltic pump for spraying upwardly. The draft tube was positioned on the air distributor with 30 mm space, unless otherwise indicated. The gap between the draft tube and the distributor allows horizontal movement of particles from the bottom of downbed to the inside of the draft tube where a higher velocity of airstream is generated, creating a steady circulating flow of particles. A laminated bag-filter with about 1- μm opening was set throughout all experiments.

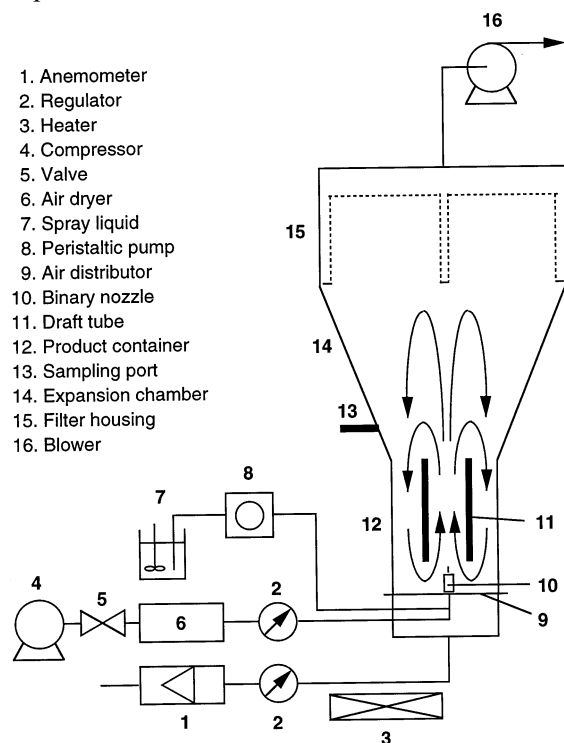


Fig. 1. Schematic diagram of spouted bed assisted with a draft tube and bottom-spray (Grow Max (140)).

Table 1
Formulation of microagglomerates

Raw material	
Pulverized phenacetin powder (g)	250
Anhydrous silica (g)	5
Spray dispersion	
Eudragit® RS30D (g)	125
Triacetin (g)	6.25
Water (g)	ad.
Total (g)	625

2.3. Particle size analysis

Sieve analysis was performed. All samples were premixed with anhydrous silica of 1% prior to the analysis. An Alpine 200LS air jet sieve was operated at a charged weight of 3 or 5 g in the range of 32 to 53 μm ; below 20 μm , microsieves of 10 and 20 μm were used at a charged weight of 1 g each, and the sieving was repeated until a constant weight was gained after 2 min of operation.

2.4. Droplet size analysis

The droplet size of the spray dispersion was measured by a laser scattering size analyzer (LDSA-2400A, Tonichi Computer Applications, Tokyo, Japan) at room temperature and humidity. The measurement was conducted at 50 mm apart from the tip of the spray nozzle.

2.5. Scanning electron microscopy

Morphology of microagglomerates was assessed by a scanning electron microscopy (SEM, JEOL JSM-5300 LV, JEOL, Japan).

3. Results

3.1. Effect of liquid flow rate

The composition of spray dispersion and the operating conditions are shown in Tables 1 and 2, respectively. In latex systems, agglomeration abruptly occurred when their softening temperature, T_s , became lower than inlet air temperature

Table 2
Operating conditions and characteristics of products

	Run 1	Run 2	Run 3
<i>Operating conditions</i>			
Inlet air temperature (°C)	60	60	60
Outlet air temperature (°C)	22–24	23–26	21–24
Inlet air flow rate (m ³ /min)	0.06–0.11	0.05–0.14	0.17
Liquid flow rate (ml/min)	4.9	6.3	7.0
Spray air pressure (MPa)	0.25–0.29	0.25–0.30	0.30–0.33
Spray air flow rate (l/min)	71–76	71–84	84–90
<i>Drying conditions</i>			
	Inlet air flow rate of 0.05 m ³ /min for 10 min		
<i>Droplet</i>			
D_{50} (μm)	8.0	8.1	7.7
D_{99} (μm)	21.0	21.2	20.3
<i>Product</i>			
Yield (%)	98	99	101
Mass median diameter (μm)	21	25	33

(Ichikawa et al., 1993). In fact, when intact Eudragit® RS30D ($T_s = 83^\circ\text{C}$) was plasticized by adding 10% of TA and thereby its T_s was lowered to 49°C , all fluidized particles massed at the beginning of operation at inlet air temperature of 60°C , leading to defluidization. On the other hand, agglomeration was most likely more suppressed as T_s became higher beyond the inlet air temperature. However, excessively high T_s should lead to insufficient deformation of polymer particles, resulting in poor adhesion of sprayed latex particles to drug particles. As a result, the agglomeration efficiency would be low. Therefore, TA was added to the latex so as to adjust its T_s to a temperature slightly higher than that of inlet air (60°C). T_s of Eudragit® RS30D plasticized by 5% TA was 65°C . The solid content in the polymer dispersion was kept at 20% (w/w). The phenacetin powder of 250 g was premixed with 5 g of anhydrous silica. This premixing was effective for the fluidization of the adhesive raw powder at the beginning of operation. The polymeric dispersion was sprayed up to 50% as weight ratio of the applied polymer on a solid basis to the raw powder, W_r , unless otherwise indicated. Drying was not performed at the time of each sampling and was performed only at the end of operation. This was because the mass median diameters were not

significantly different between the wet sample and the dry one. Thus, microagglomerates taken from the expansion chamber were sieved for particle size analysis without further drying. Operating conditions were not changed throughout the whole process.

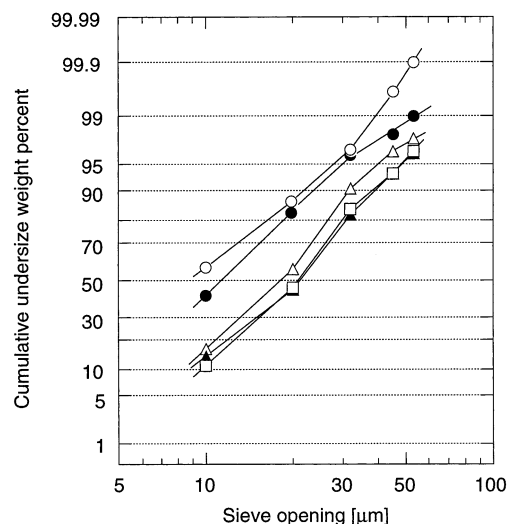


Fig. 2. Typical cumulative undersize distributions of microagglomerates produced at spray liquid flow rate, F , of 4.9 ml/min. W_r is equal to (open circle) 0, (closed circle) 12.5, (open triangle) 25, (closed triangle) 37.5 and (open square) 50%.

The cumulative undersize distributions of the microagglomerates taken from the sampling port at predetermined W_r are shown in Fig. 2. The mass median diameter of the final product at $W_r = 50\%$ was 21 μm . The particles smaller than 20 μm which occupied 86% of the raw powder were rapidly decreased to 34% with increasing the amount of the polymer applied, and then only gradually decreased above $W_r = 25\%$. On the other hand, the production of particles larger than 53 μm was suppressed to only 3.4% even when sprayed up to $W_r = 50\%$. During the operation, steady circulation of particles was observed near $W_r = 25\%$, and the particle size distribution was only slightly shifted by further spraying the polymer latices. These results indicated that agglomeration proceeded at the early stage of the process and the polymer latices made a contribution to covering of particles rather than formation of agglomerates in the range of W_r over 25%. On the other hand, it was found on scanning electron microscopic observation that even the particles smaller than 10 μm were covered with the polymer (data not shown). This implied that the particles of 10 μm or smaller could be discretely coated possibly due to a low binding strength of insufficiently soften polymer latices; however, they seemed too small to be applied as cores for subsequent film-coating.

In general, particle growth is accelerated with increasing the liquid flow rate, F . Hence, one

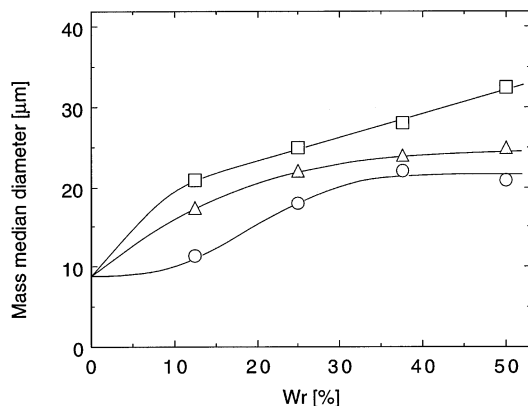


Fig. 3. Effect of spray liquid flow rate, F , on change of mass median diameter of microagglomerates. (Open circle) 4.9, (open triangle) 6.3 and (open square) 7.0 ml/min.

would expect that elevation of the liquid flow rate allows more agglomeration of the particles smaller than 20 μm . The effect of the liquid flow rate on the change of mass median diameter is shown in Fig. 3. At higher liquid flow rates over-wetted particles tended to deposit at the bottom of the product container, so that inlet air rate and spray air pressure must be increased to secure the steady circulation of the particles (Table 2). In the case of $F = 7.0$ ml/min, the short draft tube had to be used instead of the long one to avoid the adhesion of sprayed particles on the inner surface of the draft tube. When sprayed at $F = 4.9$ or 6.3 ml/min, the mass median diameter was gradually enlarged up to $W_r = 25\%$, and it reached a plateau at $W_r = 37.5\%$. Although the similarly rapid increase of the mass median diameter was observed up to $W_r = 12.5\%$ at $F = 7.0$ ml/min, it thereafter continued to increase with the amount of the polymer applied.

Fig. 4 shows the effect of liquid flow rate on the change of weight percent of particles in each size fraction during the process. The weight fraction of 10–20 μm particles was decreased with increase in the liquid flow rate. The particles smaller than 10 μm were more rapidly decreased at the earlier stage as the liquid flow rate was elevated. However, about 10% of the product still remained smaller than 10 μm even when the liquid flow rate was high ($F = 7.0$ ml/min). In contrast, the weight of particles larger than 53 μm was gradually increased in every case. The faster the liquid flow rate was, the higher the growth rate became. On the other hand, the weight fraction of microagglomerates of 20 to 50 μm was increased with the amount of the polymer applied, when the liquid flow rate was below 6.3 ml/min. When sprayed up to $W_r = 25\%$ at $F = 6.3$ ml/min, the fraction of 20 to 50 μm reached about 60%, while the production of particles larger than 53 μm was suppressed to 2.8%. These results indicated that by selecting the appropriate liquid flow rate microagglomerates of 20–50 μm could be obtained with a high product yield.

The particle size distributions of the finally obtained microagglomerates are shown in Fig. 5. Again the increased liquid flow rate was effective to reduce the weight of particles smaller than 20

μm . However, it was difficult to selectively enhance the agglomeration of the particles smaller than $10\ \mu\text{m}$ only by elevation of liquid flow rate: such fine particles were no longer agglomerated even though the liquid flow rate was elevated up to $7.0\ \text{ml/min}$. The survived particles smaller than $10\ \mu\text{m}$ as well as the more produced particles larger than $53\ \mu\text{m}$ clearly made the particle size distribution broader as shown in Fig. 5.

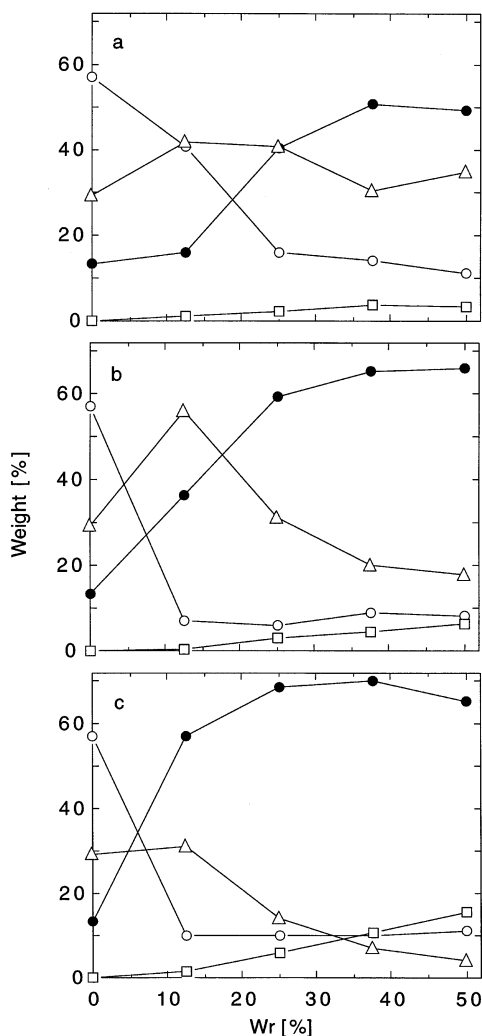


Fig. 4. Variation of the weight of microagglomerates in size fractions of (open circle) smaller than $10\ \mu\text{m}$, (open triangle) $10\text{--}20\ \mu\text{m}$, (closed circle) $20\text{--}50\ \mu\text{m}$ and (open square) larger than $53\ \mu\text{m}$. F is equal to (a) 4.9 , (b) 6.3 and (c) $7.0\ \text{ml/min}$.

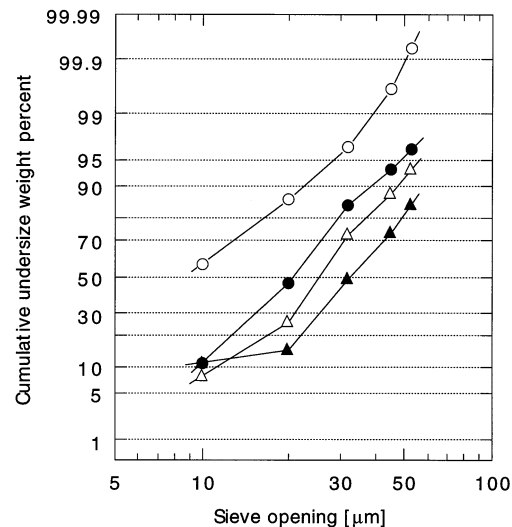


Fig. 5. Effect of spray liquid flow rate, F , on cumulative undersize distributions of microagglomerates at W_r equal to 50% . (Open circle) raw powder, (closed circle) 4.9 , (open triangle) 6.3 and (closed triangle) $7.0\ \text{ml/min}$.

3.2. Effect of the addition of glass beads

In order to preferentially agglomerate the particles smaller than $10\ \mu\text{m}$ and to disintegrate the coarse agglomerates, glass bead bed was set up on the air distributor. Table 3 lists the operating conditions in microagglomeration process using three kinds of beds composed of the glass beads with different diameter. Static bed height of the glass beads alone was set to be approximately $25\ \text{mm}$ by adjusting the charged weight of the glass beads. The draft tube was spaced at $40\ \text{mm}$ from the air distributor in every run. It was estimated by visual observation that the minimum inlet air rate required to just start the fluidization of glass beads was $0.15\ \text{m}^3/\text{min}$ for GB06, $0.23\ \text{m}^3/\text{min}$ for GB08 and $0.24\ \text{m}^3/\text{min}$ for GB10, respectively. In this study, the maximum inlet air rate required for obtaining a steady circulation of the microagglomerated particles with no addition of glass beads was $0.15\ \text{m}^3/\text{min}$. Therefore, glass beads smaller than $600\ \mu\text{m}$ were not employed because it was anticipated that they should circulate under the above conditions. The operational parameters among the three trials were set to be as same as possible. In these run, the operation was finished

Table 3
Operating conditions in microagglomeration process using glass beads^a

Type of glass beads	GB06	GB08	GB10
<i>Operating conditions</i>			
Inlet air temperature (°C)	60	60	60
Outlet air temperature (°C)	21–24	22–24	23–26
Inlet air flow rate (m ³ /min)	0.08–0.16	0.11–0.15	0.08–0.15
Liquid flow rate (ml/min)	5.1–5.8	5.1–5.8	5.1–5.8
Spray air pressure (MPa)	0.30	0.30	0.30
Spray air flow rate (l/min)	58	61	59
<i>Drying conditions</i>			
	Inlet air flow rate of 0.10 m ³ /min for 10 min		
<i>Glass beads</i>			
Charged weight (g)	500	600	650
Minimum fluidization air rate (m ³ /min)	0.15	0.23	0.24
<i>Product</i>			
Yield (%)	97	99	99
Mass median diameter (μm)	18	20	23

^a Formulation is the same as that in Table 1 except that the amount of spray dispersion was half of that in Table 1.

at $W_r = 25\%$ since particle growth did not significantly proceed by further spraying the polymer (Fig. 2).

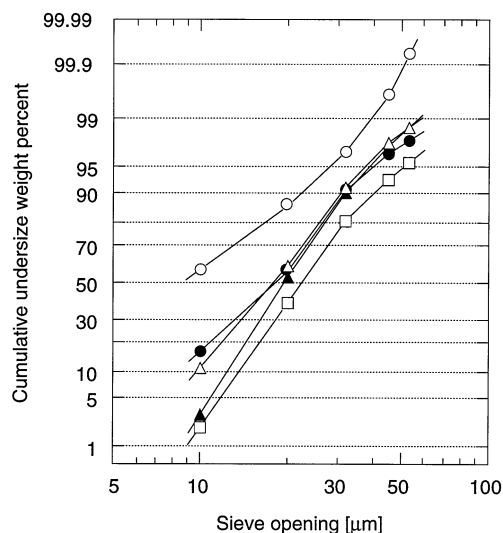


Fig. 6. Effect of the addition of glass beads on cumulative undersize distributions of microagglomerates at W_r equal to 25%. (Open circle) raw powder, (closed circle) without glass beads, (open triangle) with GB06, (closed triangle) with GB08 and (open square) with GB10.

Fig. 6 shows cumulative undersize distributions of the microagglomerates prepared with assistance of glass beads at $W_r = 25\%$. Agglomeration of the particles smaller than 10 μm was clearly enhanced by equipping the glass bead bed, though the weight of particles smaller than 20 μm was not significantly decreased. In addition, coarse agglomerates larger than 53 μm were not excessively produced. Neither phenacetin powders nor atomized droplets of the polymer were adhered onto the glass beads, indicating that the glass beads did not circulate in the chamber during the operation. Moreover, large, weakly flocculated powders blown up from the draft tube during this operation became relatively small in size, compared to the case without glass beads.

3.3. Effect of length of draft tube

In the Wurster process, collision of particles to the inner surface of the draft tube provides an impact which gives rise to a disintegration force as well as a compaction force for the circulating particles. The force is so strong that crystalline particles can easily be fractured, depending on the operating conditions employed. From this aspect,

Table 4
Operating conditions in microagglomeration process using various types of draft tube^a

Type of draft tube	Long	Middle	Short
<i>Operating conditions</i>			
Inlet air temperature (°C)	60	60	60
Outlet air temperature (°C)	21–24	21–23	22
Inlet air flow rate (m ³ /min)	0.08–0.16	0.08–0.16	0.08–0.16
Liquid flow rate (ml/min)	5.1–5.8	5.1–5.8	5.1–5.8
Spray air pressure (MPa)	0.30	0.30	0.20
Spray air flow rate (l/min)	58	58	40
<i>Drying conditions</i>	<i>Inlet air flow rate of 0.10 m³/min for 10 min</i>		
Charged weight of GB06 (g)	500	500	500
<i>Product</i>			
Yield (%)	97	100	100
Mass median diameter (μm)	18	19	23

^a Formulation is the same as that in Table 1 except that the amount of spray dispersion was half of that in Table 1.

variation of the disintegration force would be expected to lead to control of the sharpness of particle size distribution. In order to regulate the disintegration force, the length of the draft tube was changed and its effect on the size distribution of the products was examined. Operating conditions are listed in Table 4. Here, three types of draft tube with different length were used. When the short draft tube was used, the spray air pressure had to be lowered to 0.2 MPa, because such a high air pressure as 0.3 MPa in the case of the other types of draft tube led to unsteady circulation flow of the particles.

Fig. 7 shows the effect of the length of draft tube on cumulative undersize distributions of the products at $W_r = 25\%$. Obviously, agglomeration of the particles smaller than 10 μm was more enhanced as the length of draft tube was shorter.

This was further supported by the SEM photographs of the microagglomerates shown in Fig. 8. However, they demonstrated more insufficiently compacted, irregular shapes and rough surfaces as the length of the draft tube became short.

4. Discussion

The pulverized phenacetin powder used as a model in this study comes under Group C powders in Geldart's classification (Geldart, 1973). It is well known that the Geldart's C powders can be hardly fluidized due to their cohesive and/or adhesive characteristics resulting from the interparticle forces such as Van der Waals, electrostatic force and liquid bridges by moisture. At low gas velocities the C powders easily make channel(s) in the bed, so that the gas passes through the channels, leading to the lowering of pressure drop. As a result, the powders can no longer form a stably fluidized bed. In order to improve this poor ability of fluidization, several approaches have been proposed so far. For instance, it was reported that the group C powders could be fluidized in the cases where twisted vibration (Mori et al., 1989,

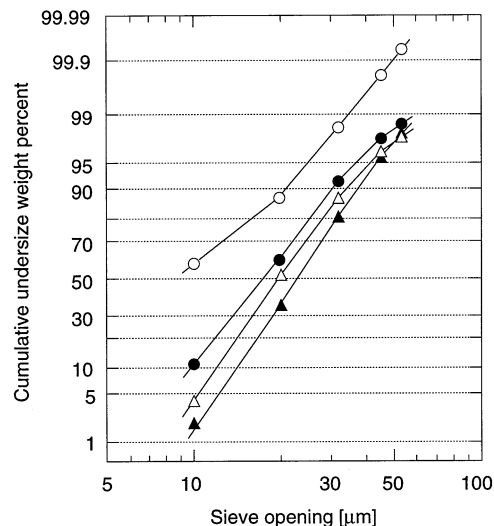


Fig. 7. Effect of the length of draft tube on cumulative undersize distributions of microagglomerates at W_r equal to 25%. (Open circle) raw powder, (closed circle) long, (open triangle) middle and (closed triangle) short draft tube.

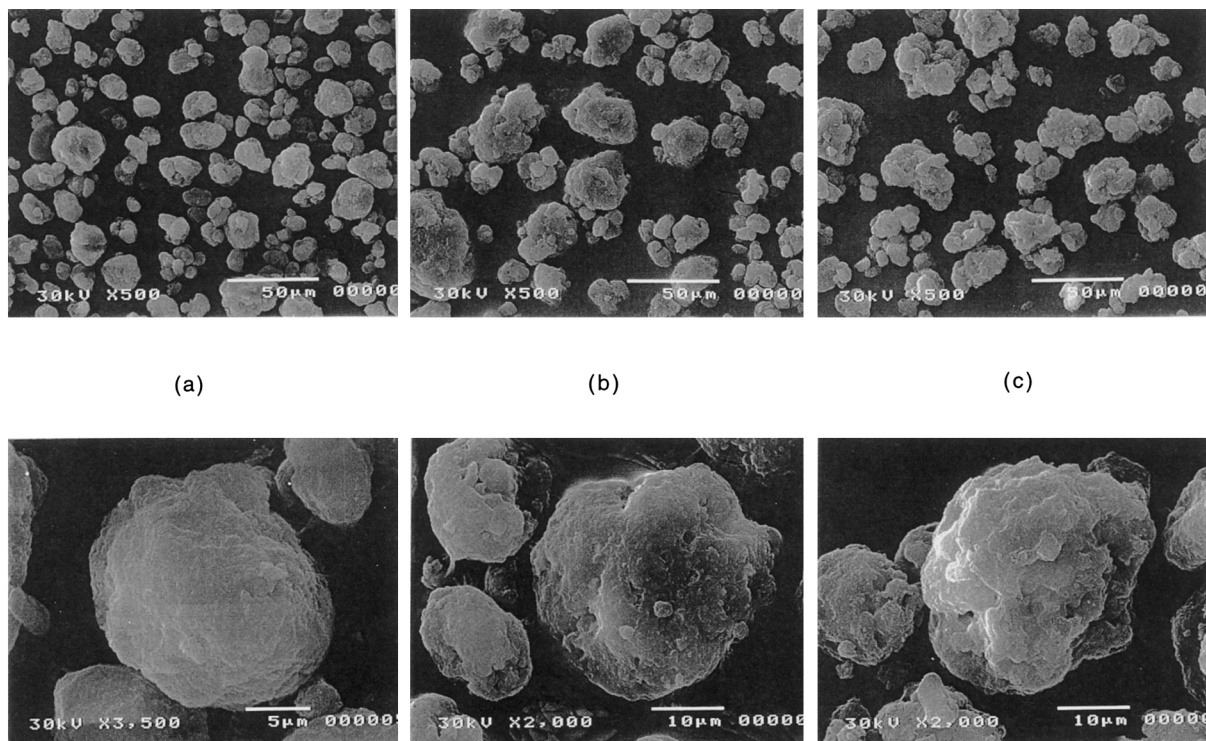


Fig. 8. SEM photographs of microagglomerates produced under the operating conditions given in Table 4. (a) Long, (b) middle and (c) short draft tube.

1990), vibration under reduced pressure (Noda et al., 1997), sound waves (Nowak et al., 1993; Leu and Huang, 1994; Russo et al., 1995) or coarse particles (Kato et al., 1991) was applied into the system. A fluidized bed with a top-spray mode, which has been used traditionally for pharmaceutical agglomeration and coating, would have difficulty in handling the group C powders without such an additional hydrodynamic or mechanical agitation force. On the other hand, the Wurster process does not contain any fluidized bed regions in the traditional sense (Christensen and Bertelsen, 1997). The particle motion in this process mainly consisted of upward flow as a dilute vertical pneumatic transport at the spout zone and downward flow as a moving bed at the annulus. Due to this intrinsic particle flow, well-regulated, relatively uniform particle motion is possibly obtained even though the fines such as the group C powders are hard to be fluidized in the conventional fluidized bed process (Ijichi et

al., 1996). In this perspective, the Wurster process seems to have a potential advantage for processing fine powders. However, it is not so easy to achieve a steady circulation of the group C powders even in the Wurster process, because of a significant particle adhesion to the chamber wall arising from the electrostatic charge (Fukumori et al., 1991a,b). On the other hand, it is well known that the A particles in Geldart's classification exhibit good ability of the fluidization (Geldart, 1973). In this study, therefore, a conversion of the C powders into the smallest A particles in size by agglomeration was intended to produce microagglomerates as cores which could be steadily circulated in a subsequent film-coating process. The boundary between the A particles and the C powders is around 20 μm in most of pharmaceutical powders whose density is about 1500 kg/m^3 . This size of 20 μm was critical in microencapsulation of particles without agglomeration by the Wurster process (Fukumori et al., 1991a), al-

though it would be possible to shift to 10 μm , depending on the binding strength of the coating material employed and the operating conditions (Ichikawa et al., 1994). In view of these considerations, the smallest size of microagglomerates designed here was targeted to be 20 μm .

The intrinsic particle flow pattern in the Wurster process also results in the particle size dependency of the number of cycle through the spray zone and the velocity of circulating particles, as has been reported by Wesdyk et al. (1990, 1993). Actually, they revealed that the larger and heavier beads within a batch received a thicker film in the particle coating process by the Wurster apparatus, when compared to smaller and lighter beads. This implied that the number and/or time of the contact with spray mist were greater in larger and heavier particles than those in smaller and lighter ones. In the agglomeration process, there is a possibility that the increased separation force exerted on the large particles due to the particle size dependency of the separation force may contribute to the reduction of particle growth, but that this trend furthermore induces a predominant agglomeration of larger particles in a subsieve-sized range. In fact, the previous studies demonstrated that production of coarse agglomerates and consequent broadening of the particle size distribution unavoidably occurred in the microagglomeration and subsequent encapsulation process of pulverized phenacetin powder with organic solvent-based ethylcellulose solution (Fukumori et al., 1991a). The attention in this study, therefore, was paid to investigate what operating techniques were required to avoid the production of excessively coarse agglomerates and insufficiently agglomerated fine particles, which led to broadening of the particle size distribution, in the Wurster process.

The mechanism of agglomerate formation and growth has been investigated by the many researchers and it can be summarized as follows (Kristensen and Schæfer, 1987): (1) nucleation of primary particles by random coalescence; (2) coalescence between colliding agglomerates; (3) layering of primary or fine particles from degradation of established agglomerates; and (4) ball growth. The particle growth mechanisms in a top-sprayed

fluidized bed process have been also described by Schæfer and Wörts (1978a). Based on the above-mentioned growth mechanisms, the effect of liquid flow rate on particle growth in the microagglomeration process studied here was discussed below, although there were fundamental differences between the top-sprayed fluidized bed and the Wurster process in terms of a spray mode, an agitation force and a particle flow pattern.

Apparently the microagglomeration process in this study seemed to be corresponded to the nuclei growth region. The size of the nuclei should depend on the droplet size of sprayed materials (Schæfer and Wörts, 1978b; Sugimori et al., 1988). According to Sugimori et al. (1988), who analyzed their experimental results from top-spray fluidized bed granulation with 5% hydroxypropyl cellulose aqueous solution by computer simulation, the relation of the mean nucleus size (the number of primary particles constructing a nucleus), NN , to the mean droplet size, D_d , was given by Eq. (1).

$$NN = 6.44 (D_d/D_p)^3 \quad (1)$$

where D_p is the mean size of primary particles. Assuming that Eq. (1) could be also applied to the present study, though derived from the results under the specified experimental conditions, the number of primary particles which could be agglomerated by nucleation under the conditions shown in Table 2 was roughly estimated to be around 6. This six-membered agglomerates had almost two times greater size than the primary particle under the assumption that their structure was regarded as the same as the agglomerate structure model in our previous study (Fukumori et al., 1992). Hence, the mean size of the nuclei which would be produced from the pulverized phenacetin powder used here ($D_p = 8.5 \mu\text{m}$) was estimated to be 17 μm . This size was well coincided to the mass median diameter of the microagglomerates obtained at $F = 4.9 \text{ ml/min}$ and $W_r = 25\%$ where significant particle growth was no longer observed by further spraying. These estimation suggested that the nuclei particles, which were once formed at the early stage of the process, might be coated by the sprayed polymer latices without further significant agglomeration.

It was also conceivable that the nuclei thus produced at $F=4.9$ ml/min might be well-packed structure possibly due to their consolidation caused by the relatively strong agitation in the Wurster process.

According to Schæfer and Wørts (1978a), agglomerate growth proceeded primarily by the nucleation mechanism insofar as there were primary particles present. This was because the reduced particle size gave rise to increased binding, so that it was easier to bind a primary particle to another one or to a nucleus than to bind two nuclei to each other. As a result, a decrease in the content of fines gave a lower growth rate, which was reflected by a break or leveling of the growth curve. The growth curve and the pattern of decrease in the weight of particles smaller than $10\ \mu\text{m}$ shown in Figs. 3 and 4 were in good agreement with the above-mentioned growth mechanism qualitatively. As seen in Fig. 4, however, the particles smaller than $10\ \mu\text{m}$ accounting for approximate 10% of the product still survived in the stage above $W_r = 25\%$, indicating that they could not bind to the established nuclei in spite of their small size such as $10\ \mu\text{m}$ or less. This trend was in contrast to the results of previously reported microagglomeration process; the weight of particles smaller than $10\ \mu\text{m}$ was predominantly decreased and finally disappeared even when only 12% of binder was applied (Fukumori et al., 1991a). As reported previously, the polymeric latices demonstrated a low binding strength which made it possible to exhibit a very low agglomeration tendency even in the coating of 32–44 μm lactose, whereas the polymer solution system induced an unavoidable agglomeration due to its strong binding strength (Ichikawa et al., 1993). Considering this, the survive of the fine particles observed in the present study was possibly ascribed from such a relatively low binding strength of the polymeric latices. In addition, there was a possibility that due to the formation of the well-compacted nuclei which might not have plastically deformable bodies such smaller particles could not take part in the nuclei any further. The remaining primary particles and/or small agglomerates finer than $10\ \mu\text{m}$ seemed to be unfavorable because they were most likely to lead to an unexpected agglomera-

tion in the subsequent film-coating process, depending on the properties of the coating materials employed. Some additional techniques were therefore necessary to more agglomerate the remains while they did not produce any further coarse particles.

It is generally experienced that the particle agglomeration in spraying process is enhanced by increasing the size of sprayed droplets, the viscosity of the droplets, the concentration of materials in the droplets and the strength of interparticulate bridges formed by the sprayed materials relative to the applied agitation. Unlike a polymer solution system, the latter three were hard to increase in the case of the commercially available polymeric dispersion used in this study. On the other hand, the droplet size can be changed easily by altering air-to-liquid mass ratio at a constant concentration (Schæfer and Wørts, 1978b). At a constant spray air flow rate, an increased liquid flow rate should result in larger droplet size and, consequently, in greater agglomeration due to the formation of strong interparticulate bridge and/or increase in the size of nuclei. The increased liquid flow rate did not lead to production of larger droplets because the spray air flow rate had to be simultaneously increased to maintain the steady particle circulation (Table 2). However, it should increase the number of droplets produced per unit time. At this condition, the probability that particle collisions led to agglomeration by interparticulate bridging should become higher. This clearly explained the increase in agglomeration rate at the high liquid flow rate. In addition, it also might lead to the rising of the humidity in the bed and the lowering of the water-evaporation rate, provided that the temperature and rate of the inlet air were kept constant. Even when the inlet air rate became higher (Table 2), however, the particle growth tended to be enhanced, indicating that the effect of spray conditions would be more predominant factors on the agglomerate growth. The enhancement of film-formation resulting from the above-mentioned conditions might also contribute to the increase in agglomeration rate at the high liquid flow rate (Ichikawa et al., 1994). In this case, the use of short draft tube might additionally contribute to it as will be described later.

Unfavorably, simple elevation of liquid flow rate did not lead to enhancing the agglomeration of fine particles smaller than 10 μm , whereas it contributed to the enhanced production of coarse agglomerates larger than 53 μm . Although the samples for particle size analysis were taken from particles circulating in the expansion chamber, some particles would remain adhered to the inner wall of apparatus due to the overwetting and/or the electrostatic charging. Therefore, it was not clear whether about 10% of the product still remaining smaller than 10 μm resulted only from the low binding strength of insufficiently softened polymer latices (Ichikawa et al., 1993) or the adhesion to the chamber wall due to the overwetting and/or the electrostatic charging made an additional contribution to it. In the Wurster process, on the other hand, particles transported up from a draft tube fall down into the downbed region by the gravitational drag force, and the fluidized particles in the product container are sucked into the spray zone from bottom of the container. Therefore, heavier and/or larger particles are faster circulated (Wesdyk et al., 1990, 1993). Consequently, larger particles would receive a larger amount of sprayed droplets. Due to this intrinsic particle flow pattern, coalescence of the overwetted coarse particles and/or layering of fine particles onto the overwetted coarse particles would more frequently proceed when the liquid flow rate became high. This would lead to the predominant increase of weight fraction of coarse particles (Fig. 4). The microagglomerates containing around 10% of particles smaller than 10 μm and larger than 53 μm were not available in this study which aimed at producing fine core particles for subsequent microencapsulation by film-coating. However, the products might be found useful for other applications (Mikami et al., 1996).

Setting up a fixed bed of glass beads at the bottom of the product container made the size distribution of agglomerates narrow. It was noted that the remaining particles smaller than 10 μm were decreased by using the glass beads when compared with the case of no addition of the glass beads. This implied that such small particles could more steadily circulate in the Wurster chamber without the significant retardation resulting from

the temporary and/or permanent adhesion on the apparatus wall and/or the intrinsic particle flow pattern. In usual fluidized beds consisting of a binary particle-mixture, it is well known that when such systems are fluidized, a dynamic mixing/segregating equilibrium is set up, depending on the density, size and shape of the particles and the gas flow rate (Rowe and Nienow, 1975; Chiba et al., 1979; Noda et al., 1986; Bai et al., 1996; Tanaka et al., 1996). As reported by Mikami et al. (1997), in a binary system the sedimentation distance of the particles which behaved as jetsam should depend on their size as well as their density; larger or heavier particles would tend to exhibit greater sedimentation into the bottom of the beds as flotsam. Considering this, the produced agglomerates in the present system might be unevenly distributed in the glass bead bed due to the size-dependent motion of circulating particles, provided that the circulating agglomerates could percolate into the glass bead bed. As the agglomeration was proceeded, larger agglomerates would tend to land more frequently at the bottom of the bed whereas smaller particles including primary and/or small agglomerates spent a greater percentage of their time in the upper region of the glass bead bed. Due to this event, therefore, residence time of larger agglomerates in the glass bead bed might be longer while the smaller particles would be faster sucked into the spray zone again, resulting in predominant agglomeration of the smaller particles. However, the glass bead bed was possibly not fluidized during the process, because the inlet air rate employed was below the minimum fluidizing air rate of the glass beads (Table 3). Under such a condition, the agglomerates could hardly percolate into the bed. Therefore, the aforementioned mechanism was unlikely to occur in the present system. In addition, the non-fluidization of the glass beads also suggested that the enhanced agglomeration of particles smaller than 10 μm by the addition of glass beads might not be ascribed to preventing deposition of the particles at the bottom of the product container and/or scraping off the particles adhered on the apparatus wall.

In the present work, the difference of the microagglomeration process with and without the

aid of the glass beads cannot be well explained. The glass bead bed formed on the air distributor might generate more complicated hydrodynamic conditions in the Wurster process. In particular, this might be significant in the region with horizontal pneumatic transport of the circulating particles, where the air movement is very complex (Christensen and Bertelsen, 1997). Ishida et al. (1980) reported the dynamic behavior of the flow of solid particles in an aerated inclined open channel with air flow introduced through a porous base plate. According to their report, smaller particles (glass beads) demonstrated higher longitudinal particle velocity than larger ones under the condition where the ratio of air velocity to minimum fluidization velocity equaled unity. An analogous situation might be induced by the glass bead bed in the present study. Further study is needed to elucidate the detailed mechanism of the effect of the glass beads. It was, however, found that the microagglomeration process with the assistance of the glass bead bed at least made it possible to provide the production of the microagglomerates having narrow size distribution.

The dimension of the draft tube in the Wurster process was an important factor which was related to two requisites of cores for subsequent microencapsulation by film-coating: the narrow size distributions of the agglomerates and the smooth surface morphology. It was, however, unfortunate that these were in conflictive relations. As shown in Fig. 7, the size distributions of the agglomerates became narrow with decrease in the length of the draft tubes. The frequency of the particle collision to the inner surface of the draft tube should become less as the length of the draft tube was shorter. In addition, the particles should be exposed to an air of high velocity for shorter time, as the draft tube became shorter. Therefore, it was reasonable to consider that these would lead to the enhanced growth of agglomerates as a result of the totally decreased disintegration force. The enhanced agglomeration in the case of short type would be in part attributable to the lowered spray air pressure (Table 4). On the other hand, the surface and shape of the products became more rough and irregular as the draft tube was

shortened (Fig. 8). This clearly resulted from the weakening of both compaction force and disintegration force acted on the agglomerates. If the core particles would have an irregular shape or loosely packed structure, it would exhibit unfavorable behavior such as attrition and/or disintegration in the subsequent film-coating process. In this perspective, the long draft tube was preferable because it could provide dense, spherical, surface-smoothed microagglomerates applicable for subsequent microencapsulation by film-coating. It would be difficult to obtain both the narrow particle size distributions and the desirable particle morphology by only changing the dimension of the draft tube, but it would be possible when the appropriate glass beads are used together as shown in Fig. 6.

From the pharmaceutical point of view, the microagglomeration process designed here will be expected to provide some possible applications. This process can be characterized as a concurrent size-enlargement process including coating and agglomeration. A pulverized drug powder thus processed should form free-flowable agglomerates of a high drug content, composed of the individual drug-particles with a thin polymer coat. Based on this structural feature, it can be expected to provide a variety of possible applications, depending on materials and formulations to be employed. For instance, it will be applicable for the processing of a poorly water-soluble drug using a water-soluble polymer to improve the poor bioavailability arising from its low dissolution rate, the directly compressible microagglomerates for controlled-release matrix tablet, the surface treatment of an adhesive/cohesive drug powder to improve its low flow ability and so on. Actually, some of these are now in progress by the present authors and co-workers. The details are reported elsewhere (Fujimoto et al., 1994; Yano et al., 1994; Mikami et al., 1996).

5. Conclusions

Microagglomeration process of a pulverized pharmaceutical powder with an aqueous polymeric dispersion using a spouted bed assisted with

a draft tube was studied to prepare the cores applicable for subsequent microencapsulation by film-coating. The obtained results could be summarized as follows:

(1) With the aqueous colloidal dispersion of acrylic polymer (Eudragit® RS30D), inlet air temperature had to be slightly lowered than the softening temperature of the polymer film to successfully process the powder without defluidization.

(2) Increase of liquid flow rate did not contribute to predominant agglomeration of the particles smaller than 10 μm , whereas it enhanced particle growth of coarse agglomerates, leading to broadening of particle size distribution. By selecting the appropriate liquid flow rate, however, dense microagglomerates of 20–50 μm were prepared at 60% yield, with the production of particles larger than 53 μm being suppressed to 2.8%.

(3) By setting up the fixed bed of glass beads on the air distributor, agglomeration of the smaller particles tended to be predominantly enhanced, while large agglomerates were not excessively produced.

(4) Compaction of agglomerates and smoothening of their surfaces were enhanced as the draft tube became long.

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