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Computer Simulation of Agglomeration in the Wurster Process

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A simplified model for computer simulation of agglomeration in the Wurster coating process was constructed using droplet size distribution and the relation between the size of agglomerates and the number of primary particles composing them experimentally determined. Computer simulations were applied to the cases where a 2.5% aqueous solution of hydroxypropyl cellulose (containing sodium carboxymethyl cellulose of 10% on a dry basis) was sprayed on four kinds of sharply fractionized lactose powders between 32 and 75 μm. With cores larger than 53 μm, the agitation exerted on particles strongly suppressed the growth of agglomerates, but the fraction of produced agglomerates reached about 50%. The smallest droplet size that was contributable to agglomeration (critical droplet size) was estimated to be 37.1—49.0 μm, increasing with core size, and the weight fraction of droplets larger than this critical size was only 0.5—2.7%, decreasing with increase in core size. The production of even such a minor amount of coarse droplets could be responsible for significant agglomeration.

Keywords coating; Wurster process; agglomeration; droplet size distribution; computer simulation; hydroxypropyl cellulose; lactose

The most serious problem in the spray coating process of fine particles is agglomeration.[1] The agglomeration takes place through the formation of interparticulate bridges of membrane materials dissolved in spray droplets. Hence, it must be related to the size of sprayed droplets, the concentration of membrane materials and the strength of dried interparticulate bridges relative to the applied agitation. A decrease in the concentration of membrane materials would surely contribute to suppressing the agglomeration, but this leads to a time-consuming operation, since fine powder has a large specific surface area. Reduced droplet size can also suppress the agglomeration; however, one problem is that the size of each droplet is widely distributed in general, though the mean size can be reduced to around 10 μm. Coarser droplets would accelerate the agglomeration. Practically speaking, a large quantity of spray solution is necessary to use with the fine powder coating, so that even if coarse droplet production is very low it can be lead to significant agglomeration.

This study elucidated the physical factors related to the agglomeration in the Wurster process by computer simulation; special interest was focused on the relation of droplet size distribution to the agglomeration. Hydroxypropyl cellulose (HPC) was selected as a model of coating material, because the mechanism of top-sprayed granulation using HPC had been studied in detail,[2] in addition to its wide application in the granulation process.

Experimental

Materials All materials were used as purchased or supplied without any purification. As a core material, lactose (DMV 200M) was used. The lactose powder was fractionized into 32—44, 44—53, 53—63 and 63—75 μm by an air jet sieve (200LS, Alpine). HPC (HPC-L, Nippon Soda, Co., Ltd.) was used as a membrane material. Sodium carboxymethyl cellulose (CMC-Na, FT-1, a grade with specially low viscosity, Gotoku Pharmaceutical Co., Ltd.) was used as an additive to HPC, and an anhydrous silica (Aerosil ♯200, Nippon Aerosil Co., Ltd.) was used as a sieving aid in particle size analysis.

Coating A Glatt GPCG-1 Wurster was used, and throughout all experiments a spray nozzle of 0.8 mm diameter and a filter with an opening of about 5 μm were used.

Particle Size Distribution of Powders The sieve analysis of microcapsules was performed as previously reported.[1]

Droplet Size The sprayed droplets were collected at a distance of 50 mm from the nozzle on silicone oil (KF 54, Shin-Etsu Chemical Co., Ltd.) applied to a glass plate and immediately covered with silicone oil applied to another glass plate. The Heywood diameters of at least 3000 droplets embedded in silicone oil were determined by an image analysis system (LA 525, PIAS Co., Ltd.).

Number of Primary Core Particles Composing Agglomerates The agglomerates in each sieved fraction were sandwiched between the two glass plates, 1 : 1 ethanol–methylene chloride was injected between the plates, and the plates were then slightly compressed to deform the agglomerates. The number of primary cores composing an agglomerate was microscopically counted for at least 30 agglomerates in each fraction. The size of sieved agglomerates was represented by the arithmetic mean of corresponding sieve openings.

Results and Discussion

Coating of Sharply Fractionized Cores The coating conditions and characteristics of the products are shown in Table I. Four kinds of lactose powders were used which were sharply fractionized. HPC is well known to have strong binding strength. Hence, the spraying of aqueous HPC solution led to an extreme agglomeration, especially with cores smaller than 53 μm. Hence, CMC-Na of 10% relative to HPC was added to the spray solution. In addition to its effect in suppressing agglomeration, CMC-Na was also effective in hindering the particles from adhering to the

TABLE I. Operating Conditions in the Coating of Lactose Powders with HPC

	Core size (μm)			
	32—44	44—53	53—63	63—75
Core weight (g)	25			
Spray solution: HPC (g)	10			
CMC-Na (g)	1			
Water	Added			
Total (ml)	400			
Operating conditions:				
Inlet air temperature (°C)	80			
Outlet air temperature (°C)	26—31			
Inlet air rate (m^3/min)	0.35	0.5	0.7	0.7
Spray rate (ml/min)	3.7	3.9	4.0	4.0
Spray pressure (atm)	2.3			
Product: Yield (%)	72	87	87	86
Mass median diameter (μm)	80	71	71	81

chamber wall due to electrostatic charging. In the coating with powders finer than 53 μm, inlet air rate and spray rate had to be reduced to avoid the ejection of a large quantity of powder to the bag filter.

Droplet Size Distribution Agglomeration takes places through the interparticulate bridging. Strength of the bridge is primarily dependent on the amount of membrane material supplied to the interparticulate contact points. The amount of bridging material at each contact point is determined by the size of sprayed droplets, when the concentration is kept constant. Thus, droplet size is one of the predominant factors in the agglomeration process.

Droplet size distribution was determined using water, HPC and HPC–CMC-Na (10:1) spray solutions; the concentration of HPC was 2.5%. The mass median diameters were 12.2, 17.1 and 17.0 μm, respectively. The measured size distributions for water and HPC–CMC-Na (10:1) are shown in Fig. 1. Reduction in the spray rate with the two finer powders (Table I) and the addition of 10% CMC-Na to HPC had no significant effect on the droplet size distribution. The results (Fig. 1) showed that droplets varied greatly in size; even with water, droplets larger than 20 μm were detectable.

Critical Droplet Size As reported by Sugimori *et al.*,[2] droplet size should determine the size of nuclei produced in the granulation process. They reported that the relation of the number of primary particles composing a nucleus, NN, to the mean sizes of droplets and cores, D_d and D_c, was given by Eq. 1.

$$NN=6.44\,(D_d/D_c)^3 \qquad (1)$$

where D_d/D_c was 0.677, when $NN=2$. This corresponded to the case where the agglomeration occurred only by the simple coalescence of two particles; then, the probability of coalescence of primary particles was unity and that of agglomerates was inversely proportional to the square of the size of the smaller particle.[2] Those two particles were agglomerated, when the number between 0 and 1 sampled at random was smaller than the coalescence probability.

Although only mean sizes of cores and droplets were dealt with in the studies of Sugimori *et al.*[2] (Eq. 1), droplet size was greatly varied as shown in Fig. 1. For example, in spite of the mass median diameter of 17.0 μm with HPC–CMC-Na, droplets larger than 40 μm could be produced. According to Eq. 1, the droplet of 17 μm would coalesce two particles of 25 μm (17/0.677). The droplets of 40 μm would have a higher ability to coalesce; therefore, they would coalesce a larger number of primary cores or larger particles.

In a specified coating operation, it can simply be assumed that droplets smaller than a critical size, D_m, cannot produce agglomerates; therefore, the agglomerates can be produced only by the doplets larger than D_m. This means that the strength of interparticulate bridge formed by this critical droplet balances with the separation force exerted on two primary cores by fluidization.

Structure of Agglomerates The Wurster process can cause a relatively strong agitation on particles. Hence, it was assumed that the agglomerates had the closest packing structure. The constructed agglomerates are illustrated in Fig. 2. Agglomerate size was defined as the smallest square sieve opening through which the agglomerate could pass. For example, the size of a four-membered agglomerate is shown in Fig. 3; its particle size was $1.707\times D_c$, where D_c was the size of primary cores. By defining the agglomerate size, D_g, in such a manner, the relation of the number of primary cores composing the agglomerate, N_g, to the reduced agglomerate size, D_g/D_c, was determined; the results are shown by closed circles in Fig. 4. On the other hand, the relation between N_g and D_g could be experimentally

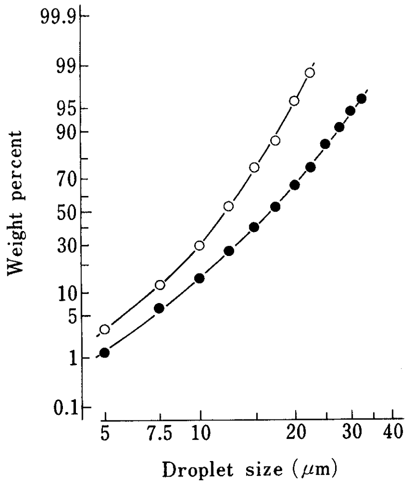

Fig. 1. Cumulative Undersize Distributions of Droplets

Spray solution: ○, water; ●, HPC–CMC-Na (10:1).

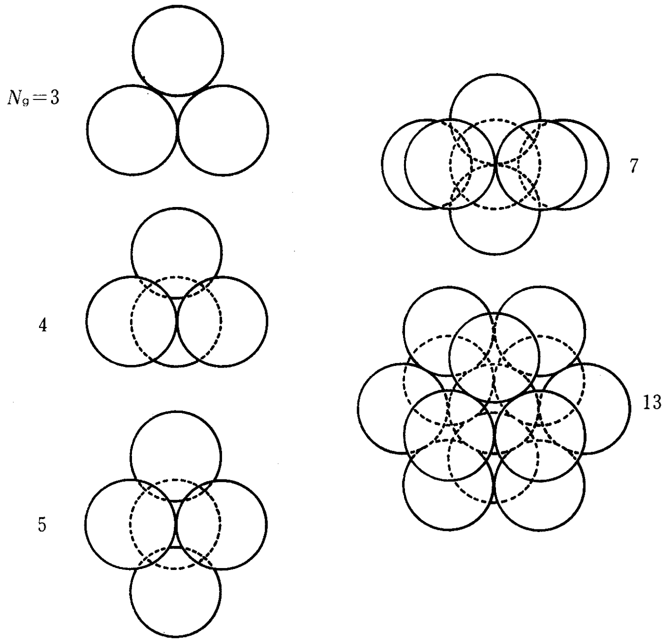

Fig. 2. Simplified Structures of Agglomerates

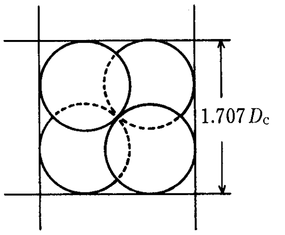

Fig. 3. An Example of Determination of Agglomerate Size

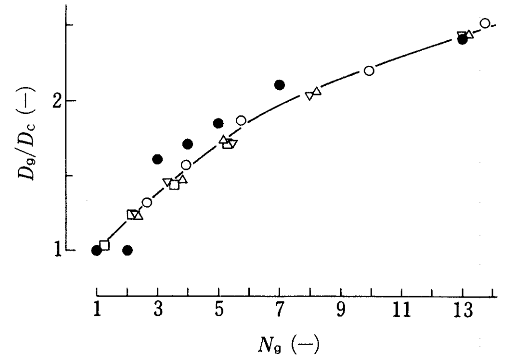

Fig. 4. Relation between the Reduced Agglomerate Size, D_g/D_c, and the Number of Primary Cores Composing an Agglomerate, N_g

Experimental data: ○, 32—44; △, 44—53; ▽, 53—63; □, 63—75 μm. ●, estimated from the models shown in Fig. 2.

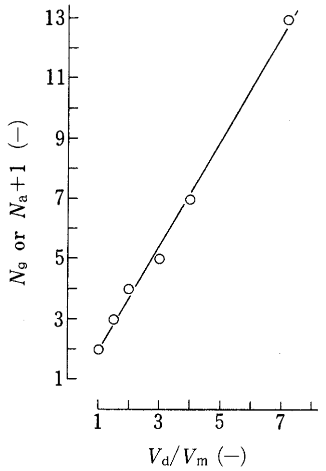

Fig. 5. Relations of N_g of Agglomerates Produced by Coalescence or the Total Number of Primary Cores Composing the Particles Adhering in Layering, N_a, to the Reduced Droplet Volume, V_d/V_m

determined; the results are shown by open symbols in Fig. 4, where D_c has been estimated under the assumption that membrane density has been 1.22 g/cm^3, identical to that of HPC, and the coating has proceeded at 100% efficiency with no agglomeration. Although the models in Fig. 2 had the closest packing structure, the real agglomerates seemed to be even more closely packed (Fig. 4). The irregular shape of lactose crystals, the strong agitation in the Wurster process and/or an overestimation of D_c might account for the observed closed packing.

Relation between Droplet and Agglomerate Sizes Let V_m be the volume of critical droplet. One droplet, whose volume is V_d, was assumed to be evenly divided and distributed to every interparticulate contact point of the primary cores to be coalesced. The relation of N_g to the volume of the smallest droplet that could produce the N_g-membered agglomerate was estimated from the models in Fig. 2. For example, the four-membered agglomerate with tetrahedral structure illustrated in Fig. 3 has 6 contact points and each core particle is agglomerated with three of these. Therefore, the droplet of $2 \times V_m$ volume is the smallest one that can produce the four-membered agglomerate. For all typical agglomerates (Fig. 2), the estimated relation is shown in Fig. 5; this relation shown in Fig. 5 was expressed by Eq. 2.

$$N_g=(V_d/V_m-1)/0.573+2 \quad \text{(in coalescence)} \tag{2}$$

There are many layering situations. When the primary core particles independently adhere to an agglomerate, the critical droplet volume should simply be V_m for each core particle. In the interactive layering where more than two particles adhere to an agglomerate larger than they are and also to one another, the critical condition of agglomeration is more complicated. In the coalescence, the droplet volume required for the growth of agglomerate was $0.573 \times V_m$ per primary core (Fig. 5 and Eq. 2). In this study, the particle growth in the layering was assumed by analogy to proceed at the same rate. Namely, when the total number of primary cores composing the particles except for the largest among all particles to be agglomerated was N_a, the critical droplet volume was assumed to be $0.573 \times V_m \times N_a$; consequently, Eq. 3 was obtained.

$$N_a+1=(V_d/V_m-1)/0.573+2 \quad \text{(in layering)} \tag{3}$$

Evaluation of the separation force exerted by agitation is difficult, since the spray air makes the fluidization in the partition of the Wurster apparatus complicated. However, it can empirically be assumed that the separation force is dependent on the particle size. Considering such a particle size dependency of separation or disintegration force, Eqs. 2 and 3 were modified as Eq. 4.

$$N_g \text{ or } N_a+1=K(V_d/V_m-1)/0.573+2 \tag{4}$$

where K is a parameter which can be called an agglomeration enhancing factor. It is a function of particle size in general; therefore, it changes with the growth of agglomerate. For simplicity, K was assumed to be constant in a specified coating operation in this study and thus was a kind of mean of intrinsic K values of all particles in the system.

Procedure of Simulation In the simulation, the population of cores was made 32000-membered. The core size was simply assumed to be the theoretical size of the cores coated without agglomeration. The increase in particle size by coating was not considered. Core weight was made 36 g (the total weight of lactose and membrane materials in Table I) and the particle density was made the weighed mean (1.44 g/cm^3) of those of lactose (1.54 g/cm^3) and membrane (1.22 g/cm^3).

To construct the population of droplets, the arbitrary values of D_m and K were selected and the number of droplets which could produce the N_g-membered agglomerate ($N_g=2, 3, \cdots$) by coalescence was calculated from the measured droplet size distribution (Fig. 1), the weights of core (36 g) and spray solution (400 g) used in the coating (Table I) and Eq. 4.

First, one droplet (let its reduced volume be $V_r=D_d/D_m$) and core particles were selected at random. In the coalescence where the selected particles were always primary particles, core particle selection was repeated until the agglomerate became $N_{g,i}$-membered, where $N_{g,i}$ was the number of primary core particles composing the largest agglomerate that the selected droplet could produce by coalescence. In the layering, the selection of core particles was repeated until the total number of primary core particles composing the particles, except for the largest among the selected particles, became larger than the value of N_a calculated from V_r by Eq. 4. After the finally selected particle was omitted (only in the layering), a new agglomerate composed of all the other particles was produced. This process was repeated until the number of unused droplets became zero.

Next, from the population of particles produced in the above manner, a particle size distribution was calculated using the experimentally determined relation shown in Fig. 4. By varying D_m and K, the particle size distribution best fitted to the measured size distribution of product was obtained.

Results of Simulation With 63—75 μm lactose cores, agglomerate size distributions simulated by D_m and K varied around their best fitted values of 49.0 and 0.32, respectively, are shown in Fig. 6. D_m determined the weight fraction of spray solution which could produce agglomerates, according to the droplet size distribution (Fig. 1). The spray solution was divided into droplets that could agglomerate N_g or N_a+1 ($=2, 3, \cdots$) cores, according to the given value of K, Eq. 4 and the droplet size distribution. As K became smaller at a constant D_m (Fig. 6b), fewer droplets with higher binding ability were produced; consequently, the production of coarse agglomerates were further decreased (Fig. 6). Thus, D_m parallel shifted the agglomerate size distribution (Fig. 6a) and K varied its standard deviation (Fig. 6b). With 63—75 μm cores, the growth of agglomerates was more restricted ($K=0.32$) than in the estimation (Eq. 3, $K=1$) from the models shown in Fig. 2. This indicated that the separation force exerted on the agglomerates might be raised by their large particle sizes.

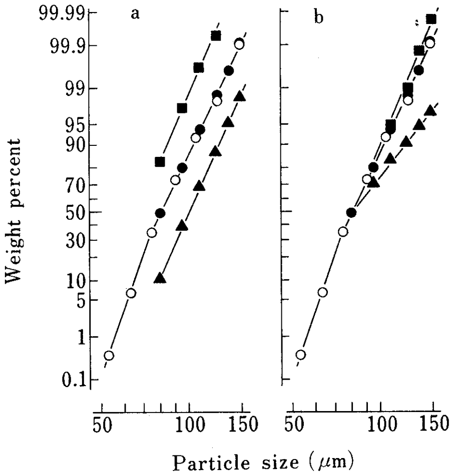

Fig. 6. Variation of Particle Size Distribution with the Parameters, D_m and K

a: △, $D_m=45$; ○, 49.0; □, 55 μm; K was kept constant (0.32). b: △, $K=1.0$; ○, 0.32; □, 0.1; D_m was kept constant (49.0 μm). Open symbols, from experiments; closed, from simulations.

In Fig. 7, the measured and simulated size distributions are shown for four kinds of cores. The estimated values of D_m and K are shown in Table II. The proposed model can well explain the agglomeration. The values of D_m and K varying with core size reflect the separation force which increases with core size. The values of D_m/D_c for the particles smaller than 63 μm are larger than the result (0.677) found by Sugimori *et al.* where the mean particle size of powder used was 40 μm.[2] This may reflect the stronger separation force in the Wurster process. The weight fractions of agglomerates and droplets larger than D_m shown in Table II show that the production of coarse HPC–CMC-Na droplets of only 0.5—2.7% has led to the remarkable agglomeration observed experimentally.

The particularly large value of K (1.50) was obtained with 32—44 μm (Table II), indicating that the agglomeration was enhanced in that case by the growth of particles, different from the cases of other larger cores. With 32—44 μm lactose processed at the very low inlet air rate (Table I), the separation force against coarse agglomerates might be remarkably reduced. On the other hand, with the coarser

Table II. Results of the Simulation of Agglomeration

	Core size (μm)			
	32—44	44—53	53—63	63—75
D_c (μm)	44.0	56.2	67.2	79.9
D_m (μm)	37.1	41.9	45.7	49.0
D_m/D_c	0.842	0.746	0.680	0.613
K	1.50	1.01	0.60	0.32
Fraction of agglomerates	0.956	0.751	0.587	0.518
Maximum of N_g	35	21	12	9
Weight percent of droplet larger than D_m	2.73	1.31	0.74	0.46

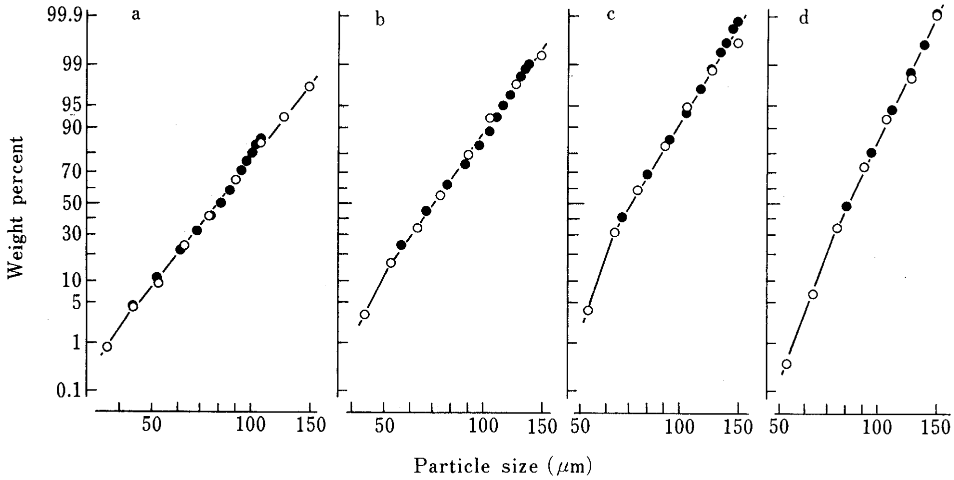

Fig. 7. Cumulative Undersize Distributions of Products

○, from experiment; ●, from simulation. Core size (μm): a, 32—44; b, 44—53; c, 53—63; d, 63—75.

fractions of lactose powder, the coating might proceed under the conditions where the agglomeration was suppressed. Thus, the value of K seemed to appropriately reflect the size dependency of the separation force exerted on particles.

Conclusion

Agglomeration in the aqueous coating with HPC was simulated using a newly proposed model which elucidated the basic factors and their relations. The droplet size distribution, the critical droplet size effective for agglomeration, the strength of agitation effective in separating the agglomerates and its dependency on the particle size determined the agglomeration. To construct the model, information on the structure and size of produced agglomerates was also required.

A practical and important finding was that the agglomeration in the coating process could be induced by a very small quantity of large droplets. This fact seems to make the fine powder coating very difficult. Since the reduction of mean droplet size will be limited to around 10 μm and the droplet size distribution unavoidably becomes broad, the infrequent production of 20—30 μm droplets will also be unavoidable. This may cause enlargement of the smallest size of microcapsules that the Wurster process can produce for practical use. How finely microcapsules can be prepared by the Wurster process will be dependent on how well D_m, the critical droplet size, can be enlarged by the design of membrane materials and how strongly and/or effectively the agglomerates can be separated by the coating machinery and operations.

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