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Control of fluidized bed granulation

V. Factors affecting granule growth

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Granule growth in a fluidized bed granulator (Glatt, WSG 15) was evaluated by examining the correlation between quantity of binder solution and granule size and size distribution under varying experimental conditions using mixtures of lactose and maize starch as starting materials.

The highest growth rates were obtained at the largest droplet size and liquid flow rate and at the highest lactose content and the lowest inlet air temperature. Growth rate was further found to be affected by type of binder. An increase in the quantity of binder solution resulted in a narrower size distribution. It was shown that alteration of bed load from 10 to 15 kg could be compensated for by keeping the relative quantity of binder solution constant, granule size distribution, however, being slightly narrower at a lower bed load. On basis of the results obtained possible granule growth mechanisms are finally discussed.

Binding mechanisms, acting in agglomeration of powder particles, were first described by *Rumpf* (13), but only a few of these mechanisms are relevant to wet granulation used in the pharmaceutical industry (11, 21). By addition of binder solution liquid bridges are formed between particles, which are held together due to the surface tension at the liquid-air interface and the hydrostatic suction pressure in the bridge. *Newitt & Conway-Jones* (6) distinguished between three states of water content as shown in Fig. 1. After evaporation of liquid in the drying phase the particles are held together by solid bridges resulting from hardening of binders, crystallization of dissolved substances or deposition of suspended particles.

Granule growth is initiated by formation of small nuclei consisting of particles held together by pendular or funicular bridging. Further growth results from coalescence of agglomerates, redistribution of broken fragments, abrasion transfer or snowballing (14). Various authors (1, 3, 4, 6,

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Figure 1. Binding mechanisms by liquid bridges.

14) described different growth mechanisms, probably due to the use of varying starting materials (4). These experiments were carried out in rotating pans or drums, all liquid being added at once in contrast to fluidized bed granulation, where granules are formed by continuous addition of binder solution. In the latter case, therefore, granule growth may proceed in a different way.

Investigation of granule size as a function of quantity of binder solution may be a useful approach to study the granule growth mechanisms in fluidized bed granulation. In the experiments described in literature quantities of binder solution of 20-40 % of the starting materials have ordinarily been used. Since a great deal of liquid evaporates during the granulation phase (17), the quantity of binder solution is usually larger than for granulation by massing and screening.

Ormós et al. (7, 8) found granule size to be directly proportional to the quantity of binder solution, whereas size distribution was unaffected, and they derived equations for the estimation of granule size and size distribution based on these observations. *Shinoda et al.* (20) observed a linear correlation between the quantity of binder solution and the logarithm of average granule size. Other authors (5, 21) found a rise in granule size until a certain point, after which it remained constant by further addition of binder solution. This fact was accounted for by a change in liquid bridges from the pendular to the capillary state (21).

The somewhat varying results indicate that granule growth may depend on the actual experimental conditions.

The purpose of the present study has been to elucidate the growth mechanisms in fluidized bed granulation by studying the effects of other variables on the correlation between quantity of binder solution and granule size.

Experimental

Materials and formulation

Starting materials were 10 or 15 kg of mixtures (4:1 and 1:4) of fine-crystalline lactose and maize starch (15). Aqueous solutions at 40° C of gelatine (Ph. Nord. 63) (4 %), sodium carboxymethylcellulose (7L1, Hercules) (CMC) (3 %), Kollidon® 25 (10 %) and Kollidon® 90 (BASF) (4 %) were used as binder solutions and were prepared as previously described (16).

Equipment and procedures

A fluidized bed spray granulator (Glatt, model WSG 15) was used. Nozzle, instrumentation and general procedure were as previously described (15, 16). Values of droplet size (d_{50}) were calculated from an empirically derived droplet size equation (16). Granule size distributions were estimated using sieve analysis and were characterized by d_{gw} and s_g as in a previous study (15). Unless otherwise stated sieve analyses were carried out on tray-dried samples in order to estimate granule size distribution at the end of the granulation phase as previously described (17, 18).

Results and discussion

A granule growth curve was determined from five experiments, samples of about 400 g of granules being drawn after addition of 1,000, 1,500, 2,000, 2,500 and 3,000 g of binder solution and at the end of the granulation phase using a total quantity of 3,500, 4,000, 4,500, 5,000 and 6,000 g, respectively. The results were compared with those of ten experiments where only one sample was drawn per experiment (Table 1). Since it was shown that granule size and size distribution were unaffected by the actual sampling procedure, the method of drawing two samples per experiment was used in the subsequent investigations in order to reduce the number of experiments.

Quantity of binder solution

To investigate the influence of quantity of binder solution on attrition in the drying phase granule size and size distribution were estimated before and after drying. The granule growth curve is discussed and compared with others below. The results, given in Table 1, show that a rise in quantity of binder solution results in a narrower size distribution and that attrition in the drying phase causes a slightly wider size distribution. Since an increase in quantity of binder solution results in a higher binder concentration in the granulation an accompanying decrease in attrition is seen. After addition of 3,500 g of binder solution, however, attrition was found to be approximately constant, indicating that the optimum binder concentration might have been attained. In a previous study (18) a continuous fall in attrition was observed with increasing concentration of gelatine, the quantity of binder solution being kept constant. This may be explained by the fact that the effect of binder concentration in the present experiments is counteracted by an increase in attrition due to prolonged drying time when a larger quantity of binder solution is used.

Table 1. Influence of quantity of binder solution on granule size (d_{gw}), size distribution (s_g) and attrition in the drying phase when using two sampling procedures.
Starting materials: 80 % lactose + 20 % maize starch.
Binder solution: Gelatine 4 %. Liquid flow rate: 150 g/min.
Nozzle air flow rate: 8 Nm³/h. $\triangle T_{gran}$: 20° C, $\triangle T_{drying}$: 35° C.

Quantity of binder solution (g)	Before drying, 2 samples per experiment		Before drying, 1 sample per experiment		After drying, 1 sample per experiment		Attrition	
	d_{gw} (μm)	s_g	d_{gw} (μm)	s_g	d_{gw} (μm)	s_g	$\triangle d_{gw}$ (μm)	%
1,000	82	2.19	104	2.08	91	2.07	13	13
1,500	111	2.29	112	2.25	86	2.24	26	23
2,000	145	2.17	147	2.12	103	2.23	44	30
2,500	174	2.09	173	2.05	135	2.22	38	22
3,000	204	2.02	226	1.90	181	2.12	45	20
3,500	207	1.88	203	1.80	183	1.90	20	10
4,000	235	1.78	220	1.73	193	1.82	27	12
4,500	228	1.70	221	1.64	196	1.73	25	11
5,000	252	1.66	246	1.68	224	1.73	22	9
6,000	281	1.61	281	1.58	257	1.66	24	9

Droplet size

Granule growth was investigated using different droplet sizes (Fig. 2). As can be seen, a break on the growth curves was observed after addition of about 3,000 g of binder solution, this being most noticeable when using the largest droplet size.

When the atomized droplets reach the fluidized particles, nuclei consisting of two or more primary particles held together by liquid bridges are formed. Since a large droplet is able to bind more particles together than a small one a decrease in nozzle air flow results in fewer, but larger nuclei. At the start of spraying large droplets give an uneven wetting of the bed, which is reflected in the geometric standard deviations (Tables 1 and 2), as a wider granule size distribution is observed with larger droplet size. The differences in geometric standard deviation diminish with increasing quantity of binder solution since this gives a more uniform wetting.

Starting materials

In a previous paper (15) a smaller granule size was observed at a higher content of maize starch, a fact which was accounted for by incomplete

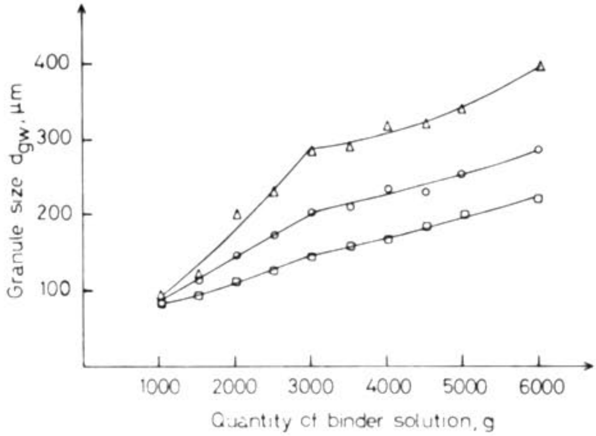

Figure 2. Influence of quantity of binder solution on granule size at varying droplet sizes (d_{50}).
Starting materials: 80 % lactose + 20 % maize starch. Bed load: 15 kg.
ΔT_{gran}: 20° C. Liquid flow rate: 150 g/min. Binder solution: Gelatine 4 %.
△: d_{50} = 142 µm, nozzle air flow rate: 6 Nm^3/h
○: d_{50} = 106 µm, nozzle air flow rate: 8 Nm^3/h
□: d_{50} = 71 µm, nozzle air flow rate: 12 Nm^3/h

wetting of the larger surface area and absorption of water. Similar results were obtained when using varying quantities of binder solution (Fig. 3). The quantities of this were not sufficient to induce a satisfactory agglomeration in the case of 80 % of maize starch, indicating that a higher liquid flow rate combined with a larger quantity of binder solution should be used.

This assumption was confirmed by an experiment carried out at a liquid flow rate of 400 g/min, a nozzle air flow rate of 10.6 Nm^3/h and using 6,000 g of binder solution. The granule size (d_{gw}) was found to be 303 µm before and 242 µm after drying, corresponding to an attrition of 20 %, which can be explained partly by a higher attrition at increased liquid flow rate (9, 17) and partly by weaker agglomerates because of a narrower size distribution of the starting materials (4).

Temperature of inlet air

As previously described (17) granule size is inversely proportional to the difference between inlet air and wet bulb temperatures in the granulation phase ((ΔT_{gran}). In accordance with these results the granule growth rate was found to be lower at higher ΔT-values (Fig. 3), which results in a reduction of the number of liquid bridges. However, a fall in growth rate was still observed after addition of about 3,000 g of binder solution.

Table 2. Influence of quantity of binder solution on granule size distribution (s_g) at the end of granulation phase under varying experimental conditions.
Starting materials: 80 % lactose + 20 % maize starch. ΔT_{gran}: 20° C.

	Binder solution	Gelatine 4 %	Gelatine 4 %	Gelatine 4 %	Gelatine 4 %	Kollidon 90 4 %	Kollidon 25 10 %	CMC 3 %
	Bed load (kg)	15	15	10	10	15	15	15
	Nozzle air flow rate (Nm^3/h)	12.0	6.00	8.00	6.39	8.00	8.00	8.00
	Liquid flow rate (g/min)	150	150	150	100	150	150	150
Quantity of binder solution (g)	1,000	2.01	2.31	2.24	2.30	2.48	2.09	2.03
	1,500	2.01	2.57	2.04	2.23	2.46	2.14	2.28
	2,000	1.98	2.32	1.82	2.03	2.26	2.07	2.18
	2,500	1.94	2.25	1.74	1.74	2.09	1.93	2.19
	3,000	1.81	2.10	1.61	1.64	1.97	1.85	2.19
	3,500	1.80	1.93	1.62	1.62	2.09	1.81	2.01
	4,000	1.70	1.87	1.50	1.49	2.18	1.85	2.05
	4,500	1.67	1.78	1.39	1.44	1.96	1.76	1.89
	5,000	1.63	1.72	1.40	1.42	1.94	1.70	1.88
	6,000	1.52	1.62	1.37	1.39	1.83	1.72	1.74

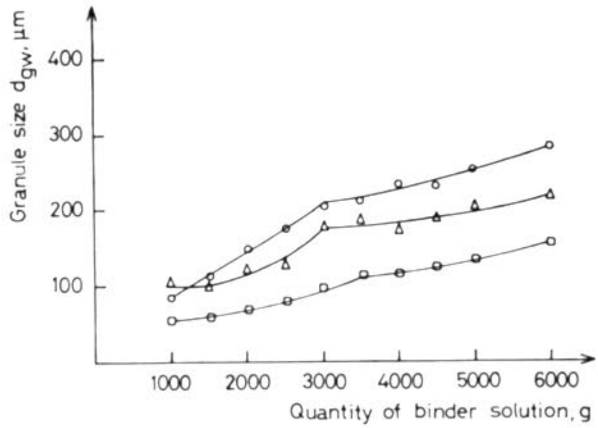

Figure 3. Influence of quantity of binder solution on granule size at varying inlet air temperatures and starting materials.
Bed load: 15 kg. Nozzle air flow rate: 8 Nm^3/h.
Liquid flow rate: 150 g/min. Binder solution: Gelatine 4 %.
○: 80 % lactose + 20 % maize starch, ΔT_{gran} = 20° C
□: 20 % lactose + 80 % maize starch, ΔT_{gran} = 20° C
△: 80 % lactose + 20 % maize starch, ΔT_{gran} = 35° C

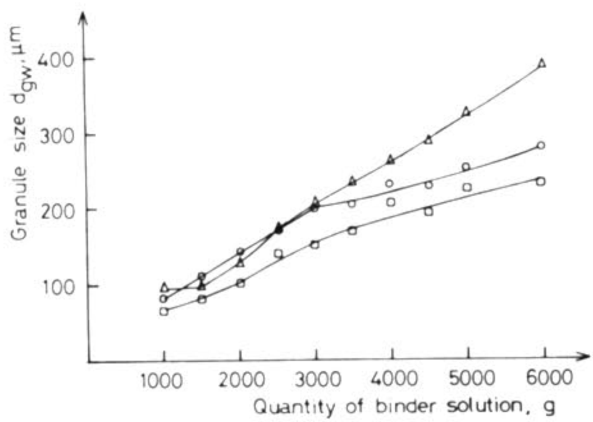

Figure 4. Influence of quantity of binder solution on granule size at varying liquid flow rates.
Starting materials: 80 % lactose + 20 % maize starch. Bed load: 15 kg.
ΔT_{gran}: 20° C. Binder solution: Gelatine 4 %. Droplet size, d_{50}: 106 μm.
□: Liquid flow rate: 100 g/min. Nozzle air flow rate: 6.39 Nm^3/h.
○: Liquid flow rate: 150 g/min. Nozzle air flow rate: 8.00 Nm^3/h.
△: Liquid flow rate: 200 g/min. Nozzle air flow rate: 9.48 Nm^3/h.

Liquid flow rate

Previous experiments (17) showed granule size to be directly proportional to liquid flow rate. As is to be expected, the largest growth rate was observed at the highest liquid flow rate (Fig. 4), but contrary to the other growth curves an almost linear relationship between granule size and quantity of binder solution was observed at a flow rate of 200 g/min, indicating a constant granule growth rate.

Bed load

All the previous experiments were carried out with a bed load of 15 kg of starting materials. Changes in bed load are possible within certain limits. *Ormós et al.* (10) found the optimum height of the bed of starting materials to be between ½ and ⅔ of the diameter of the bed. Higher as well as lower bed loads may result in chanelling or slugging.

Bed load was shown to affect the drying rate (19), and in order to obtain the same granule size and to keep the water content constant when altering the bed load other experimental conditions have to be modified. Other authors (2, 10, 12) used a quantity of binder solution directly proportional to the bed load, i.e. a constant, relative quantity, and kept the liquid flow rate constant. This correction results in an unchanged water content of the granulation during the granulation phase, provided that the drying rate (expressed in g water/min) is independent of the bed load. However, ambiguous conclusions were obtained (2, 10, 12). If the drying rate (g water/min), on the other hand, is directly proportional to the bed load, a constant water content is obtained when using the same relative quantity of binder solution and the same relative liquid flow rate.

In the present experiments bed loads of 10 and 15 kg were compared by using both of these correction methods (Fig. 5). The best correction was obtained when using the same relative quantity of binder solution and keeping the liquid flow rate constant at 150 g/min. This indicates that the drying rate (g water/min) is independent of the bed load, which may be explained by the fact that the drying air is nearly saturated with water due to the intimate contact between air and product during fluidization.

As can be seen from Tables 1 and 2 a decrease in bed load results in a slightly narrower size distribution which also has been found by *Gupte* (2). The effect probably results from a more uniform distribution of binder solution with lower bed height.

Type of binder

Granule growth was found to be dependent on the type of binder (Fig. 6). In agreement with previous findings (18) Kollidon 90 and gelatine showed

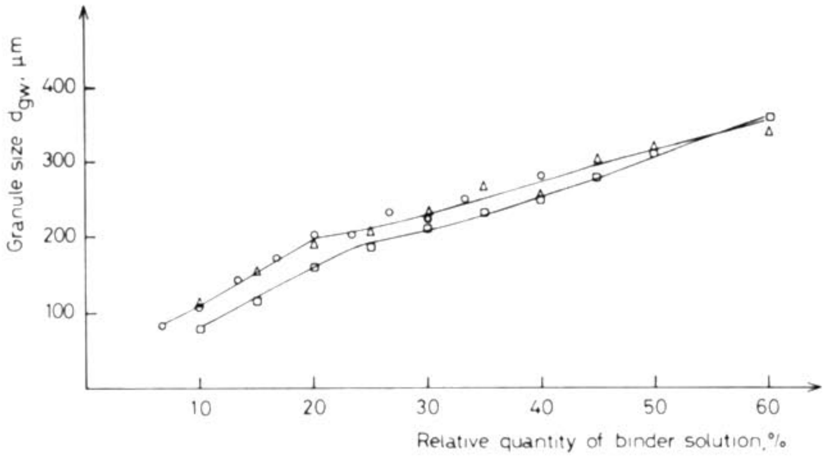

Figure 5. Influence of relative quantity of binder solution on granule size at varying bed loads.
Starting materials: 80 % lactose + 20 % maize starch. ΔT_{gran}: 20° C.
Binder solution: Gelatine 4 %. Droplet size, d_{50}: 106 µm.
○: Bed load: 15 kg. Liquid flow rate: 150 g/min.
△: Bed load: 10 kg. Liquid flow rate: 150 g/min.
□: Bed load: 10 kg. Liquid flow rate: 100 g/min.

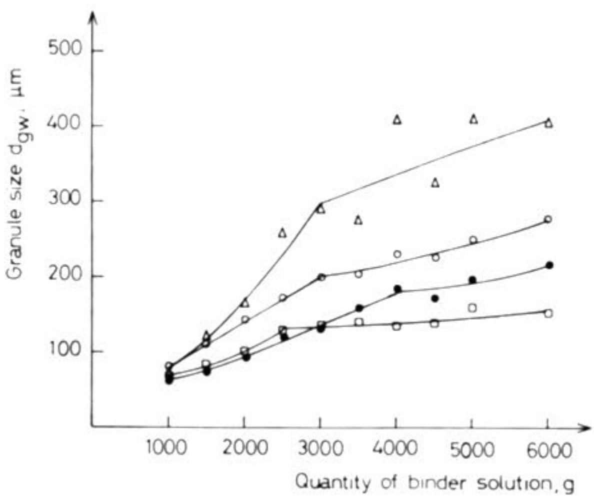

Figure 6. Influence of quantity of binder solution on granule size with varying binder solutions.
Starting materials: 80 % lactose + 20 % maize starch. Bed load: 15 kg.
ΔT_{gran}: 20° C. Nozzle air flow rate: 8 Nm³/h. Liquid flow rate: 150 g/min.
○: Gelatine 4 %, droplet size, d_{50}: 106 µm
△: Kollidon 90 4 %, droplet size, d_{50}: 148 µm
□: Kollidon 25 10 %, droplet size, d_{50}: 106 µm
●: CMC 3 %, droplet size, d_{50}: 135 µm

the best agglomeration properties. The above-mentioned break on the growth curve was observed for all binder solutions.

Irregular granule growth is seen after the addition of about 3,000 g of binder solution when using Kollidon 90, indicating a poor reproducibility. These and previous results (18) show that it may be difficult to control granule growth in the case of a large granule size.

Growth mechanisms

Variations in the content of fines in the granules were examined on the basis of results of the sieve analyses (Figs. 7 and 8). At first a considerable fall in particles smaller than 74 μm can be seen, nuclei being formed from primary particles, corresponding to the high granule growth rate observed at the start of the growth curves (Fig. 2-6). After addition of a certain quantity of binder solution the growth rate decreases due to a diminished content of fines. *Ormós et al.* (8) obtained similar results, and curves corresponding to Figs. 7 and 8 were derived from the remaining experiments.

Granule growth in a rotating drum can be divided into three stages, nucleation, transition and ball growth regions (14). The same designations are used below to describe stages of granule growth in a fluidized bed, but due to the previously mentioned fundamental differences in ways of adding liquid growth mechanisms assigned to the regions in question are different.

At the start of the nucleation region nuclei of two or more primary particles are formed, held together by liquid bridges which primarily are pendular. The size of these nuclei will depend on that of atomized droplets. In the nucleation region further growth occurs, the remaining primary particles being bound to nuclei by pendular bindings. It is easier to bind a primary particle to another one or to a nucleus than to bind two nuclei to each other, because the tensile strength of liquid bridges is inversely proportional to the diameter of the particles (13). A decrease in content of fines therefore gives a lower growth rate, reflected in a break on the growth curves.

The most appreciable break is observed (Fig. 2) at the largest droplet size, because this gives the steepest fall in the content of fines (Figs. 7 and 8). The difference is most pronounced in the case of fines smaller than 125 μm. The explanation could be that tensile strength increases from the pendular to the capillary state (6), larger droplets thus being able to bind larger particles together due to formation of funicular or capillary bindings. The number of bindings of these types and, thus, granule growth rate in the nucleation region, increase simultaneously with a rise in amount of

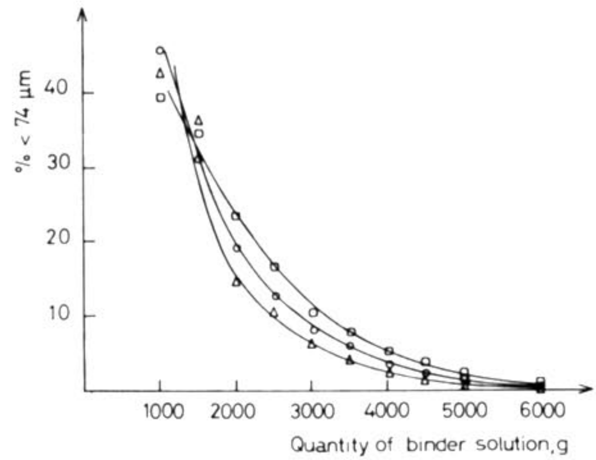

Figure 7. Influence of quantity of binder solution on content (% by weight) of fines < 74 µm in the granulations in Figure 2.
△: d_{50} = 142 µm, nozzle air flow rate: 6 Nm^3/h
○: d_{50} = 106 µm, nozzle air flow rate: 8 Nm^3/h
□: d_{50} = 71 µm, nozzle air flow rate: 12 Nm^3/h

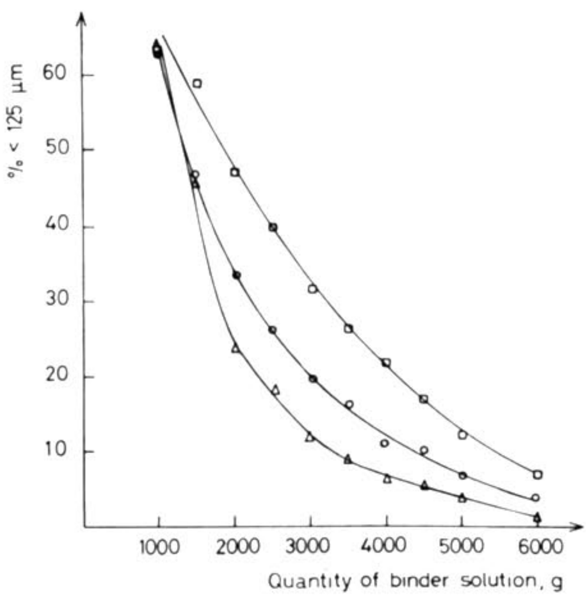

Figure 8. Influence of quantity of binder solution on content (% by weight) of fines < 125 µm in the granulations in Figure 2.
△: d_{50} = 142 µm, nozzle air flow rate: 6 Nm^3/h
○: d_{50} = 106 µm, nozzle air flow rate: 8 Nm^3/h
□: d_{50} = 71 µm, nozzle air flow rate: 12 Nm^3/h

water on the surface of the particles which may be caused by decreasing inlet air temperature and increasing liquid flow rate, lactose content and droplet size. In the latter case the increase in surface wetting is due to an uneven distribution of binder solution, as mentioned above.

Contrary to this a high inlet air temperature leads to weaker agglomerates due to evaporation of water from the liquid bridges. The tensile strength of hese depends further on the type of binder (18). When using a weak binder the agglomerates formed are broken down because of the high mechanical stress in a fluilized bed.

After addition of binder solution in a certain quantity most of the primary particles are agglomerated and the nucleation region passes into a transition region reflected in a fall in growth rate. In the transition region liquid bridges change gradually from the pendular into the funicular state and finally into the capillary state due to continuous addition of liquid and to consolidation of agglomerates caused by mechanical stress and hydrostatic suction in the liquid bridges.

A few primary particles remain in the transition region and are bound to granules just as fine particles formed by abrasion of agglomerates are. These growth mechanisms result only in a minor granule growth, and the tendency to growth by coalescence of two or more granules primarily affects growth rate in the transition region. If the liquid bridges are weak because of low liquid flow rate, high inlet air temperature, small droplet size or weak binders, growth rate in the transition region will be low. When using a high liquid flow rate agglomerates attain to the capillary state at the start of the transition region, and coalescence of granules is possible, causing a constant growth rate (Fig. 4). In this case distinction between nucleation and transition regions is impossible.

As most of the liquid bridges change into the capillary state due to further addiion of liquid, a considerable growth will occur through coalescence of granules. From a certain time the transition region proceeds into a ball growth region manifested by a sudden and uncontrollable growth.

Cohesion forces between granules are augmented with increasing water content, which necessitates an increased air velocity in order to keep the granules fluidized. The fluidizing air will tend to separate the granules and thus counteract agglomeration. In that way the intense growth in the ball growth region is counteracted, and this is why no sharp distinction between transition and ball growth regions is seen on the growth curves.

The maximum fluidizing air velocity of the apparatus sets, however, an upper limit for the quantity of binder solution to be added, and upon further addition of liquid the critical water content of the bed will be reached and fluidization stops. Granules of several cm in diameter were observed in a few unsuccessful experiments when using inexpedient combinations of fluidizing air velocity and water content of the granulation, indicating that the ball growth region was attained.

As can be seen from Tables 1 and 2, a narrower size distribution is obtained with larger quantities of binder solution. This could be explained by the fact that agglomeration of small particles is easier than that of large particles, resulting in a narrowing of the granule size distribution. In accordance with previous results (18) gelatine caused a lower geometric standard deviation than the other binders examined.

Conclusions

A quantitative description of granule growth in fluidized bed granulation was not possible on basis of the experiments, various growth mechanisms being active simultaneously with abrasion of agglomerates and granule growth being dependent of the experimental conditions. The present results indicate that the varying growth curves obtained by different authors might be explained by the different experimental conditions.

Fluidized bed granulation is a convenient method of controlling granule growth, since growth regions can be separated by a suitable choice of levels for the variables. A low growth rate in the transition region is advantageous from a production point of view, resulting in a good reproducibility. Ball growth usually being undesirable, addition of liquid has to be stopped during the transition region.

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