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Control of fluidized bed granulation

IV. Effects of binder solution and atomization on granule size and size distribution

Torben Schæfer & Ole Wørts***

Granulations were prepared in a fluidized bed granulator (Glatt, WSG 15) using aqueous solutions of gelatine, polyvinylpyrrolidone, sodium carboxymethylcellulose and methylcellulose in varying concentrations as binder solutions. Granule size was found to be directly proportional to binder concentration for a given binder and to droplet size for a given binder solution. A wider granule size distribution was observed with increased droplet size. The type of binder was found to affect granule size due to influence on droplet size and granule growth. Gelatine and Kollidon® 90 showed the best agglomeration properties as a given droplet size resulted in the largest granule size when these binders were used.

Pharmaceutical granules are primarily obtained by wet granulation methods. Particles are held together in the wet state by liquid bridges and in the dry state by solid bridges, which are caused by hardening binders, crystallization of dissolved substances or deposition of suspended colloidal particles (12,16). Spraying water on powders did not lead to agglomeration in a fluidized bed, whereas granules were obtained due to crystallization when aqueous solutions of sucrose (14,20) were used. Fluidized bed granulations are usually prepared, however, by applying solutions of different binders, such as gelatine (1-3,8-11,14,15,20), polyvinylpyrrolidone (3,8,13,15,20), methylcellulose (7,20), hydroxypropylcellulose (3), and starch (5,8,20). Distributing the binder in the starting materials before wetting resulted in a smaller granule size (8,20). Aqueous solutions of

* The Royal Danish School of Pharmacy, Department of Pharmaceutics, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

** Novo Industri A/S, Pharmaceutical Research and Development Laboratory, Novo Allé, DK-2880 Bagsværd, Denmark.

binders are ordinarily preferred since organic solvents are more expensive and give rise to pollution and explosion risks. Furthermore, use of such solvents results in a smaller granule size (15,20) and they are thus less suitable for fluidized bed granulation.

Davies & Gloor (3) compared different binders and found a significant influence of binder type on granule size. The concentration of binder in the granules is directly proportional to that of binder in the solution if the quantity of the solution is unchanged. Under such circumstances several authors have found a rise in granule size with increasing binder concentration (1,3,5,9), whereas contradictory results were found with respect to the influence of binder concentration of the solution, if the final binder concentration in the granules was kept constant by varying the quantity of binder solution (4,5,7,9). In the latter case it is difficult to distinguish the effect of binder concentration from that of different water content, and it therefore seems reasonable to evaluate the influence of binder concentration on granule size on the basis of experiments with an unchanged quantity of binder solution.

Atomization of the binder solution is controlled by the air-to-liquid mass ratio in the nozzle. Several authors (2,5,13,15,20) found that increased air pressure and, consequently, increased air-to-liquid mass ratio resulted in a fall in granule size. *Thurn* (20) examined the corresponding droplet sizes and found a simultaneous decrease in these, and in a previous paper (18) a slight increase in the mass ratio was shown to cause a significant fall in droplet size. *Ormós et al.* (11) found, however, no influence on granule size of mass ratios varying between 1.14 and 5.17, but droplet sizes were not examined. Although many experiments on the influence of nozzle air flow rate on granule size have been described in the literature, no systematic evaluation of the effect of droplet size on granule size has as yet been carried out.

Type and concentration of binder were shown (18) to have a significant influence on droplet size, indicating that the different effects of binders on granule size described by other authors might be accounted for by differences in droplet size. The purpose of this work has therefore been to examine the correlation between droplet size and granule size by using solutions of different binders in varying concentrations in order to elucidate the influence of type of binder on agglomeration in a fluidized bed.

Experimental

Materials and formulation

Starting materials were 15 kg of a mixture of fine-crystalline lactose and maize starch (4:1) (17). 3,500 g of aqueous solutions of gelatine (Ph. Nord. 63), polyvinylpyrrolidone (Kollidon® 25 and Kollidon® 90, BASF), sodium carboxymethylcellulose (7L1, Hercules) (CMC) and methylcellulose 15 (DAK 63) (MC) in varying concentrations were used as binder solutions. Their preparation and viscosities were described previously (18).

Equipment and procedure

A fluidized bed spray granulator (Glatt, model WSG 15) was used. Nozzle, instrumentation and general procedure were as previously described (17,18). Liquid flow rate was 150 g/min, and ΔT-values (19) were 20° C in the granulation phase and 35° C in the drying phase.

Granule size and size distribution

Granule size distributions were estimated using sieve analysis and were characterized by d_{gw} and s_g as described in a previous study (17). Granule size and size distribution at the end of the granulation phase, determined as previously described by tray drying (19), were ordinarily used as dependent variables in the present experiments, as these values are unaffected by attrition in the drying phase. Size distribution of the final granules, dried in the fluidized bed, was estimated in some of the experiments in order to investigate the attrition.

Results and discussion

Binder concentration

Binder concentration is expressed in percentage by weight of binder in the solution. Regression analysis showed that the correlation between binder concentration and granule size could be described by straight lines (Fig. 1). A larger granule size is produced with increasing binder concentration, but, in accordance with the results of *Davies & Gloor* (3), this effect is profoundly affected by the type of binder.

It was seen from the confidence limits of the intersections of the regression lies with the Y-axis that the granule size approaches the particle size of the starting materials (about 50 μm), except for gelatine, as the concentration of binder approaches zero. In the case of gelatine the granule size corresponding to a concentration of 2 % is slightly lower than expected on basis of the regression line, indicating a curvature at low concentrations of gelatine. The reason why gelatine differs from the other binders is discussed below.

Attrition is expressed as the difference in granule size (Δd_{gw}) before and after drying, or as the percentage of granule size (d_{gw}) before drying. As can be seen from Table 1 attrition is considerably reduced at increased binder concentration in the case of Kollidon 90 and gelatine, whereas only a slight influence is seen when the other binders are used, indicating a higher mechanical strength of solid bridges of Kollidon 90 and gelatine.

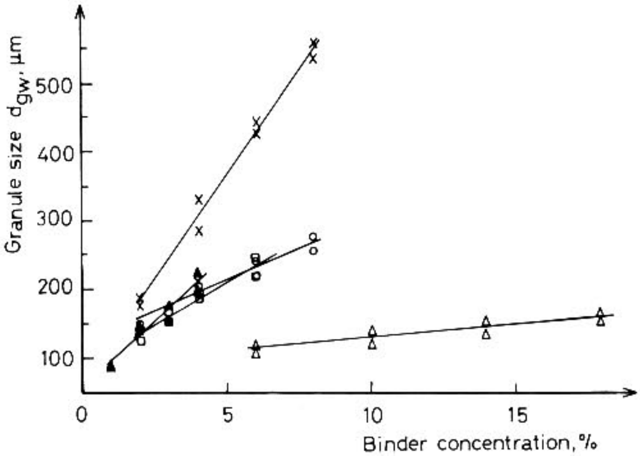

Figure 1. Correlation between binder concentration of the binder solution and granule size at the end of the granulation phase.
Liquid temperature: MC: 30° C, other binders: 40° C.
Air-to-liquid mass ratio: 1.15.

○: gelatine	△: Kollidon 25	X: Kollidon 90
□: CMC	▲: MC	

Viscosity

Viscosity of binder solution has previously been found to affect droplet size (18) and in order to investigate whether this may account for the influence of type and concentration of binder on granule size, the correlation between viscosity and granule size was examined. It was shown by analysis of regression that the correlation could be described by straight lines in semilogarithmic scale (Fig. 2).

As can be seen, the results in Fig. 1 cannot be explained solely by differences in viscosity. Direct comparison of results obtained when using solutions of gelatine and Kollidon 25 is possible, the viscosities being alike. The effects of viscosity and type of binder on granule size were found by a two-factor analysis of variance to be significant at the 0.1 %-level, interaction at the 1 %-level.

The effect of viscosity on droplet size (18) may explain the influence on granule size. However, since higher viscosity is caused by an increase in binder concentration, a simultaneous increase in the strength of liquid bridges may as well result in a larger granule size. Probably the increased granule size is a result of both effects.

In a previous study (18) gelatine was found to cause a slightly higher droplet size than Kollidon 25. The difference in effect of these binders on granule size is, however, so pronounced that it cannot solely be accounted

Table 1. Influence of type and concentration of binder on attrition (Δd_{gw} (μm) and %) in the drying phase of the granules in Fig. 1.

Gelatine			Kollidon 25			Kollidon 90			MC			CMC		
Binder conc.	Attrition		Binder conc.	Attrition		Binder conc.	Attrition		Binder conc.	Attrition		Binder conc.	Attrition	
%	Δd_{gw}	%	%	Δd_{gw}	%	%	Δd_{gw}	%	%	Δd_{gw}	%	%	Δd_{gw}	%
2	33	22	6	29	26	2	51	28	1	20	22	2	31	23
4	33	16	10	33	25	4	57	19	2	34	23	3	28	17
6	20	9	14	31	22	6	8	2	3	25	15	4	37	20
8	17	6	18	34	21	8	7	1	4	40	19	6	29	13

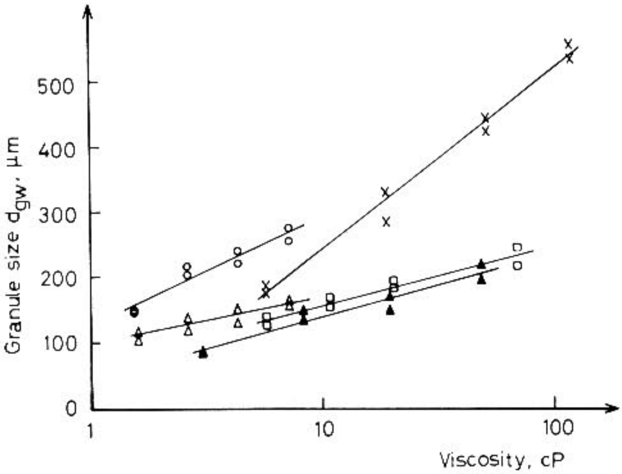

Figure 2. Correlation between viscosity of the binder solution and granule size at the end of the granulation phase of the granules in Figure 1.

○: gelatine △: Kollidon 25 X: Kollidon 90
□: CMC ▲: MC

for by the slightly different influence on droplet size. Gelation of gelatine solutions may begin during contact with the atomizing air at the nozzle orifice and it could explain the above-mentioned increase in droplet size. Product temperature being below gelation temperature, gelation is likely to proceed when the atomized gelatine solution reaches the fluidized particles, and an increased mechanical strength of the liquid bridges due to gelation may thus account for the observed larger granule size. This assumption is confirmed by the above-mentioned deviation from the regression line (Fig. 1).

Since the gelation tendency falls with decreasing concentration of gelatine, a descending curvature is observed at low concentrations, and for the same reason an interaction between viscosity and type of binder, reflected in an increasing influence of the latter at higher viscosity, is observed.

Fig. 2 shows no appreciable differences in effect on granule size for solutions of the same viscosity when CMC, MC and Kollidon 25 are used as binders, whereas gelatine and Kollidon 90 result in a larger granule size. In a previous study (18) the latter binders resulted in a larger droplet size than the others, but this effect was less pronounced, which indicates that gelatine and Kollidon 90 possess properties affecting atomization as well as agglomeration.

In the case of Kollidon 90 the results cannot be explained by gelation, but may be accounted for by differences in mechanical strength of the

Table 2. Influence of temperature of binder solution on granule size (d_{gw}, μm) at the end of the granulation phase. Air-to-liquid mass ratio: 1.15.

CMC			Kollidon 90		
Binder conc.	Liquid temperature		Binder conc.	Liquid temperature	
%	40° C	80° C	%	40° C	80° C
3	168	140	4	284	241
	155	137		327	222
6	217	214	8	555	344
	245	193		535	343

binders. *Healey et al.* (6) have investigated the tensile strength of films of different binders including gelatine and polyvinylpyrrolidone (Plasdone K29-32) and found that the former showed the highest and the latter the lowest tensile strength. The results suggest a possible correlation between tensile strength of binder films and agglomeration properties of binders. However, further experiments permitting a direct evaluation of this correlation are necessary before definitive conclusions can be drawn.

In order to examine the influence of viscosity on granule size without changing type and concentration of binder, experiments were carried out at two temperatures of binder solution (Table 2). The effects of temperature on granule size were found by analyses of variance to be significant at the 5 %-level (CMC) and at the 0.1 %-level (Kollidon 90). A rise in temperature of binder solution causes a smaller granule size.

In a previous study (18), the effect of temperature on droplet size could not be clearly determined because of a high experimental error. Due to the intimate contact between particles and fluidizing air the atomized droplets are expected to cool down to product temperature in a very short time. The effect of temperature of the binder solution must therefore be due to an influence on atomization as a fall in viscosity caused by a rise in temperature gives a smaller droplet size and, consequently, a decreasing granule size. Since a change in viscosity has a more pronounced influence on droplet size in the case of Kollidon 90, as shown earlier (18), the liquid temperature was found to affect granule size to a greater extent when solutions of Kollidon 90 instead of CMC were used.

Droplet size

The correlation between the previously examined droplet sizes (18) and granule size was investigated by granulation experiments. Some of the results have been described above, and further experiments were carried out

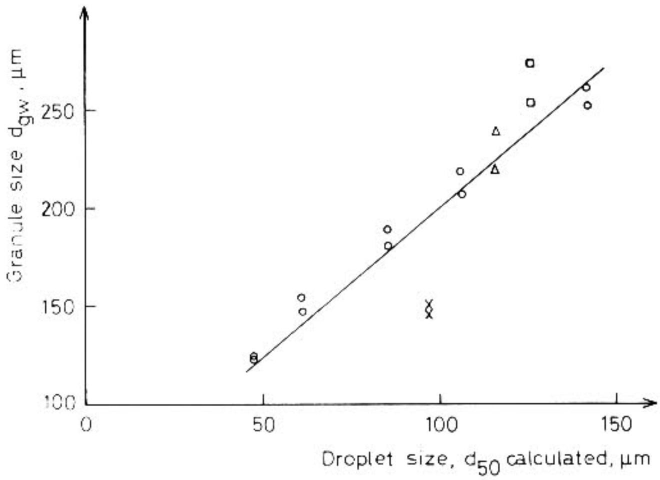

Figure 3. Correlation between droplet size calculated from the empirical droplet size equation (18) and granule size at the end of the granulation phase.
Binder: Gelatine.
Binder concentrations:
X: 2 % ○: 4 % △: 6 % □: 8 %

at air-to-liquid mass ratios of 0.86, 1.43, 2.01 and 2.58 when using gelatine 4 %, Kollidon 25 10 %, Kollidon 90 4 %, CMC 3 % and MC 2 %, and at mass ratios of 0.86 and 2.58 when using Kollidon 90 8 % and CMC 6 % as binder solutions.

No general correlation was found between droplet size and granule size neither when experimentally determined droplet sizes nor when values calculated from the empirical droplet size equation (18) were used. This could be explained by the fact that, as shown above, the type of binder affects agglomeration. Correlations were therefore examined for the binders individually.

An example of this is shown in Fig. 3 for gelatine. The best fitting linear trend line was calculated by analysis of regression, but the hypothesis of linearity was rejected at the 5 %-level. As can be seen, the deviations from the regression line may be explained by an influence of binder concentration, since the lowest concentration results in a smaller and the highest concentration in a larger granule size than is to be expected on basis of the regression line. Similar results were obtained when using the other binders. The effect of binder concentration on granule size at a constant droplet size is explained by a higher mechanical strength of the liquid bridges between particles with increased binder concentrations.

Figs. 4 and 5 show the correlation between droplet size and granule size for unchanged binder concentration. Regression lines were calculated

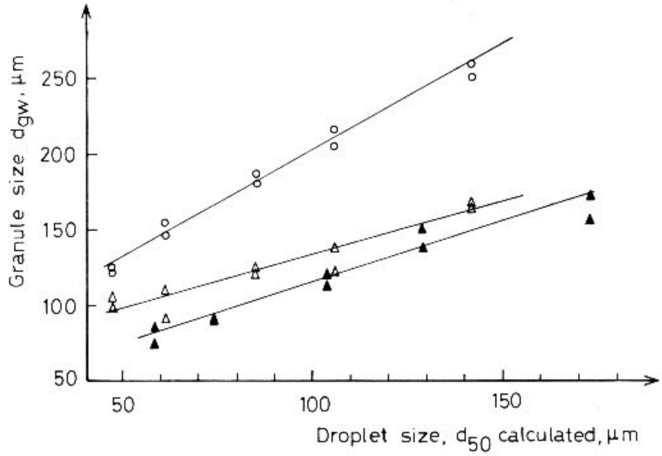

Figure 4. Correlation between droplet size calculated from the empirical droplet size equation (18) and granule size at the end of the granulation phase.
Binder solutions:

○: gelatine 4 % △: Kollidon 25 10 % ▲: MC 2 %

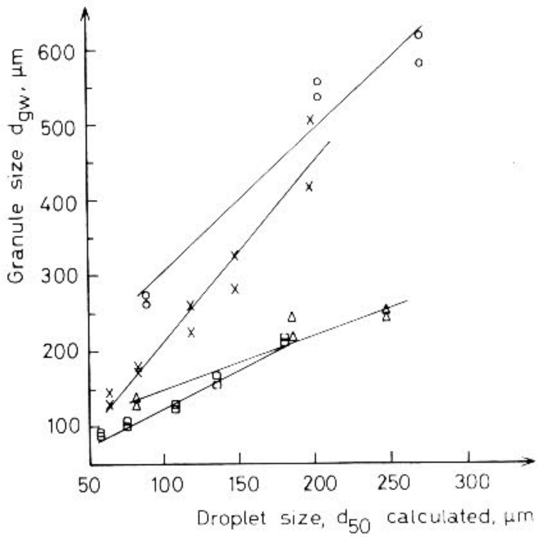

Figure 5. Correlation between droplet size calculated from the empirical droplet size equation (18) and granule size at the end of the granulation phase.
Binder solutions:

X: Kollidon 90 4 % ○: Kollidon 90 8 %
□: CMC 3 % △: CMC 6 %

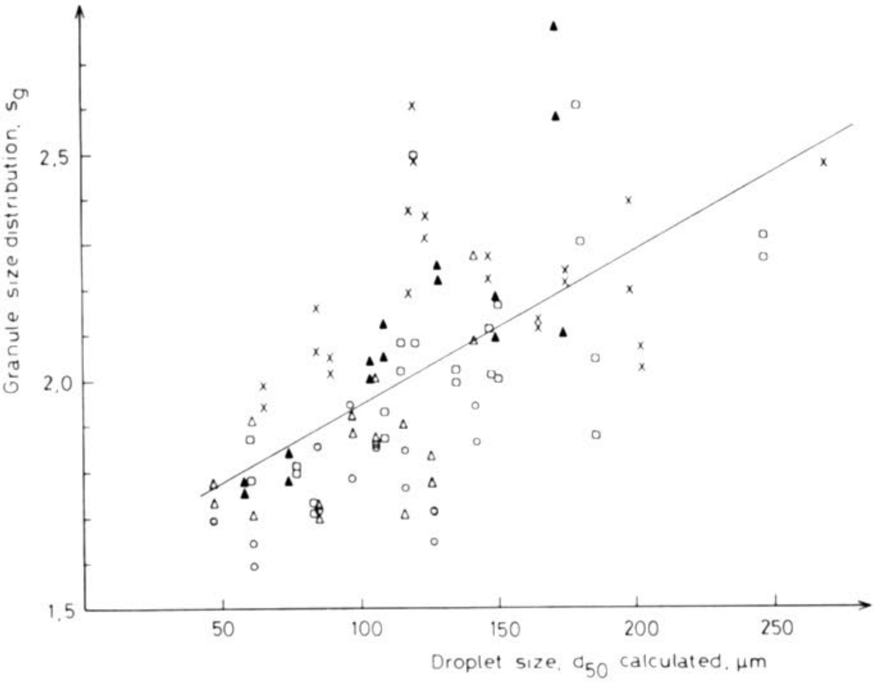

Figure 6. Correlation between droplet size calculated from the empirical droplet size equation (18) and granule size distribution at the end of the granulation phase.
○: gelatine △: Kollidon 25 X: Kollidon 90
□: CMC ▲: MC

and a linear correlation was accepted if the hypothesis of linearity was accepted at the 5 %-level. This was the case except for Kollidon 90 8 %. The deviations when using the latter may be explained by the fact that high viscosity of the binder solution causes atomization problems (18). In accordance with the above-mentioned results Kollidon 90 and gelatine give a larger granule size than the other binders, indicating better agglomeration properties. The same conclusions were drawn when the correlation between experimentally determined droplet sizes and granule sizes was investigated. The former being dependent on the type of binder (18), the differences in effect on granule size were less pronounced, though still significant.

The correlation between droplet size and granule size distribution is shown in Fig. 6. Although the hypothesis of linearity was rejected at the 5 %-level, the regression line shows that a wider granule size distribution is obtained at increased droplet size. A linear correlation was accepted, however, if type and concentration of binder were kept constant. In other words, an increase in granule size results in a wider granule size distribution, provided that quantity of binder solution is unchanged. In a previous study (17) an increase in standard deviation was observed with decreasing granule size, but variations in granule size were caused by a change in mixing ratio of the starting materials.

As can be seen from Fig. 6, a narrower size distribution is observed when using gelatine. This may possibly be explained by a more uniform granule growth due to gelation in liquid bridges.

The size distributions of the final granulations were found to be slightly wider than shown in Fig. 6 on account of attrition in the drying phase.

Reproducibility

The reproducibility of the granulation experiments is expressed as the standard deviation of the mean granule size (d_{gw}). On basis of results from analyses of variance and analyses of regression in the present and previous (17,18,19) papers estimates of standard deviations were found to be about 10 μm when using gelatine, Kollidon 25, CMC and MC and about 25 μm when using Kollidon 90. The higher standard deviation observed in the latter case is probably due to the larger granule size, which may cause a tendency to uncontrollable granule growth. In the experiments carried out with Kollidon 90 under experimental conditions resulting in a smaller granule size, the standard deviation seemed to be lower. However, experiments were not performed primarily to evaluate reproducibility and, thus, further experiments are necessary to decide whether the relative standard deviation is independent of type of binder and granule size.

Conclusions

The effect of binder solution on granule size of granulations prepared in a fluidized bed was found to be due to an influence partly on droplet size of the atomized binder solution and partly on granule formation and growth. Agglomeration is caused by the formation of liquid bridges between particles, and differences in mechanical strength of liquid bridges due to variation of type and concentration of binder may explain the different agglomeration properties of binder solutions.

It was shown that varying the droplet size is a simple and sensitive way of controlling granule size of the final granulations since a linear correlation exists between droplet size and granule size. A wider granule size distribution was observed simultaneously with the rise in granule size that is caused by increasing droplet size. When using a given binder solution droplet size can be varied primarily by changing the air-to-liquid mass ratio in the nozzle and secondarily by alteration of the temperature of binder solution.

Kollidon 90 and gelatine seem to possess the best agglomeration properties of the binders examined, a given droplet size resulting in the largest granule size and, further, they were found to give the lowest attrition in the drying phase. When choosing binders for tablet formulations, however, the influence of the binder on other properties such as dissolution rate should be taken into consideration.

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