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A COMPARISON BETWEEN BINDERS IN THE WET PHASE OF GRANULATION IN A HIGH SHEAR MIXER

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ABSTRACT

The effects of binder solutions on granule size, intragranular porosity and liquid saturation in a high shear mixer are examined during the liquid addition phase of the granulation process. The power consumption profiles of impeller motor are recorded. Five different binders (PVP, PVP-PVA-copolymer, hydrolysed gelatine and two HPMC's) are investigated.

The PVP and hydrolysed gelatine produce granules with a higher mean granule size. This is shown to be due to the higher densification caused by these binders.

The power consumption profiles for PVP are significantly higher than for the other binder solutions. It is suggested that the high power consumption profiles are a result of the strength of mobile liquid bondings caused by the high surface tension of PVP solutions.

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INTRODUCTION

Binding agents are used in tablet formulations in order to improve the compressibility of the formulation and to improve the mechanical properties of granules and tablets. The major concern of the comprehensive literature on tablet binders is therefore the dry state of granules and the processing of granules into tablets. Though wet-granulation is an integral part of the tabletting process only little attention has been paid to the significance of the binder solution to granule formation and growth.

The distribution of the binder within the granules prepared by precompressing, wet massing and spray drying is investigated by Seager et al. (1). The distribution of the binder was affected by the process of granule manufacture. They present the binder structure in granules prepared by the wet massing technique as an irregularly shaped sponge-like structure.

Effects of types and concentrations of binders are investigated in fluidized bed granulators (2,3). However, the results found in a fluidized bed granulator are not directly applicable to a high shear mixer because in a fluidized bed drying occurs simultaneously to wetting and the agitation of the mass is less intense. The results by Seager et al. (1) also indicate that the granule structure might not be the same in these two granulators.

Kristensen et al. (4,5) claimed that the binder solution reduces particle interactions and thus facilitates densification of the moist agglomerates with effects on liquid saturation and granule growth. They found that in this respect a solution of a PVP-PVA-copolymer was more efficient than purified water. On this basis they suggested that the binder type and its concentration in the binder solution may have an effect on the granule growth.

Below, a comparison between five binders which are of different chemical nature is presented. The purpose of the investigation was to study whether the binder and its concentration influences the granule growth by granulation in a high shear mixer.

MATERIALS

The following five binders which are regularly used in pharmaceutical practise were investigated: a polyvinylpyrrolidone-polyvinylacetate copolymer (Kollidon VA64, BASF), a polyvinylpyrrolidone (Kollidon 90, BASF), a hydrolysed gelatine (Byco C or Protein S, Croda Foods Ltd.) and two hydroxypropyl-methylcellulose binders (Methocel E5 and Methocel E15, Dow Chemicals). The binders and the concentrations used as well as the viscosities and the surface tensions of the aqueous binder solutions are shown in Table 1. The object for choosing these concentrations was that the low concentration of each binder solution had enough binding effect to form granules which have sufficient strength in the dry state and that the high concentration was not too viscous to pump through the nozzle used.

The binder solutions were pumped to the nozzle at a temperature of 30 ^{o}C. Calcium hydrogen phosphate (dicalcium phosphate) Ph.Eur. (Albright & Wilson Ltd.) was chosen as starting material. The geometric weight mean diameter was 9.5 μm determined by the Coulter Counter[1] technique. The density was 2.34 g/cm^3 measured by Beckman air comparison pycnometer[2].

[1]Producer: Coulter Counter Electronics Ltd., Coldharbour Lane, Harpenden, Herts (England)
[2]Producer: Beckman, Fullerton, Cal. (USA)

TABLE 1

Concentrations, viscosities and surface tensions of the aqueous binder solutions

Binder	Type	Concen-trations	Viscosity Pa·s 10^3 (30°C) *	Surface tension mNm^{-1} (25°C) **
Kollidon 90	PVP	8	109	67
		5	31	68
		3	9	68
Kollidon VA64	PVP-PVA-copolymer	30	77	46
		20	15	47
		10	4	50
Protein S	hydrolysed gelatine	30	69	48
		20	12	49
		10	3	53
Methocel E5	HPMC	8	91	48
		6	43	48
		3	6	48
Methocel E15	HPMC	4.5	119	47
		3.5	59	48
		2	11	50

*) Brookfield viscosimeter, Model LVT
**) Drop-weight method (6).

EQUIPMENT

A laboratory-scale high shear mixer, Fielder PMAT 25 VG[3] with a cooling jacket was used for the granulation experiments. During the process the power consumption of the impeller motor was recorded by an El-Fi power consumption meter[4] (7).

[3]Producer: T.K. Fielder, Mayflower Close, Chandlers Ford Industrial Estate, Eastleight, Hampshire (England)
[4]Producer: El-Fi Innovationer, Box 7125, 25007 Helsingborg (Sweden)

METHODS

8.0 kg of dicalcium phosphate were used for each experiment. Dicalcium phosphate was sieved through a 300 µm sieve and dry-mixed for a few minutes in the Fielder mixer until the power consumption signal had stabilized. The experiments were carried out at two rotation speeds of the impeller, 200 and 400 rpm, respectively. The speed of the chopper was kept constant at 3,000 rpm. The liquid addition rate was 150 ml/min. The liquid was added by spraying it with a binary nozzle[5] in a narrow angle. The mean droplet size was kept within the range of 80-120 µm. The experiments were carried out in the liquid addition phase only.

Samples of about 330 g were taken after 6, 8.5, 9.5, 10.5 and 11 minutes of liquid addition. The actual moisture contents were estimated by drying samples of 5-10 g to constant weight at room temperature. A portion of the sample was tray-dried and 100 g of the dried sample were used for sieve analysis (8). The geometric mean diameter, $\bar{d}_{gw}$ and the granule size distribution of the granulate were calculated. The liquid distribution was found to be uniform when measured according to the method described in (8).

The 250-1000 µm fractions from the sieve analysis were used to determine the intragranular porosity of the granules. The porosity was measured by the pycnometric method described before (9). Ordinarily the intragranular porosity (ε) is calculated by the formula:

$$\varepsilon = 1 - \frac{\rho}{\rho_t} \qquad (1)$$

[5]Producer: Gustav Schlick GmbH & Co., Coburg (FR Germany)

where ρ is the apparent density of the granules measured by mercury and ρ_t is the true density of the granules calculated from the true densities of the ingredients (air comparison pycnometer).

In order to compare porosity values of the granules with varying binder concentrations, the porosity measurement has been corrected for the volume of binder deposited in the granules. This corrected porosity value reflects the true porosity of the wet granules provided that all the binder is deposited in the pores during the subsequent drying. The liquid saturation of the granules has then been calculated as the ratio between the volume of the binder solution and intragranular voids, determined on basis of the corrected porosity.

The volume of binder solution has been calculated from the loss on drying data.

The contact angle of the binder solution to dicalcium phosphate was measured by the drop-height-method (10) and it was found to be close to zero for all the solutions presented in Table 1. Since the method is inaccurate with low contact angles it is impossible to give any precise contact angle data.

RESULTS AND DISCUSSION

Granule formation and growth

Impeller speed

The impeller speed was found to have no effect on granule growth in the beginning of the granulation process, but at the end of the process a higher geometric mean diameter of the granules was achieved at high rotation speed.

Due to the more intense agitation the granules become more compact when using the high impeller speed resulting in a higher liquid saturation. The high liquid saturation causes the difference in the growth. These results are in accordance with the results of earlier experiments (8).

Types of binders

A comparison of the effect of five binders on granule growth is shown in Figure 1. Additional results are shown in Figure 5.

The granule size obtained when using Kollidon 90 or Protein S is larger than that obtained using any of the three other binders when the volume of binder solution exceeds 30%. From the porosity data (Figure 2) it appears that Kollidon 90 and Protein S result in a significantly lower intragranular porosity at the same volume of binder solution than the other binders.

Agglomeration is primarily influenced by the degree of liquid saturation which is dependent on intragranular porosity and the volume of binder solution. By that means the effects of process conditions on the granulation process were satisfactorily described (11). The porosities start to decrease very rapidly after the nucleation phase at binder solution volumes of about 28-30%, which is the same point where the granule growth by coalescence starts. The lower porosities of Kollidon 90 and Protein S granules have the effect that the granules are saturated with the solution at lower volumes of the binder solution, and that causes the earlier granule growth seen in Figure 1. In order to elucidate the effects of binder type, the mean granule size $\bar{d}_{gw}$ was plotted against the liquid saturation, S (Figure 3).

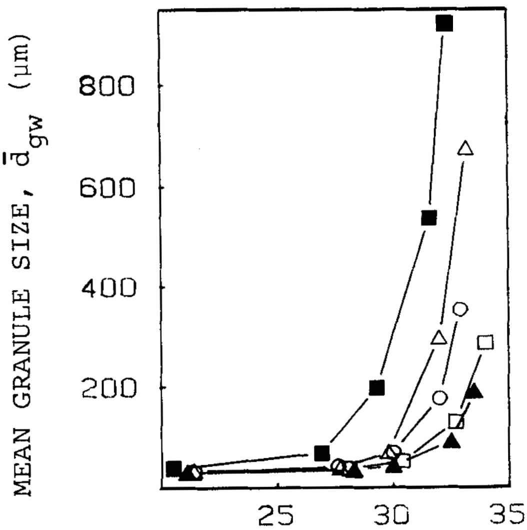


FIGURE 1
Correlation between mean granule size, $\bar{d}_{gw}$, and % v/v binder solution added. Impeller speed 400 rpm. ■ = Protein S 10%, o = Kollidon VA64 10%, Δ = Kollidon 90, 3%, □ = Methocel E15 2%, ▲ = Methocel E5 3%.

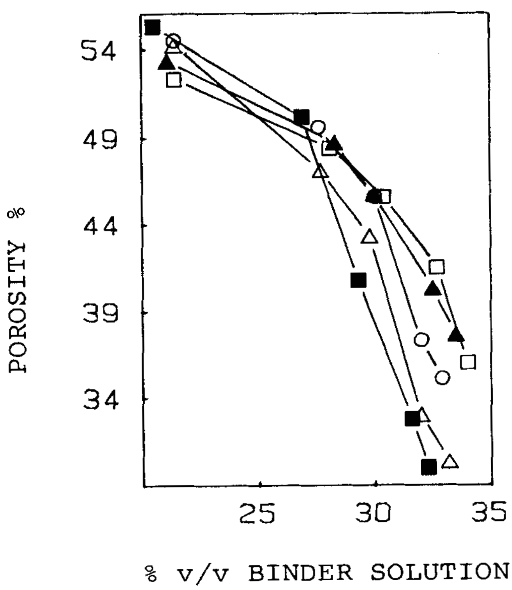


FIGURE 2
Correlation between intragranular porosity and % v/v binder solution added. Impeller speed 400 rpm. ■ = Protein S 10%, o = Kollidon VA64 10%, Δ = Kollidon 90 3%, □ = Methocel E15 2%, ▲ = Methocel E5 3%.

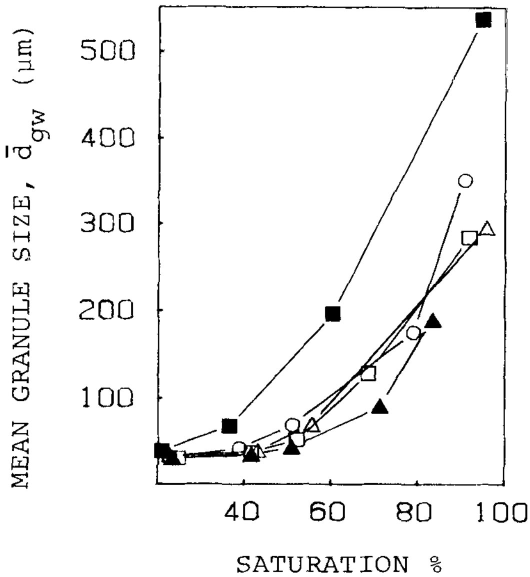


FIGURE 3
Effect of liquid saturation on granule growth. Impeller speed 400 rpm. ■ = Protein S 10%, o = Kollidon VA64 10%, Δ = Kollidon 90 3%, □ = Methocel E15 2%, ▲ = Methocel E5 3%.

As can be seen the differences between the four binders, Kollidon 90, Kollidon VA64, Methocel E5 and Methocel E15 have nearly disappeared indicating that the differences shown in Figure 1 were caused by the differences in porosities.

Protein S differs from the other binders in that the granules made with any of the Protein S binder solutions are seen to grow at a lower liquid saturation. In other words Protein S needs less liquid for the growth. No experimental reason for this phenomenon has been found.

In accordance with the growth curve in Figure 3 the fraction of fines (% granules < 75 µm) is decreasing at lower liquid saturations for Protein S than for the other binders. In Figure 4 Methocel E15 is an ex-

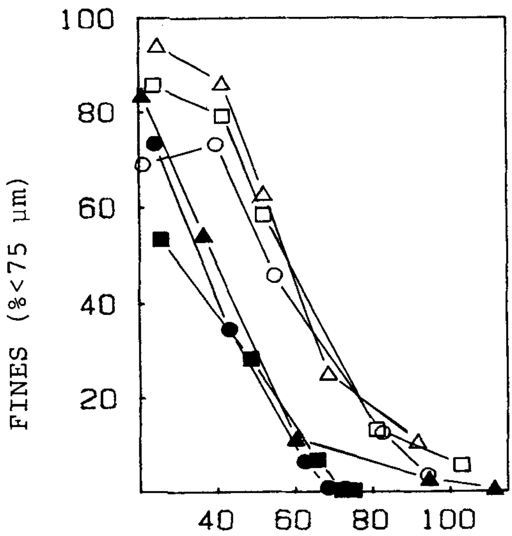
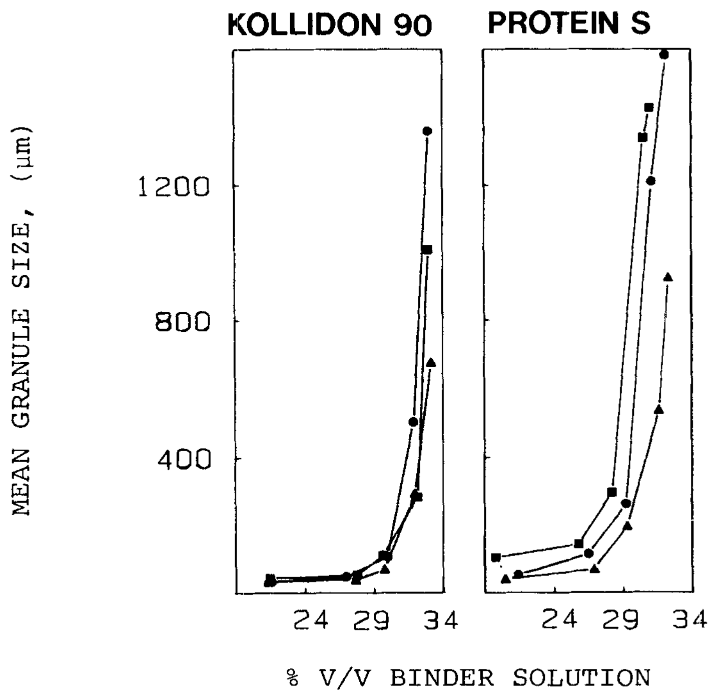


FIGURE 4
Effect of liquid saturation on the amount of fines. Impeller speed 400 rpm. ■ = Protein S 30%, ● = 20%, ▲ = 10%. □ = Methocel E15 4.5%, o = 3.5%, Δ = 2%.

ample of the other binders investigated which all show the same tendency of disappearing fines.

Concentrations of binder solutions

The effect of the concentration of the binder solution on granule growth is most apparent when using Protein S solution. The high concentration of a binder solution usually results in the largest granule size at a certain volume of the binder solution. With the solutions of the other binders, Kollidon 90, Kollidon VA64, Methocel E5 and Methocel E15 the binder concentration only has a minor effect on the granule growth (Figure 5).



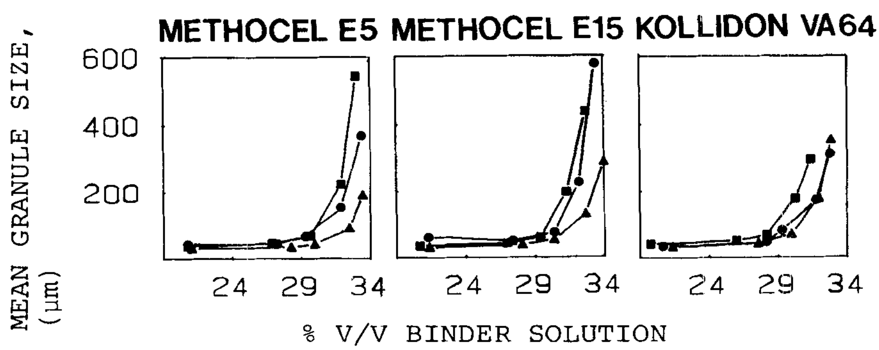


FIGURE 5
Correlation between mean granule size, $\bar{d}_{gw}$, and % v/v binder solution added at varying binder concentrations. Impeller speed 400 rpm. ■ = high concentration, ● = middle concentration, ▲ = low concentration.

Only small differences were seen in the porosities of granules obtained at different concentrations of the binder solutions. Methocel E5 exemplifies this in Figure 6. The other binder solutions investigated behave like Methocel E5 in this respect.

At a certain volume of the binder solution, however, the high concentration gives the lowest porosity if the agitation is sufficient. I.e. the mass is easier to densify if the high concentration of a binder solution is used. The binder solution thus acts more effectively as a lubricant decreasing the particle interactions between dicalcium phosphate particles (4). Consequently the lower concentration results in the largest amount of fines.

Power consumption

The power consumption of the impeller motor was recorded during addition of the binder solution as described in (7). The correlation between the power consumption and the granule size at the low concentrations of the five binder solutions is presented in Figure 7. In the beginning of the granulation process (nucleation phase) the power consumption increases rapidly, but no changes in granule sizes are observed. The nucleation causes an increasing cohesiveness of the dicalcium phosphate particles (11). The low concentration of a binder solution results in higher power consumption than the high concentration. The lubricant effect is more pronounced when using high binder concentrations resulting in lower power consumption. An example of this is shown in Figure 8.

The power consumption curves in Figure 7 show that the energy requirements for granulation with Kollidon 90 are significantly higher than the ones for the other

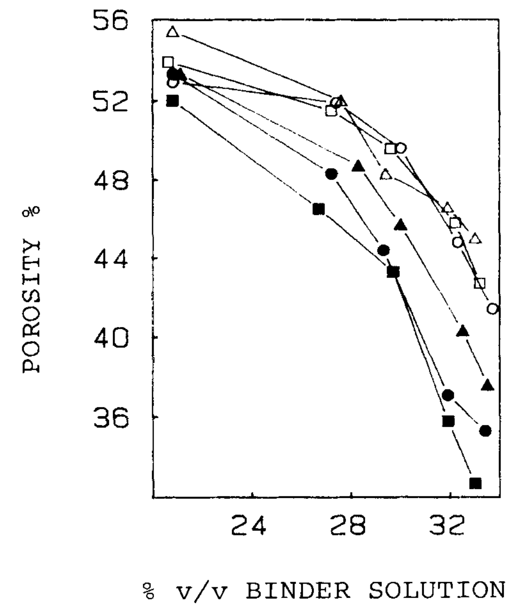


FIGURE 6
Correlation between intragranular porosity and % v/v binder solution. Methocel E5 binder solution. Impeller speed 400 rpm: ■ = 8%, ● = 6%, ▲ = 3%. 200 rpm: □ = 8%, ○ = 6%, Δ = 3%.

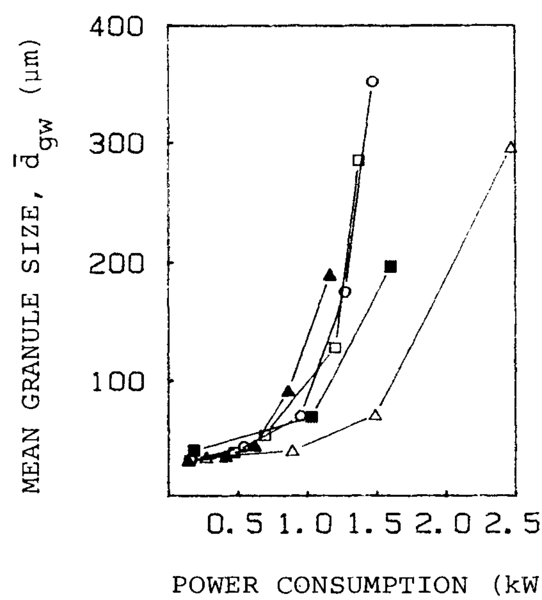


FIGURE 7
Correlation between mean granule size, $\bar{d}_{gw}$, and power consumption of impeller motor. Impeller speed 400 rpm. ■ = Protein S 10%, ○ = Kollidon VA64 10%, Δ = Kollidon 90 3%, □ = Methocel E15 2%, ▲ = Methocel E5 3%.

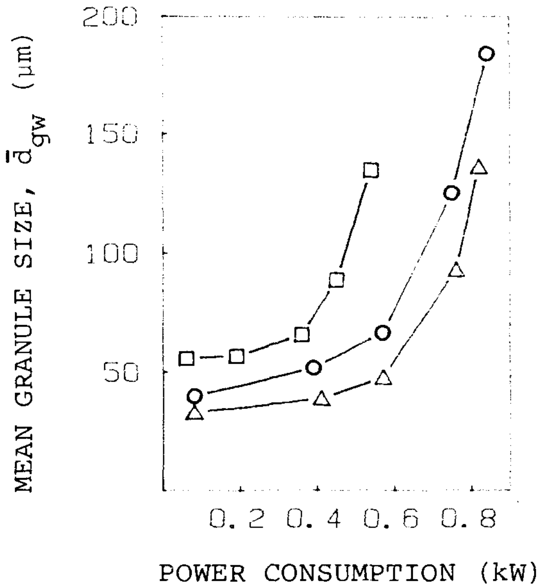


FIGURE 8
Correlation between mean granule size, $\bar{d}_{gw}$, and power consumption of impeller motor. Impeller speed 200 rpm. Methocel E15 □ = 4.5%, o = 3.5%, Δ = 2%.

binder solutions. One probable explanation of this is the high surface tension of the binder solutions containing Kollidon 90. Table 1 shows the surface tensions of the different binder solutions. The surface tension of Kollidon 90 solutions varies from 67 to 68 mNm^{-1} and for the other solutions from 46 to 53 mNm^{-1}. Surface tension probably affects the strength of the mobile liquid bondings acting in the moist granules. Therefore the high surface tension increases the strength of the mobile liquid bondings which leads to a high resistance of the wet granules against the agitation and consequently the power consumption increases.

CONCLUSIONS

There are differences in the granule growth pattern between the five binders investigated. Three of them, Kollidon VA64, Methocel E5 and Methocel E15 behave similarly. By using either Kollidon 90 or Protein S the granule growth is facilitated. In the fluidized bed granulator (2,3) Kollidon 90 was found to result in an enhanced granule growth, too. The concentration of the binder solution has only a minor effect on the granule growth. The effect of the concentration is most evident when using Protein S binder solutions.

When using Kollidon 90 binder solutions a significantly higher power consumption of the impeller motor was recorded compared to the other binder solutions. The high power consumption is likely to be caused by the higher surface tension of Kollidon 90 solutions compared to the surface tensions produced by the other binder solutions. Since the contact angles between the solutions and dicalcium phosphate were small, the effect of the surface tension may be due to effects of the strength of the mobile liquid bondings acting in the moist granules. If so, the experiments demonstrate a significant effect of liquid bonding strength on densification during the granulation and the energy required to obtain granule growth by coalescense. The effect of surface tension is more accurately dealt with in a subsequent paper.

Protein S differs from the other binders in that it gives rise to a granule growth at an earlier stage of the process, i.e. the Protein S solutions have a higher mean granule size at a certain binder volume. An explanation of this phenomenon might be that the wet granules in the case of Protein S are more adhesive due to the fact that the viscosity of Protein S solutions is more temperature dependent than the viscosity of the other binder solutions. The viscosity of Protein S solutions increases rapidly when the temperature is decreased because of the starting gel formation.

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