DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(8), 1041-1060 (1988)

INFLUENCE OF LIQUID BONDING STRENGTH ON POWER CONSUMPTION DURING GRANULATION IN A HIGH SHEAR MIXER

M.Ritala*, P.Holm, T.Schaefer and H.G.Kristensen
Department of Pharmaceutics
Royal Danish School of Pharmacy
2 Universitetsparken
DK-2100 Copenhagen Ø
Denmark

ABSTRACT

A comparison between the effects of different binders on power consumption and granule growth by granulation in a Fielder PMAT 25 high shear mixer demonstrates that the power consumption is influenced by the intragranular porosity and the surface tension of the binder solution. It is suggested that the effects are due to a correlation between the power consumption and the strength of mobile liquid bondings in the moist agglomerates. It is shown that the power consumption reflects the change of the intragranular porosity for a particular granulation process with dicalcium phosphate.

---

* Present address: Orion Corporation Ltd., Orion Pharmaceutica, P.O. Box 65, SF-02101 Espoo, Finland

INTRODUCTION

In a previous investigation[1] on the influence of binder solution on granule growth in a high shear mixer differences between binders were noticed. The PVP binder solutions (Kollidon 90, BASF) gave rise to significantly higher mean granule sizes than did the solutions of a PVP-PVA-copolymer (Kollidon VA64, BASF) and HPMC (Methocel E5 and E15, Dow Chemicals). Likewise, granulation with the PVP binder solutions gave rise to higher power consumptions of the impeller motor than the other binder solutions. It was suggested that the observed differences between the binders could be attributed to the surface tension of the binder solution. The differing problem, characteristics of the Protein S binder solution[1], are not dealt with in this publication which concentrates on the mobile liquid bondings.

Holm et al.[2] and Kristensen et al.[3,4] have shown that a large deformability of the moist agglomerates is essential for the granule growth by coalescence. The deformability is influenced by the agglomerate strength and the ability of the agglomerates to be strained without being crushed. Hence, the amount of liquid phase expressed in terms of the liquid saturation is a major factor influencing the granule growth[4,5].

In addition to the liquid saturation, the strength of the mobile liquid bondings, cf. Rumpf[6] may affect the granule growth and the power consumption. According to Leuenberger[7] changes in power consumption occur as a result of a growing cohesiveness or tensile strength of the agglomerates formed in the moistened granulating mass. It means that binder solution characteristics like surface tension and contact angle to solid influence the power consumption. Therefore, it should be possible to interpret the power consumption curves recorded during granulation on the basis of the theory of mobile liquid bondings.

The purpose of the present investigation has been to study the effects of the surface tension of the binder solution on granule growth and power consumption. The results are interpreted on the basis of the theory for mobile liquid bonding strength.

MATERIALS

Two PVP-solutions (Kollidon 90 and Kollidon 25, BASF), one PVP-PVA copolymer solution (Kollidon VA64, BASF), and two HPMC solutions (Methocel E5 and Methocel E15, Dow Chemicals) were used. The concentrations, viscosities and surface tensions of the aqueous binder solutions are shown in Table 1.

Three different concentrations of a surfactant, Polysorbate 80, Ph.Eur. grade, were added to the 3% Kollidon 90 binder solution. The concentrations, viscosities and surface tensions are given in Table 2. Calcium hydrogen phosphate (dicalcium phosphate) Ph.Eur. grade (Albright & Wilson Ltd.) was granulated. The geometric weight mean diameter, $\bar{d}_{gw}$, was 21 µm determined microscopically. The density was 2.34 g/cm^3 measured by the Beckman air comparison pycnometer. The contact angle between dicalcium phosphate and binder solution, determined by the "h and ε" method[9] was 0° in all experiments.

A few granulation experiments were made with sulphur (sulphur medicinale, Ph.Nord. 63), $\bar{d}_{gw}$ was 29 µm and density 2.01 g/cm^3 measured by the same methods as mentioned for dicalcium phosphate. The contact angles between the sulphur and the binder solutions were 56°

TABLE 1

Binding agents and characteristics of the aqueous solutions used in the granulation experiments

Trade name	*Composition*	*Concentration* % w/w	*Viscosity*1) mPas (30 °C)	*Surface*2) tension mNm^{-1} (25 °C)
Kollidon 90	PVP	3	9	68
		5	31	68
		8	109	68
Kollidon 25	PVP	3	1	68
		20	10	67
Kollidon VA64	PVP/PVA copolymer	3	1	50
		10	4	50
		20	15	47
		30	77	46
Methocel E5	HPMC	3	6	48
		6	43	48
		8	91	48
Methocel E15	HPMC	2	11	50
		3.5	59	48
		4.5	119	47

1)Viscosity determined by a Brookfield Viscosimeter, Type LVT.
2) Surface tension determined by drop weight method[8]

TABLE 2

Viscosities and surface tensions of an aqueous 3% Kollidon 90 solution added various concentrations of Polysorbate 80

Polysorbate 80 concentration w/w %	Viscosity mPas (30 °C)	Surface tension mNm^{-1} (25 °C)
0	9	68
0.02	9	57
0.4	9	46
0.8	10	44

TABLE 3
The contact angles between sulphur and various binder solutions

Binder solution	Contact angle[1]) to sulphur grade	Surface tension mNm^{-1}
Kollidon 90, 3%	56	68
Kollidon 90, 3% + Sodium lauryl sulphate 1.5%	37	44

1) Contact angle determined by the "h and ε" method[9].

and 37°, respectively (Table 3). Sodium lauryl sulphate was used as the surface active agent, because the contact angle could not be varied with Polysorbate 80.

A laboratory-scale high shear mixer, Fielder PMAT 25VG equipped 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].

METHODS

Most of the experiments were carried out in the liquid addition phase. 8 kg of dicalcium phosphate were granulated with an impeller speed of 400 rpm and a chopper speed of 3000 rpm. The liquid addition rate was 150 ml/min.

A few additional experiments were carried out in the wet-massing phase in order to study the effects of the liquid amount on the granule growth and power consumption. 8 kg of dicalcium phosphate were granulated with an impeller speed of 400 rpm and a chopper speed of 3000 rpm. The liquid addition rate was 200 ml/min and the liquid amounts were 1376, 1403 and 1440 g of a 3% Kollidon 90 binder solution. The binder solution was added by spraying[1]. The wet-massing time was 6 min. Samples were taken out at 0, 1, 3 and 6 minutes of wet massing.

The experiments with sulphur were carried out in the liquid addition phase. 6 kg of sulphur were used for each experiment. The impeller speed was 400 rpm and the chopper speed 3000 rpm. The binder liquid was added by spraying with a rate of 150 ml/min. The same procedures as for dicalcium phosphate were used in the sampling and determination of different parameters.

The binder solution was added by spraying. Sampling and determination of the granule properties have been described earlier[1,10,11].

RESULTS AND DISCUSSION

Effects of Surface Tension

Figure 1 shows the correlation between the amount of binder solution and the mean granule size obtained in the liquid addition phase of dicalcium phosphate granulation with different binder solutions in their lowest concentrations, cf. Table 1. Figure 1 shows that the solutions of Kollidon 90 and Kollidon 25 gave rise to larger mean granule sizes than the other binder solutions. It means that the liquid requirements for granulation with the PVP solutions are lower than the requirements for the other binder solutions.

When describing the amount of liquid phase in terms of the liquid saturation, no difference between the binder solutions could be revealed, Figure 2. The liquid saturation, S, is the degree of intragranular voids filled with liquid phase[1,5]. It is determined

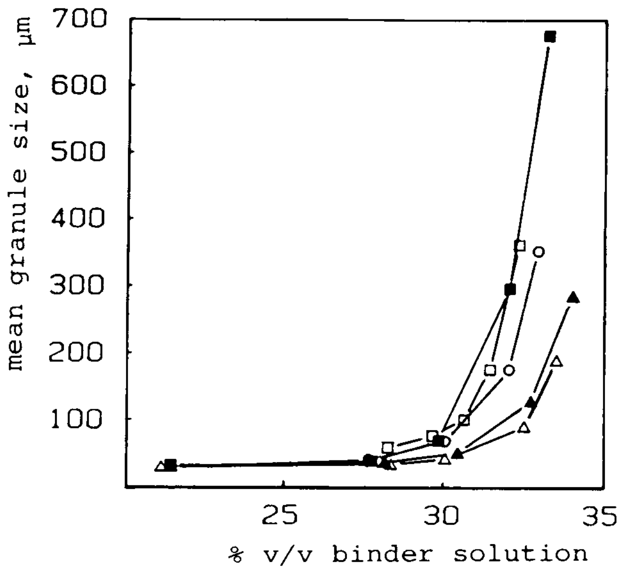

FIGURE 1

Effect of the amount of binder solution on the mean granule size in liquid addition phase. ■: Kollidon 90 3%, o: Kollidon VA 64 10%, Δ: Methocel E5 3%, ▲: Methocel E15 2%, □: Kollidon 25 3%.

from the measurements of the intragranular porosity ε, particle density ρ and the moisture content H, of the granules on dry basis.

$$S = \frac{H\,(1 - \varepsilon)}{\varepsilon}\,\rho \qquad (1)$$

Figure 2 shows the correlation between the liquid saturation and the mean granule size for all the experiments with the binder solutions mentioned in Table 1.

Since the results show good agreement in the graph, it can be concluded that the larger mean granule sizes obtained with the PVP solutions, as shown in Figure 1, are due to an effect of the intragranular porosity.

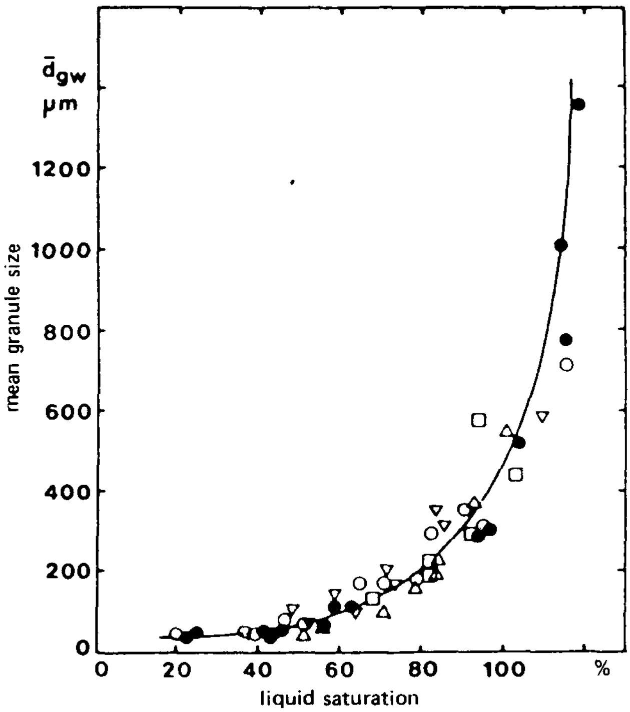

FIGURE 2
Effect of liquid saturation on mean granule size in liquid addition phase. ●: Kollidon 90 3%, 5% and 8%, o: Kollidon VA 64 10%, 20% and 30%, Δ: Methocel E5 3%, 6% and 8%, □: Methocel E15 2%, 3.5% and 4.5%, ∇: Kollidon 25 3% and 20%.

This was confirmed by plotting ε against % v/v binder solution, which showed that the PVP solutions produced denser granules than the solutions of PVP-PVA or HPMC.

Taking into account the slight effect of the binder concentration, the primary difference between the binder solutions must rely on the surface tension, Table 1. The surface tensions of the two PVP solutions were about 68 mNm^{-1} which is close to that of purified water, whereas the surface tensions of the other solutions were below 50 mNm^{-1}. The higher the surface

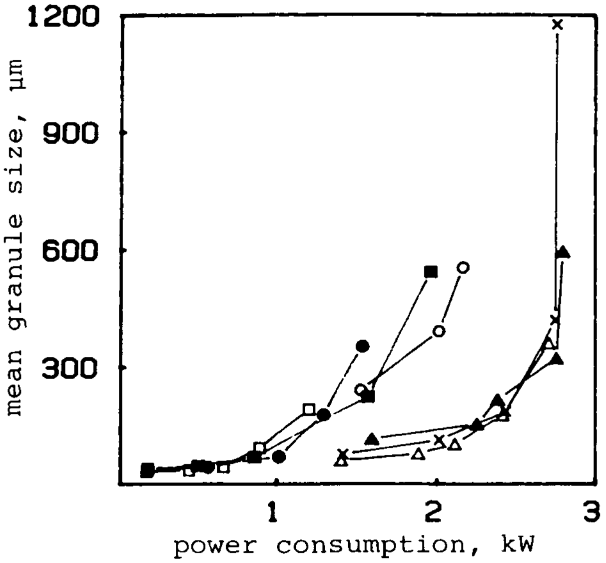

FIGURE 3

Correlation between power consumption and mean granule size in liquid addition phase. x: Kollidon 90 3%, Δ: Kollidon 25 3%, ▲: Kollidon 25 20%, o: Kollidon VA 64 3%, ●: Kollidon VA 64 10%, □: Methocel E5 3%, ■: Methocel E5 8%.

tension of a liquid, the more the liquid tries to reach the energetically most effective form, i.e. the drop form. This means that a moist agglomerate produced by a binder solution with a high surface tension tends to have a lower porosity and hence a higher liquid saturation than an agglomerate produced with a liquid with a lower surface tension. This can explain why the PVP solutions produce larger granules than the solutions of the PVP-PVA copolymer and HPMC.

Figure 3 shows the correlation between the mean granule size and the power consumption recorded during the liquid addition phase of dicalcium phosphate granulation.

It appears that the correlations fall into two classes dependent on the surface tensions of the solutions, cf. Table 1. The power consumption recorded for experiments with the PVP-solutions is significantly higher than the records of PVP-PVA and HPMC solutions. The demonstrated effect of the surface tension agrees well with the findings of Leuenberger[7] that the power consumption is influenced by the tensile strength of the moist agglomerates.

According to Rumpf[6] the tensile strength σ_t of a moist agglomerate in the funicular and capillary states is approximately:

$$\sigma_t = C \cdot S \frac{1-\varepsilon}{\varepsilon} \frac{\gamma}{d} \cos\theta \qquad (2)$$

where C is a material constant (for spheres C=6), S liquid saturation, ε intragranular porosity, γ surface tension, θ contact angle of the liquid to the solid, and, d the particle size.

In the present experiments the changes of the tensile strength, σ_t, of the moist agglomerates are controlled by porosity, ε, and surface tension, γ, only, because the remaining parameters of eq. (2) are kept constant. Though the liquid saturation, S, grows, but in experiments with continuous liquid addition or densification it must be assumed that the surface of the moist agglomerates contains free liquid which is forced to the surface by the compaction of the solid particles[12,13]. Thus the liquid saturation can be assumed to be constant. If the influence of the binder solution on the power consumption shown in Figure 3 is due to the effects of the mobile liquid bonding strength, there must be a correlation between the recorded power consumption and the variable parameters of eq. (2) i.e.

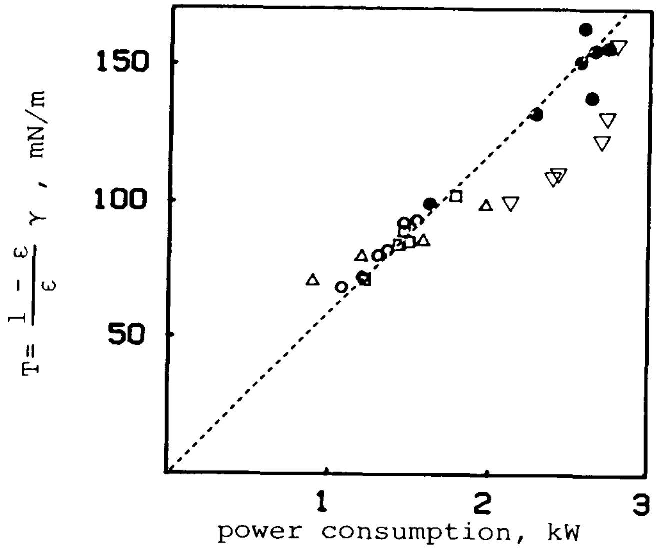

FIGURE 4

Correlation between power consumption and T for the experiments presented in Figure 2.

the value of

$$T = \frac{1 - \varepsilon}{\varepsilon} \gamma \qquad (3)$$

Figure 4 demonstrates the correlation between power consumption and T for the same experiments as shown in Figure 2. In order to assure that the agglomerate surface was saturated with liquid, only experiments with liquid saturations above 60% were included in Figure 4. The limit of 60% was chosen because Figure 2 shows that rapid granule growth by coalescence begins at liquid saturation of about 60%. Though the results for Kollidon 25 deviates slightly, Figure 4 supports the assumption that the power consumption is influenced by the liquid bonding strength in the moist agglomerates.

Effects of the contact angle

The supposed correlation between the power consumption and the liquid bonding strength implies that the contact angle of the binder solution to the solid has an effect cf. eq. (2). In order to demonstrate this effect granulation experiments with sulphur were made using the two binder solutions mentioned in Table 3. The table shows that a reduction of the contact angle between a Kollidon 90 solution and sulphur by addition of a surfactant is followed by a reduction of the surface tension of the solution. This means that the value of $\gamma \cdot \cos\theta$ remains approximately constant. Therefore, one should expect that the addition of the surfactant has no effect upon the granulation process. The agglomerates formed did not have the typical character of a granule due to the poor moistening of sulphur by the binder solutions. Only little differences between the power consumptions of these two granulation experiments were seen.The granulation experiments with sulphur showed, however, that the liquid requirements when using the Kollidon 90 solution were about twice of that for the solution added sodium lauryl sulphate.

An examination of the agglomerates, their mean granule size and power consumption records showed that the difference probably was due to a better moistening of the sulphur particles when the solution was added a surfactant.

Effect of Lowering the Surface Tension

In order to demonstrate in more detail the effect of the surface tension on granule growth and power consumption, a series of experiments was made by granulating dicalcium phosphate with a Kollidon 90 binder solution which contained 0.02%, 0.4% or 0.8% of a surfactant, Polysorbate 80. The surface tensions of these

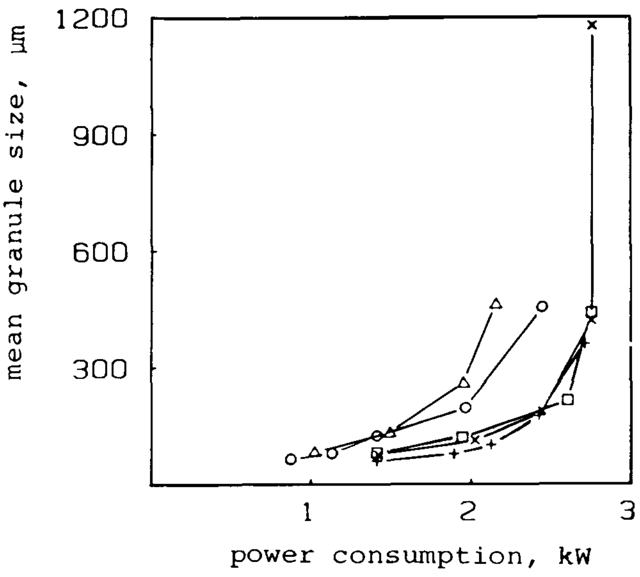

FIGURE 5

Correlation between power consumption and mean granule size in liquid addition phase for granulation of dicalcium phosphate with binder solutions of varying surface tensions. x: Kollidon 90 3%, □: Kollidon 90 3% added 0.02% polysorbate 80, o: Kollidon 90 3% added 0.4% polysorbate 80, Δ: Kollidon 90 3% added 0.8% polysorbate 80, +: Kollidon 25 3%.

solutions are shown in Table 2. In agreement with the discussion above the experiments showed that with a low surface tension the granule growth starts later. More liquid is required for the growth and the mean granule size is smaller. The effect of liquid saturation on the mean granule size was in agreement with Figure 2. The porosities were the lower, the higher the surface tensions.

Figure 5 shows that an increasing concentration of the surfactant, i.e. decreasing surface tension, reduces the power consumption required to obtain a certain mean granule size. For comparison, the figure includes the experiments with 3% Kollidon 25

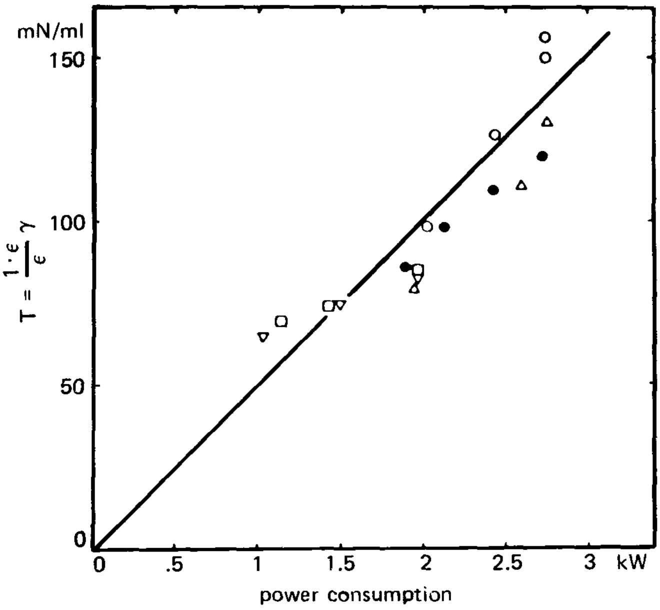

FIGURE 6

Correlation between power consumption and T for the experiments described in Figure 5. o: Kollidon 90 3%, Δ: Kollidon 90 3% added 0.02% polysorbate 80, □: Kollidon 90 3% added 0.4% polysorbate 80, ∇: Kollidon 90 3% added 0.8% polysorbate 80, ●: Kollidon 25 3%.

The correlation between the power consumption and $T = \frac{1 - \varepsilon}{\varepsilon}\gamma$ for the experiments shown in Figure 5 is presented in Figure 6. The graph supports the claimed effect of the liquid bonding strength on power consumption.

Effects of the Intragranular Porosity

The results discussed above show that the effects of the surface tension of the binder solution can be explained by the effects of the strength of mobile liquid bondings active in the moist agglomerates. The interpretation implies that differences between power consumption records of different granules are caused by the effects of the parameters controlling the bonding strength, cf. eq. (2). It presupposes of course that the granules are produced in the same mixer run with identical rotation speeds.

When a particular granulation process is considered, according to eq. (2), the tensile strength, σ_t, and hence, the power consumption are expected to grow during the process due to the effects of porosity, ε, and liquid saturation, S. The remaining parameters of the eq. (2) are constant, and the liquid saturation is considered to be constant as discussed above. This means that in the phases of the process, where measurable granule growth proceeds, the intragranular porosity is the only process parameter which influences the power consumption.

In order to assess whether the power consumption reflects the changes in the densification of the moist agglomerates, dicalcium phosphate was granulated in three experiments using different amounts of a 3% Kollidon 90 solution. Figure 7 shows the recorded power consumption profiles.

Previous experiments with dicalcium phosphate[4] have shown that the deposition of the moist mass on the wall of the mixer bowl can interfere with the power consumption. The bowl was therefore fitted with a polytetrafluor ethylene tape on the wall. Experience has shown that this tape can reduce the deposition of the mass significantly.

Even though the amounts of binder solution in Figure 7 differed only slightly from each other, they gave rise to different power consumption levels in the wet massing phase. The mean granule sizes differed accordingly as shown in Figure 8.

In agreement with eq. (1) and Figure 8, a graph of the intragranular porosity against the wet massing time

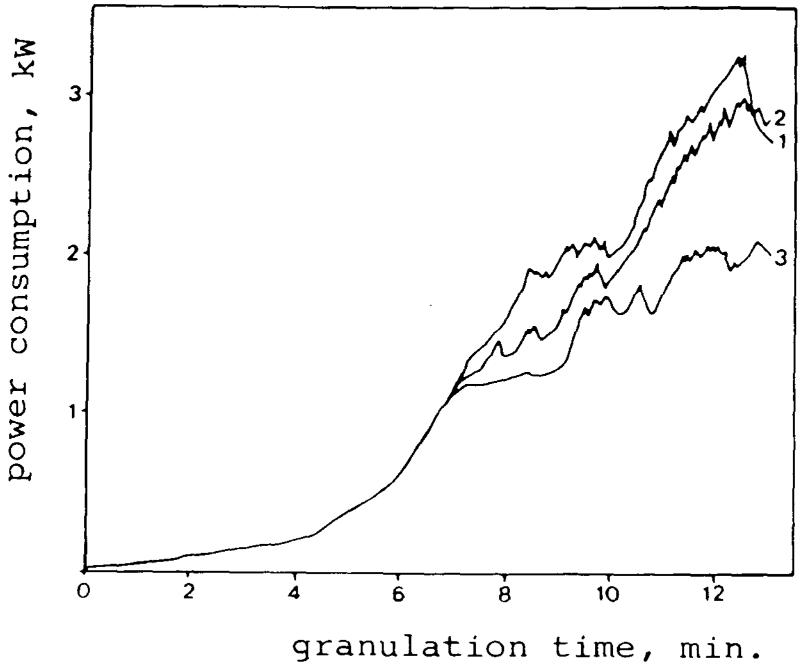

FIGURE 7

Power consumption records for granulation of dicalcium phosphate with different amounts of 3% Kollidon 90 solution. 1: 18.0 w/w %, 2: 17.5 w/w %, 3: 17.2 w/w %.

(Figure 9) showed that the higher the liquid content of the mass, the more pronounced the densification of the agglomerates and hence, the higher the liquid saturation which causes the increasing granule size.

Figure 10 shows the correlation between the power consumption and the porosity function $(1 - \varepsilon)/\varepsilon$. The graph verifies that the differences between the power consumption records shown in Figure 7 are due to the differences in the densification of the agglomerates. Therefore, the power consumption record simply reflects the changes in the porosity function caused by the densification of the agglomerates.

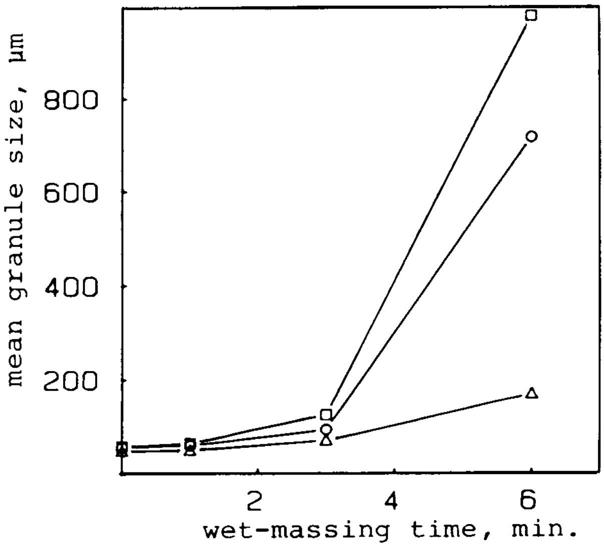

FIGURE 8

Granule growth of dicalcium phosphate in wet-massing phase with different amounts of binder solution. □: 18.0 w/w %, o: 17.5 w/w %, Δ: 17.2 w/w %.

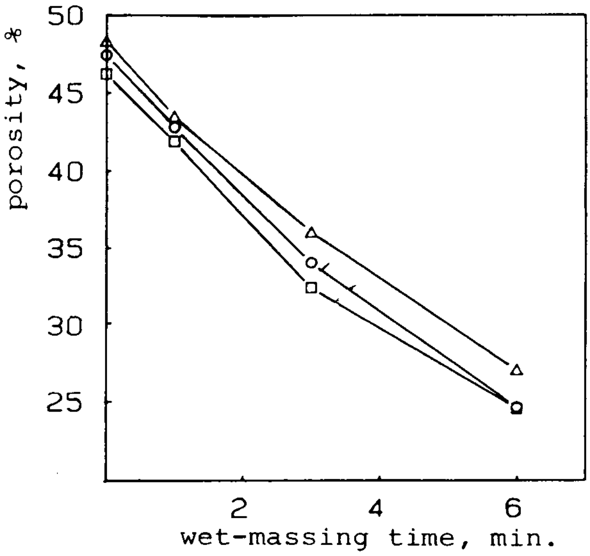

FIGURE 9

Correlation between wet-massing time and porosity for granulation of dicalcium phosphate with different amounts of binder solution. □: 18.0 w/w %, o: 17.5 w/w %, Δ: 17.2 w/w %.

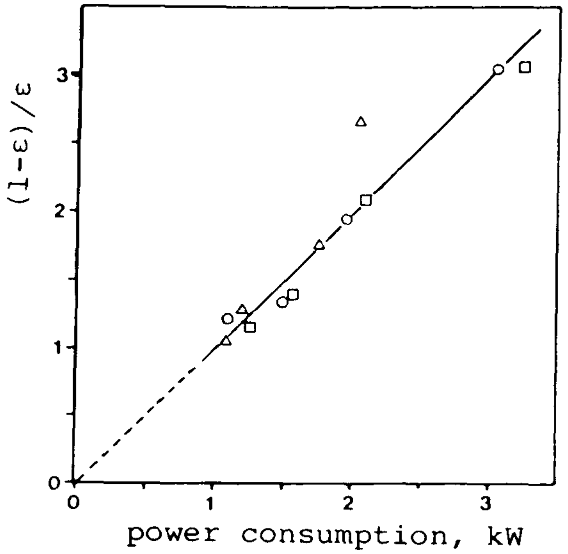

FIGURE 10

Correlation between power consumption and porosity function (1 - ε)/ε with different amounts of binder solution in the wet-massing phase. □: 18.0 w/w %, o: 17.5 w/w %, Δ 17.2 w/w %.

A graph of the correlation between the power consumption and the mean granule size showed that the curves of the three experiments coincided. This does not mean that the granule growth is controlled by the liquid bonding strength as is the case for the power consumption. Measurable granule growth, which proceeds by coalescence between the moist agglomerates, is influenced primarily by the liquid saturation[4]. Eq. (1) shows, however, that for a particular granulation process the liquid saturation in the wet massing stage is controlled by the porosity function. Therefore, a close correlation between power consumption and mean granule size must exist.

CONCLUSIONS

It has been shown that the surface tension of the binder solution influences granule growth and power consumption in granulation experiments in a high shear mixer. The effects of the surface tension are interpreted on the basis of Rumpf's equation for the strength of mobile liquid bondings in moist agglomerates.

A comparison between different binder solutions shows that a high surface tension of the binder solution, viz. PVP solutions, results in more dense granules and consequently in larger mean granule sizes than a low surface tension, viz. PVP-PVA copolymer and HPMC. This means that a growing surface tension facilitates the densification of the granules probably due to the effects of the growing liquid bonding strength.

The power consumption during granulation in a high shear mixer is influenced by the mobile liquid bonding strength in agreement with Rumpf's equation. It has been shown that the surface tension and the intragranular porosity affect the power consumption in agreement with the assumed proportionality between power consumption and tensile strength. Experiments on the effect of the contact angle between the binder solutions and the solid particles failed partially, because the surface tension of the liquid and the contact angle could not be varied independently. It was observed that the granule growth of sulphur was influenced strongly by the wetting of the particles.

For a particular granulation process it has been shown that the power consumption record reflects the changes of the granule density during the process. Since the densification process is of primary importance to the granule growth by coalescence, the record of the power consumption gives valuable information about the granulation process.

ACKNOWLEDGEMENT

The experiments were supported by the Danish Council for Scientific and Industrial Research.

REFERENCES

1. M. Ritala, O. Jungersen, P. Holm, T. Schaefer and H.G. Kristensen, Drug Dev. Ind. Pharm., 12, 1685 (1986).
2. P. Holm, T. Schaefer and H.G. Kristensen, Powder Technol. 43, 213 (1985).
3. H.G. Kristensen, P. Holm and T. Schaefer, Powder Technol. 44, 227 (1985).
4. H.G. Kristensen, P. Holm and T. Schaefer, Powder Technol. 44, 239 (1985).
5. H.G. Kristensen, P. Holm, A. Jaegerskou and T. Schaefer, Pharm. Ind. 46, 763 (1984).
6. H. Rumpf, in "Agglomeration", W.A. Knepper, ed., Interscience, New York, 1962, p.379.
7. H. Leuenberger, Pharm. Acta Helv. 57, 72 (1982).
8. A.W. Adamson, in "Physical Chemistry of Surfaces, 3rd Ed., Wiley, N.Y., 1976, p.18.
9. N.W.F. Kossen and P.M. Heertjes, Chem. Eng. Sci. 20, 593 (1965).
10. P. Holm, O. Jungersen, T. Schaefer and H.G. Kristensen, Pharm. Ind. 45, 806 (1983).
11. A. Jaegerskou, P. Holm, T. Schaefer and H.G. Kristensen, Pharm. Ind. 46, 310 (1984).
12. C.E. Capes, in "Particle Size Enlargement", Elsevier, Amsterdam, 1980, p.31.
13. P.J. Sherrington and R. Oliver, in "Granulation", Heydon & Son Ltd., London, 1981, p.27.