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Agglomeration of binary mixtures in a high-speed mixer

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Summary

The monitoring of granulation processes in high-speed mixers by power measurements enables the normalisation of the granulating liquid and the assessment of the kinetic of agglomerate growth. The agglomeration behaviour of a binary mixture depends on that of its constituents. If the constituents exhibit similar growth properties, i.e. and exponential increase of the median granule diameter as a function of the quantity of granulating liquid, additivity theorems may be formulated to describe the kinetics of agglomeration. The binary mixture, lactose/dicalcium phosphate, fitted this hypothesis when the experimental error is taken into consideration. A different behaviour was found for the mixture lactose/corn starch, since components differed tremendously in their granulating features. Depending on the proportion of the two substances three ranges were distinguished; lactose-dominance at concentrations of more than 75% (w/w) of lactose, resulting in narrow size distributions exhibiting "self-preserving" properties; corn starch-dominance, at proportions of corn starch above 50% (w/w), manifesting broad size distributions which do not show self similarity and a bicoherent range represented by the mixture lactose/corn starch 67/33 (w/w). The percolation theory was employed to explain these critical phenomena.

Introduction

Granulation is an important operation in the field of pharmaceutical technology. In recent years high-speed mixers combined with power measurement devices are being used in the pharmaceutical production to monitor the granulation process (Dürrenberger and Werani, 1985). The advantages of this technology are that blending, moistening and granulating can be performed in one piece of equipment. The power consumption curve obtained by adding the binding liquid continuously to the powder, is made up of 5 phases as described in previous papers (Leuenberger et al., 1979; Bier et al., 1979). In the first phase (S_1–S_2) the moisture is adsorbed by the powder particles without any formation of liquid bridges. In the second phase (S_2–S_3) a sharp increase in power consumption is observed due to the build-up of liquid bridges between the particles. The third phase (S_3–S_4) is characterized by a constant power level. The further addition of liquid leads to a filling-up of large areas in the particulate system until at the phase transition point, S_5, the whole interparticular void space is completely filled with liquid and the overwetted, damp mass becomes a slurry. The

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granulating liquid is normalized as follows (Imanidis, 1986)

$$\pi = (S - S_2)/(S_5 - S_2)$$

where S corresponds to the absolute liquid quantity used. Hence, the granulating liquid is expressed as the degree of liquid saturation. According to previous investigations pharmaceutical granules can be produced in the third phase ($S_3 - S_4$) (Leuenberger et al., 1981, Dürrenberger and Werani, 1985, Imanidis, 1986).

The aim of our research is to demonstrate how far the power consumption curve can serve to characterize the agglomeration performance of a binary mixture. For this purpose, commonly used pharmaceutical excipients with different physical properties were examined: lactose, dicalcium phosphate and corn starch.

Theoretical background

The kinetics and agglomeration

We define the kinetics of agglomeration as the growth of the median particle size of agglomerates as a function of the amount of the (normalized) granulating liquid added π. The continuous addition of the liquid leads to successive build-up of the agglomerates. Considering that the granulating fluid is added continuously at a constant rate, the degree of liquid saturation may well be substituated for time. This justifies the use of the term kinetics of agglomeration. The growth mechanism of coalescence was postulated to prevail during the stage of liquid addition in the range of S_3 up to S_4 (Imanidis, 1985, 1986). The resulting exponential increase of the medium diameter $d[50]$ may be written as follows:

$$\ln(d[50]) = A + k\pi \qquad (1)$$

The y-intercept, A, is of the same order as the logarithm of the initial diameter of the starting material. The median diameter is a representative characteristic of particle size distributions exhibiting "self-preserving" properties. During the growth of the agglomerates the shape of the size distributions is preserved (see e.g. Fig. 1). The slope, k, of the regression line is an estimate of the growth rate.

If the growth rate of two substances can sufficiently be described by Eqn. 1, additivity theorems may therefore be formulated to obtain an equation for any binary mixture. The arithmetic mean is employed for both the y-intercept, A, and the slope, k:

$$A_M = xaA_1 + (1 - x)A_2 \qquad (2)$$

$$k_M = xk_1 + (1 - x)k_2 \qquad (3)$$

where x = fraction by weight of substance 1; and $1 - x$ = fraction by weight of substance 2. The kinetics of agglomeration of any binary mixture using Eqns. 2 and 3 is as follows:

$$\ln(d[50])_M = xA_1 + (1 - x)A_2 + \{xk_1 + (1 - x)k_2\}\pi \qquad (4)$$

In the Eqn. 4 interactions between the substances are not taken into account. The use of the arithmetic mean in Eqn. 2 seems to be valid considering the growth rate of agglomerates by coalescence. If the slopes, k_1 and k_2, of the regression lines of substance 1 and substance 2, respectively, do not differ to a great extent, there is no significant difference between the arithmetic and the geometric or the harmonic mean.

Percolation theory

The percolation theory as a multidisciplinary research field deals with the number of clusters of occupied sites on a lattice (Stauffer, 1985). There are different kinds of percolation, e.g. site, bond, site–bond or correlated percolation (Stauffer, 1985; Stauffer et al., 1982). In relations with agglomeration phenomena we deal with site percolation. A Cluster is defined as a group of neighbouring occupied sites. Each site of a very large lattice is occupied randomly with probability P. In case of a granular unit, the virtual lattice sites are occupied either by powder particles or by pores. Because of the low porosity of the agglomerates we are neglecting the pores in the further discussion. Thus, considering a binary mixture of components A and B, the lattice sites are thought to be occupied by particles of either A or B. In the three-dimensional space the following states may be considered:

- substance A forms an infinite cluster, whereas substance B builds isolated, small clusters;
- substance B forms a continuous network, while substance A is dispersed in B;
- in a certain mixing ratio range both substances A and B form infinite networks and mutually penetrate each other. This condition, where both A and B occur as infinite clusters, can be considered as being a bicoherent system.

The critical concentration, where a constituent forms an infinite cluster, i.e. spans the whole system, is called percolation threshold, p_c. From geometrical considerations, two percolation thresholds, that of A and B, can be observed in a binary mixture of powders. The bicoherent system lies between these two percolation thresholds. The absolute value of a percolation threshold depends on the relative particle arrangement. Its accurate determination is possible only for infinite systems. A "critical" proportion of the constituents which may be obtained by experiments corresponds functionally to a percolation threshold and is of importance with regard to dosage form design (Leuenberger et al. 1987, 1989). In connection with the kinetics of agglomeration, different growth mechanisms may occur below or above a critical proportion.

Experimental

Materials

In our experiments, we used lactose 200 mesh (DMV, The Netherlands), dicalcium phosphate (Budenheim, F.R.G.) and corn starch (Maizena, F.R.G.). The powder characteristics are listed in Table 1. The median diameter of the powders was determined by means of an image analyses system (Videoplan, Kontron). Polyvinylpyrrolidon (PVP) K30 (BASF, F.R.G.) was premixed as a dry binder.

TABLE 1

Physical properties of the examined substances

	Lactose 200 mesh	Dicalcium phosphate	Corn starch
Bulk density (g/ml)	0.58	0.97	0.49
Tapped density (g/ml)	0.84	1.45	0.65
True density (g/ml)	1.54	2.82	1.51
Median particle size (μm)	40	8	20
Solubility in water	20%	insoluble	insoluble

TABLE 2

Granulation conditions

Impeller speed	270 rpm
Chopper speed	3000 rpm
Flow rate	15 $g \cdot min^{-1} \cdot kg^{-1}$
Atomizing pressure	1 bar
Premixing time	3 min

Procedure

The granulation experiments were carried out in a Diosna V10 high-speed mixer which is equipped with both a 3-blade main impeller and a chopper. The granulating liquid was sprayed continuously into the powder using a membrane pump and a binary nozzle. The process parameters are listed in Table 2.

The batch size (2–3 kg depending on the bulk density of the starting material) was chosen such that 30–45% by vol. of the mixing chamber of the high-speed mixer was occupied. The damp mass was transferred into a fluidized bed dryer (model Uniglatt) and dried for 5 min at 50 °C to prevent the formation of lumps and subsequently dried in a tray dryer at 40 °C to reach the moisture equilibrium at R.T. and 50% relative humidity. The particle size distribution was performed by sieve analysis using an ISO-Norm sieve set.

Results and Discussion

Binary mixture lactose / dicalcium phosphate

Granule size distributions

The kinetics of agglomeration of both lactose 200 mesh and dicalcium phosphate were studied by granulating the substance using the process

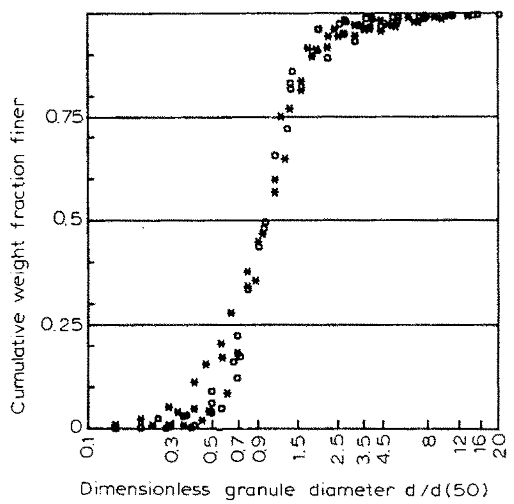

Fig. 1. Granule size distributions by weight as a function of the normalized, dimensionless diameter $d/d[50]$ at different amounts of the normalized granulating liquid π. Starting materials: lactose 200 mesh (∗); dicalcium phosphate (○).

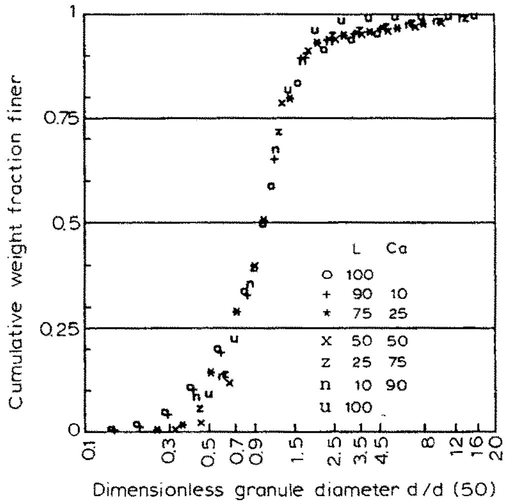

Fig. 2. Granule size distributions by weight as a function of the normalized, dimensionless diameter $d/d[50]$ at $\pi = 0.53$ for different proportions of lactose/dicalcium phosphate.

parameters summarized in Table 2 with different amounts of the normalized granulating liquid π. The resulting granule size distributions are presented in Fig. 1. The cumulative weight fraction is plotted against the log of the normalized, dimensionless granule diameter d/d [50]. The successive size distributions obtained with increasing quantities of granulating liquid are coïncidental. Thus the agglomerates exhibit a "self-preserving" growth.

The following binary mixtures were granulated with different amounts of the normalized granulating liquid π: (lactose/dicalcium phosphate) 10/90, 25/75, 50/50, 75/25, 90/10. The size distributions of each binary mixture were plotted against the normalized granule diameter providing "self-preserving"-properties as a function of the degree of liquid saturation. As Fig. 2 indicates, plotting the cumulative weight fractions of all compositions of the binary mixtures at a fixed π-value the self-similarity occurs independently of the proportion of the compounds.

Kinetics of agglomeration

The relation between the median diameter, $d[50]$, of the agglomerates of both lactose and dicalcium phosphate and the normalized granulating liquid is plotted in Fig. 3. The linear increase of the logarithm of $d[50]$ with π occurs only in the range of liquid quantity corresponding to the third phase of the power–consumption curve. The y-intercepts of the two regression lines differ significantly ($\alpha = 0.05$), whereas the slopes do not differ to a great extent in their steepness. Plotting the ratio of the median diameter to the initial diameter $d[50]/d_i$ against the normalized liquid π, the

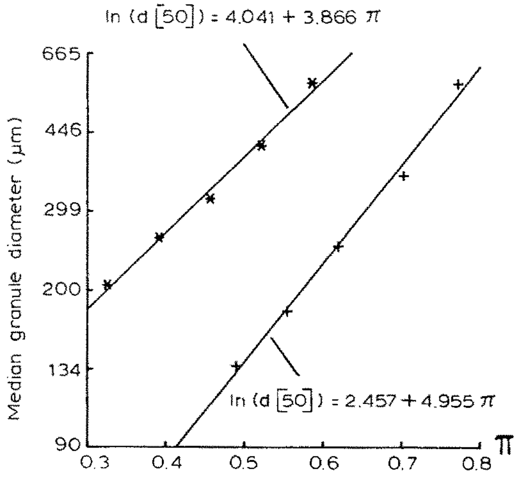

Fig. 3. Median granule diameter (in logarithmic scale) as a function of the normalized granulating liquid π. Starting materials: lactose 200 mesh (∗); dicalcium phosphate (+).

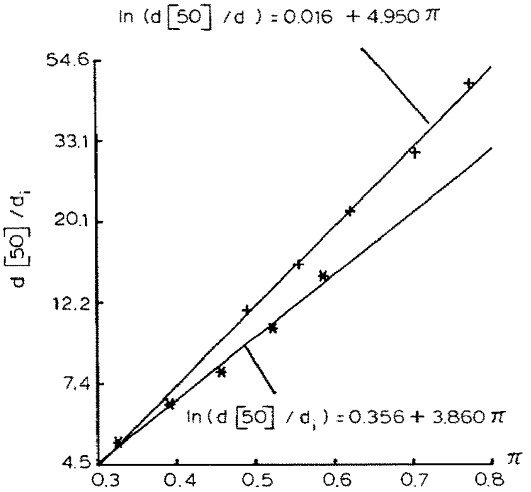

Fig. 4. Ratio of the median granule diameter to the initial particle size $d[50]/d_i$ (in logarithmic scale) as a function of the normalized granulating liquid π. Starting materials: lactose 200 mesh (*); dicalcium phosphate (+).

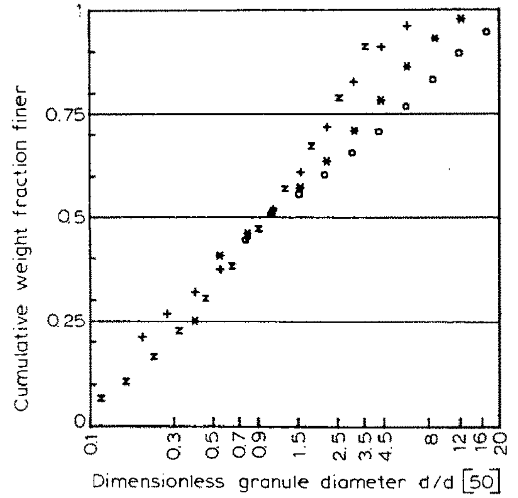

Fig. 6. Granule size distributions by weight as a function of the normalized, dimensionless diameter $d/d[50]$ at different amounts of granulating liquid (% w/w): o, 35%; *, 39%; +, 43%, z, 47%. Starting material: corn starch.

regression lines approach but are not coincidental due to the different growth susceptibility (Fig. 4).

In Fig. 5 the median diameters of all agglomerates are plotted (on a logarithmic scale) against π. Evidently the regression lines shift to higher π-values with increasing percentage of dicalcium phosphate. The y-intercepts do not seem to follow the additivity hypothesis. Our detailed analysis revealed, however, that this behaviour is only due to the statistical scatter. Thus a regression line between the y-intercepts and the mixing ratio could be calculated showing a high correlation coefficient ($r = 0.962$). The good agreement of the experimentally determined data for both the y-intercepts A_M and the slopes k_M according to Eqns. 2 and 3, respectively, with the calculated values of these two parameters confirmed the additive behaviour for this binary mixture with reference to agglomeration kinetics (Usteri, 1988).

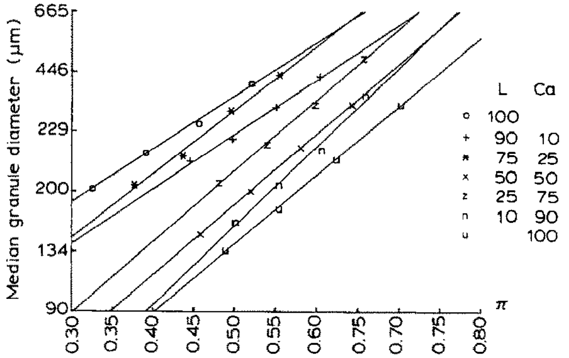

Fig. 5. Median granule diameter (in logarithmic scale) as a function of the normalized granulating liquid π for different mixtures of lactose/dicalcium phosphate.

Binary mixture lactose / corn starch

Agglomeration performance of corn starch

The power–consumption curve of corn starch fundamentally differs from that of lactose or dicalcium phosphate which may be due to the absorption of water and the subsequent swelling during the liquid addition. Four corn starch agglomerates were produced using PVP 3% as dry binder. The pump rate was increased to 25 $g \cdot min^{-1} \cdot kg^{-1}$. The granule size distributions do not exhibit self-similarity but are quite broad (Fig. 6). The percentage of each size fraction except the fines (< 90 μm) does not exceed 20%.

Granule size distributions of the binary mixtures

Four batches of granules with the following compositions were made: (lactose/corn starch) 90/10, 75/25, 67/33, 50/50, 25/75 (w/w). De-

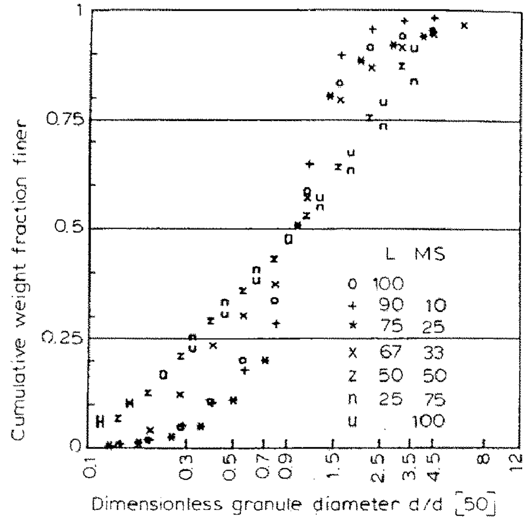

Fig. 7. Granule size distributions by weight as a function of the normalized, dimensionless diameter $d/d[50]$ at $\pi = 0.6$ for different proportions lactose/corn starch.

pending on the composition, the granule size distributions show 3 different features with regard to their shapes (see Fig. 7).

(a) The mixtures 90/10 and 75/25 provide narrow and "S"-shaped granule size distributions with "self-preserving" properties. Lactose, forming an infinite network, predominates the properties of the agglomerates, whereas corn starch, existing as isolated clusters, has no visible influence on the agglomerate growth. We call this range lactose-dominance.

(b) If the percentage of corn starch exceeds 50%, very broad agglomerate size distributions arise manifesting no self-similarity. In this case corn starch determines the growth of the granules and their properties are characteristics of corn starch-dominance.

(c) The binary mixture 67/33 lies in the range of bicoherence. Both corn starch and lactose exist simultaneously as infinite clusters. The particle size distributions are neither sigmoid nor strongly broad but are of intermediate stage. At this composition both lactose and corn starch influence the growth as well as the particle shape, i.e. surface of the agglomerates.

The granule size distributions of the different binary mixtures obtained with the highest amount of liquid used for the granulation are plotted in Fig. 7. The above-described phenomena, i.e. lactose- and corn starch-dominance as well as the bicoherent system are elucidated.

According to the percolation theory two critical properties are considered to exist. The lower p_c-value indicating the transition from lactose-dominance to the bicoherent system lies between a fraction of corn starch of 25—33%. The upper p_c-value between 33% and 50% represents the transition from the bicoherent system to the corn starch-dominance.

Kinetics of the agglomerate growth

Unlike the mixtures of lactose/dicalcium phosphate, which were discussed above, the binary mixtures of lactose/corn starch manifesting different properties (with regard to granule size distributions, self-similarity and surface roughness) are not suited for comparative analysis. The normalization of the amount of the granulating liquid could not be carried out with corn starch or its mixtures because of its tendency to swell. Thus the granule median diameter of each binary mixture has been plotted in Fig. 8 as a function of the absolute amount of granulating liquid expressed as a percentage by weight. An exponential increase in $d[50]$ occurs even in the case of corn starch-dominance. The quantity of granulating liquid required increases as expected with increasing proportion of corn starch.

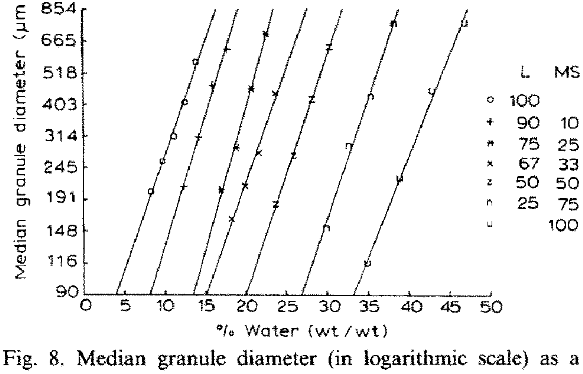

Fig. 8. Median granule diameter (in logarithmic scale) as a function of the absolute granulating liquid (% w/w) for different mixtures lactose/corn starch.

Conclusions

The method to measure the power consumption during the agglomeration step established to be an excellent tool to monitor the agglomeration process. The normalization of the quantity of granulating liquid on the basis of the power–consumption curve enabled the direct comparison of the agglomeration kinetics of different substances. In case that two substances, e.g. lactose 200 mesh and dicalcium phosphate, exhibit a similar power–consumption profile, a similar type of agglomeration kinetics can be expected, i.e. an exponential increase of the median granule diameter of self-similar size distributions as a function of the normalized liquid added. Thus additivity theorems can be formulated to quantify the agglomeration kinetics of any binary mixture of these substances.

The agglomeration behaviour of substances differing in their granulating properties, e.g. lactose and corn starch, obeys the laws of the percolation theory. From 50% to 100% (w/w) corn starch the granule size distributions are very broad, dominated by the growth kinetics of corn starch. In case of 33% (w/w) corn starch and 67% lactose it is difficult to attribute the type of kinetics to corn starch or lactose. Thus this ratio may belong to the bicoherent system. The ratios with more than 75% (w/w) lactose show sigmoidal and narrow lactose-dominated self-similar granule size distributions.

References

Bier, H.P., Leuenberger, H. and Sucker, H., Determination of the uncritical quantity of granulating liquid by power measurements on planetary mixers. *Pharm. Ind.,* 41 (1979) 357–380.

Dürrenberger, M. and Werani, J., The control of granulation process by power consumption measurement in pharmaceutical production. In Capes, C.E. (Ed.), *Proceedings Agglomeration 85,* Toronto, 1985, pp. 489–496.

Imanidis, G., *Untersuchungen über die Agglomerierkinetik und die elektrische Leistungsaufnahme beim Granulierprozess im Schnellmischer,* Ph. D. Thesis, University Basel, 1986, p. 71.

Imanidis, G., Winzap, S. and Leuenberger, H., Agglomeration kinetics and process monitoring in rapid mixers. In Capes, C.E. (Ed.), *Proceedings Agglomeration 85,* Toronto, 1985, pp. 479–487.

Leuenberger, H., Bier, H.P. and Sucker, H., Theory of the granulating-liquid requirement in the conventional granulation process. *Pharm. Technol.,* 3 (1979) 61–68.

Leuenberger, H., Bier, H.P. and Sucker, H., Determination of the liquid requirement for a conventional granulation process. *Ger. Chem. Eng.,* 4 (1981) 13–18.

Leuenberger, H., Rohera, B.D. and Haas, Chr., Percolation theory – a novel approach to solid dosage form design. *Int. J. Pharm.,* 38 (1987) 109–115.

Leuenberger, H., Holman, L., Usteri, M. and Winzap, S., Percolation theory, fractal geometry and dosage form design. *Pharm. Acta Helv.,* 64 (1989) 34–39.

Stauffer, D., *Introduction to Percolation Theory,* Taylor Francis, London/Philadelphia, 1985, p. 17.

Stauffer, D., Coniglio, A. and Adam, M., Gelation and critical phenomena. *Adv. Polymer Sci.,* 44 (1982) 105–155.

Usteri, M., *Untersuchungen über das Agglomerierverhalten pharmazeutischer Hilfsstoffe im Schnellmischer,* Ph. D. Thesis, University of Basel, 1988, pp. 164–169.