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Analysis of factors affecting the mean sizes of granules produced from ternary mixtures of powders

K. T. JAIYEOBA† AND M. S. SPRING*

Department of Pharmacy, University of Manchester, M13 9PL, U.K.

Multiple linear regression analysis has been used to relate the mean sizes of granules prepared from ternary mixtures of powders to such physical properties as particle size, solubility and wettability and to processing variables such as the amount of binder and the proportions of the different components. The major influences on granule size were the amount of binder and the affinity of the third component for the binder liquids.

The properties of granules obtained from ternary mixtures of powders have been studied (Jaiyeoba & Spring 1979, 1980 a, b). The powders were selected to represent the wide range of powder characteristics usually met in pharmaceutical systems. In all systems studied, two constituents, lactose and boric acid, were the same, while the third was changed. Small changes in the type and concentration of the third constituent resulted in large changes, both in the binder requirements of the different blends and the properties of granules prepared from them. The variations obtained were related to the properties and proportions of the compound powders in the mixture, and indicated clearly that the granule properties were influenced by the various characteristics of the constituent powders, the most important of which were solubility, wettability, absorption of binder, water, particle size and cohesiveness.

Thus a large number of factors contribute to the properties of granules produced from mixtures of powders. These controllable factors are here termed independent variables, whilst the responses or granule properties are referred to as dependent variables. Some of these variables, associated with the massing and screening technique of granulation are the physical properties of the powders, the proportions of the powder components and the binder type and quantity. Changes in these variables, using different third constituents, resulted in significant changes in the mean sizes of the resulting granules (Jaiyeoba & Spring 1979, 1980a,b).

Multiple linear regression has been used to determine the relative importance of each variable investigated, to the mean agglomerate size of the granule batches prepared.

† Present address: Dept. of Pharmaceutics, University of Ife, Ile-Ife, Nigeria.
* Correspondence.

Method of Analysis

When the constituents of the mixture being granulated were not changed, even though their proportions were altered, the mean granule size was shown to depend upon four factors: C_i, V, E and D (Jaiyeoba & Spring 1979) where C_i is the fractional concentration of the i th constituent, V is the quantity of binder fluid, which can vary if any of the constituents are soluble in the binder liquid; E is the energy transmitted to the mass and depends on the type and speed of the mixer and also, possibly, on V. D is the packing density of the particles in the granules and is also influenced by both V and E.

For the case when each granule batch was prepared in a similar way and only C_i and V were varied, the mean granule size could be expressed as a third-order polynomial with C_i and V as independent variables. The method of fitting granulation data to this type of equation and the results obtained have been given previously (Jaiyeoba & Spring 1979, 1980a,b). Good correlations were obtained for granulations with each third powder taken separately, but changing the third constituent significantly altered the values of the coefficients. In order to treat all the data as a single set it was necessary to include terms in the equation relating to the physical properties of the third constituent. The method chosen was to use multiple linear regression.

The mean granule size was, therefore, related to the quantitative values of those physical properties that were considered to be important, as independent variables, using an equation of the form

$$Y = B_0 + B_i x_i$$

where Y = fitted value of the dependent variable, x_i = i th independent variable B_0 = the estimated Y intercept when all x_i = 0, B_i = the estimated coefficient of the i th variable.

Data were fitted using a multiple linear regression program (Daniel & Wood 1971) on a computer system providing statistics and plots to aid the evaluation of the fit. The data used are those of blends containing lactose, boric acid and 10% of a third constituent. Sta-Rx behaved as a complex powder due to its combination of properties of partial solubility and high affinity for water. It therefore acted like a mixture of starch and sucrose, the measured solubility being due to dissolution of the soluble portion. Because of this, the data obtained from granulations with this material were excluded from the analysis.

The amounts of binder fluid, V, that were added were coded 5% w/w = −3 to 20% w/w = + 3. The binder solution was 5% w/v Plasdone K29-32 (GAF, UK Ltd) in all cases. The ratio of lactose to boric acid, M, in each blend, was entered as the log of the ratio of the weights of lactose to boric acid in the blend; the solubility, S, was expressed as the log of the weight of the substance, in grams, that dissolves in 100 cm^3 of water at 20 °C. The mean particle sizes, in μm, P, of the third constituent were entered as their log values, wettability (θ) was expressed as the square of the cosine of the contact angle of water into the third component, this giving a better fit than the simple cosine, and the mean granule size (Gd) was expressed in μm. These codings and log values were used in an attempt to produce a similar range of values for each independent variable. Various equations were evaluated and from a consideration of the statistical results and plots obtained, the equation found to give the best fit, overall is:

$$Gd = B_0 + B_1V + B_2 \log M + B_3 \log S + B_4\cos^2\theta + B_5\log P + B_6 (V)^2 + B_7 (\log M) (\log P)$$

The values of the subscripted coefficients are given in Table 1. The standard error of a coefficient shows how well that coefficient is estimated; the T-value is the coefficient divided by its standard error.

Table 1. The coefficients and their variabilities.

B(1)	Value of coefficient	Standard error of coefficient	T-Value
B_0	20.6		
B_1	304.5	21.3	14.3
B_2	321.8	65.1	4.9
B_3	181.7	26.3	6.9
B_4	825.0	75.4	11.0
B_5	336.4	76.2	4.7
B_6	−33.4	6.2	5.4
B_7	−80.6	57.8	1.4

The *component* effects (Daniel & Wood 1971), on mean granule size are shown in Table 2 for binder volume and the properties of the third powder. These indicate the individual effects of these variables on mean granule size each value (C_i) being

$$C_i = B_i (x_i - \bar{x}_i)$$

They also give a measure of the relative influence of each variable taken separately.

Table 2. Component effects, in units of mean granule size, of various variables of ternary blends.

Third constituent in granule	Binder level 1	2	3	$\cos^2\theta$	log solubility	log particle size
Maize starch	99	403	708	−325	−134	44
Rice starch	99	403	708	−238	−134	−80
Potato starch	99	403	708	−323	−134	168
Sucrose	−118	−814	−509	414	560	65
Magnesium carbonate	−509	−205	99	494	−134	−145
Kaolin	−509	−205	99	494	−134	−287
Sulphanilamide	−509	−205	99	−172	70	104
Salicylic acid	−205	99	403	−291	23	115

DISCUSSION

The properties of a mixture of powders rarely result from simple additivity of those of the individual constituents. It is also difficult to have direct and quantitative measures of the properties of such mixtures. However, the properties of powder mixtures can be predicted partly from those of the individual components, partly by the ways in which the components interact with each other and partly by the properties of the fluid filling the interstices bebetween the various particles. This idea has been utilized in establishing a simple model to represent the complex situation arising when powder mixtures are granulated. The factors considered in this model are shown in Table 3 in the order of their relative influence on the mean granule size, estimated from the computer analysis. Too much weight should not be placed upon the precise numerical values obtained, bearing in mind the non-ideal nature of particulate systems in general. Nevertheless, the relative order of these factors enable useful deductions to be made for the granulation systems studied.

Binder volume

The binder quantity employed in granulation is indicated to have more than twice the influence of any other variable on the growth of granules (Table 3). This supports the view that additions of binder solution to any blend of powder result in the agglomeration of most of the primary particles by liquid bridges in the pendular state. The funicular and finally the capillary states are later achieved with a continuous addition of binder which becomes distributed throughout the powder bed as massing progresses. However, the total binder quantity available for the process may be influenced by the physical properties of the powders being granulated. When a powder is capable of absorbing part of the binder, and therefore making it unavailable for granulation, the final granule size is affected in a number of ways. One is that the number of liquid bridges formed may be reduced or the strength of these bridges may not be sufficient to hold the granules together. Another is that the binding property of the powder may be impaired due to the presence of binder liquid in its internal pores. Finally, during and after drying, the granules may be so weak that they break down. On handling, the ultimate result of all these factors is the production of smaller and weaker granules, as was illustrated by the effects of starches on granule properties (Jaiyeoba & Spring 1979). In such cases, increased binder quantity is required to produce granules with adequate strength.

Table 3. The relative influence of some granulation factors on mean granule size of ternary mixtures as calculated from computer analysis.

Factors affecting mean granule size	Form of variable	Relative influence
Binder quantity	Q	1.68
Wettability of third component in water	$\cos^2\theta$	0.75
Solubility of third component	log S	0.64
Lactose to boric acid ratio	log M	0.56
Mean particle size of third component	log P	0.42

On the other hand, one of the components of the powder mixture may dissolve in the binder solution to such an extent that the liquid quantity available for granulation is increased. In such a case, the use of a smaller quantity of binder solution may be necessary to avoid overwetting the remainder of the powder mixture. Also, as shown with mixtures containing sucrose, the rheology of the binder solution can also be significantly altered as more powder is dissolved (Jaiyeoba & Spring 1980a), and this alters granule properties by influencing the way in which the binder is spread on the surface of the particles.

Wettability

The wettability of the powders also influences the distribution of the binder liquid over their surfaces. The contact angle, θ, of a drop of liquid on a flat solid surface, is a useful parameter to describe the extent to which the solid is wetted by the liquid. The cosines of the contact angles of the various powders with water were thus used to show the contribution of the wetting phenomenon to the final granule size. With a relative influence of 0.76 for $\cos^2\theta$ (Table 3) the wettability of a powder is indicated to be an important factor affecting granule size. During wet massing, liquid bridges hold the particles together both by surface tension forces and by a negative capillary pressure once the solid is wetted. A hydrophobic powder would then require more binder solution or a longer massing time in order to be wetted sufficiently.

Solubility

The influence of solubility of the powder, expressed as log (solubility) is also close to that of $\cos^2\theta$. This may be expected since the two properties, solubility and wettability, are often related. A powder which is very soluble will also be readily wetted in water although the converse is not necessarily true. In addition, a very soluble powder will directly affect the quantity of binder solution available to form liquid bridges between other particles in the mixture.

The materials used in this investigation were selected on the basis of their solubility, in water, and depending on their solubility, different component effects were calculated for the variation of log (solubility) as shown in Table 2.

Effect of changing boric acid/lactose ratio

The properties of the two powders, lactose and boric acid, common to all the mixtures, also contribute significantly to the final properties of granules prepared after the addition of a third component. Since the two powders are constant in each granule formulation, their properties are not considered as separate variables. However, the ratio of lactose to boric acid in the mixture was varied, and using the logarithm of this ratio, a relative influence of 0·57 was estimated for it.

Effect of packing

The packing of particles in the final granule is also an important factor relating to the physical properties of the dried granules. The strength of dry granules prepared with various grades of lactose was shown to be inversely related to the granule porosity by Hunter (1972). Also, similar changes in granulation conditions were found to result in increases in mean granule size and strength but decreases in granule porosity for granules prepared from blends of lactose and boric acid (Opakunle 1975). It is however, difficult to predict the packing of particles in granules from the characteristics of the dry powder. The maximum packing density that can be achieved for a powder is different in most cases for dry and wet powder systems. Denser packing is obtained for wet systems as a result of capillary forces, lubrication and changes in the dielectric between particles. The final density of the agglomerates is also affected by the consolidating actions of the mixer (Eaves & Jones 1973) and granulator. Since different powder mixtures required varying amounts of liquid to form granules, the final density shown above can be related to the packing in granules only when similar amounts of liquid are involved. All the same, limited information is provided on the state of packing in the final granules, the density of the wet granule being subject to further alterations during the screening and drying operations. The packing arrangement of the particles in a mixture of powder is also dependent on the differences in the particle-size distributions of the component powders. Closer packing is achieved by an interstitial packing of small particles in the voids between the larger particles.

Effect of particles size of third component

The ternary mixtures whose granules were studied are all composed of lactose and boric acid powders as well as a third component chosen from a list of powders with differing mean particle sizes. The relative influence of the variable incorporating the logarithm of the mean particle size of the third component is low compared to the other variables discussed above (Table 3). This would suggest that the particle size of the third component contributes rather less to the mean granule size where other properties such as solubility or wettability are large. This will be more so if enough binder is used to granulate the powders and the consolidation forces are sufficient to bring their particles close together.

Effect of cohesiveness of the third component

One other property of a bulk powder that could contribute to a closer packing of its particles is cohesiveness which is essentially the tendency of individual particles to stick together. When the cohesiveness of the various powders was given a subjective relative ranking from their behaviour during handling, in the computer analysis, the influence of this variable on mean granule size was not significant.

From the above considerations, one can predict within reasonable limits the mean granule sizes of blends of lactose and boric acid containing 10% of a third powder with known aqueous solubility, contact angle with water and mean particle size when granulated with known quantities of binder solution.

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