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GRANULATIONS IN A FLUIDIZED-BED: EFFECT OF BINDERS AND THEIR CONCENTRATIONS ON GRANULE GROWTH AND MODELING THE RELATIONSHIP BETWEEN GRANULE SIZE AND BINDER CONCENTRATION

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ABSTRACT

Lactose and mixture of lactose and microcrystalline cellulose (1:1) were granulated in a fluid-bed equipment using PVP, acacia and gelatin as binders. The effect of these binders, their concentrations, and volume of granulation liquid on granule growth and granule size distribution was studied. It has been shown that individual binder and binder concentration affect granule growth and growth mechanism. Also, the volume of

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granulation liquid and part dissolution of excipients being granulated contribute significantly to the granule size and size distribution. On the basis of granule growth data, a mathematical relationship which relates granule size as a function of binder concentration is proposed. Granule growth constant for the binders is computed from the granule size against binder concentration data. The constant describes granule growth pattern, and is termed as binder coefficient, β. The numerical value of binder coefficient, which varies with the binder, indicates relative activity and effectiveness of each individual binder. A relationship between the binder coefficients is also established. This is shown to predict granule size for a binder relative to another binder for the desired concentration. The validity and the applicability of the proposed relationship was tested on the data obtained during present investigations as well as on data reported by other authors.

INTRODUCTION

Numerous studies dealing with fluidized-bed granulation have been reported so far. However, the process can not be regarded as one that is well understood. It is clear from the literature that there are many process and formulation variables involved in the process which govern granule formation and granule properties. Among the so-called formulation variables, binder type and binder concentration are two of the most important variables. It has been reported that the size of granules is mainly determined by overall amount of the binder used (1-7). Although the critical role of binders in the granule growth process has been well recognized, a quantitative relationship between mean granule size and binder concentration has not yet been documented. It is therefore essential to carry out laboratory-scale experiments with widely used tablet excipients to develop a mathematical relationship between binder concentration and resultant mean granule size. Such a relationship would permit greater understanding of the effect of a binder and binder concentration on granule growth, and would allow to predict granule size for specific binder and its concentration.

The objective of the present study was to investigate the effect of some widely used tablet binders, their concentrations, and volume of granulation liquid on the granulation of lactose and mixture of lactose and microcrystalline cellulose (1:1), and to study granule growth behavior as a function of these variables. A mathematical relationship which relates mean granule size as a function of binder concentration is proposed. From the experimental data, granule growth constant for the binders is derived

which is termed binder activity or binder coefficient, β. Binders used in this study are classified according to this coefficient. The binder coefficient represents relative effectiveness and activity of a binder with respect to another one. The proposed relationship allows to predict mean granule size of a given formulation for the desired binder concentration of a known binder coefficient. Alternatively, concentration of a binder of known binder coefficient, β, can be predicted to obtain desired granule size.

MATERIALS AND METHODS

Materials

Lactose hydrous, N.F. (Foremost Product # 312, Foremost Whey Products, Baraboo, WI) and microcrystalline cellulose (Emcocel®; Edward Mendell Co., Inc., Carmel, NY) were used as granulation excipients. Polyvinyl pyrrolidone (Povidone K 30; American Drug House, Monsey, NY), acacia (Ruger Chemical Co., Inc., Hillside, NJ) and gelatin (P. Leiner & Sons, America Inc., St. Clair Shore, MI) were used as binders.

Formulations

The materials used in this study were selected on the basis of their widespread use in tablet formulations. For one set of granulation experiments, lactose was used as the granulation excipient (formulation A). Since combination of diluents are frequently used in tablet formulations, for another set of experiments, mixture of lactose and microcrystalline cellulose in equal proportion by weight (1:1) (formulation B) was used. Polyvinyl pyrrolidone (PVP), acacia and gelatin were used as binders.

Granulation batch size of formulation A was 500 g and that of formulation B was 300 g. Since both the formulations widely differed in their affinity for the granulation liquid, 150 mL of water was required for formulation A and 600 mL for formulation B. Both the formulations, i.e., formulation A and B, were granulated using various concentrations (ranging between 1 to 14% w/w of the excipient quantity) of PVP, acacia or gelatin dissolved in purified water.

Preparation of binder solutions

Binder solutions were prepared by dissolving appropriate amount of the binder in fixed volume of purified water, i.e., 150 mL for formulation A and 600 mL for

formulation B. PVP and acacia solutions were prepared by slowly incorporating dry binder in purified water with constant stirring. These solutions were then allowed to stand for 24 hours before use.

Gelatin solutions were prepared by first thoroughly hydrating gelatin in cold water for 10 minutes. The slurry was then gradually heated on a water bath with constant stirring to 80°C, the temperature at which gelatin solution was used.

Granulation and drying

A fluid-bed equipment (Uniglatt®, Glatt Air Techniques, Inc., Ramsey, NJ) with 1.2 liter vessel capacity was used for the granulation of all formulations. The following process variables were held constant during all granulation runs: inlet-air temperature - 50°C; atomization air pressure at the spray nozzle - 20 psi; air volume - air flap at 26, 30 and 35; rate of flow of the granulation liquid adjusted at 22 mL of water/min.

Granulation excipients were weighed and placed in the product container, pneumatically locked in place in the granulator prior to initiation of the granulation cycle. In the case of formulation B, excipient powders were mixed by fluidization in the product container for 1.5 minutes. Because of the nature of particle fluidization, ideal mixing of the powder blends could be accomplished in this relatively short time (1-3, 6). Upon completion of the mixing operation, the binder solution was pumped in an atomization form into the fluidized-bed of powders by means of a calibrated metering pump and the spray nozzle system. Since binder solutions for each formulation were prepared in a fixed quantity of purified water, the rate of wetting imparted was controlled by adjusting the metering pump to deliver 22 mL of water to the powder bed per minute.

After all the binder solution had been delivered in the granulation mass, the metering pump was turned off. The drying cycle was initiated five minutes after turning off the metering pump. Partial drying was carried out for two minutes at 65°C by elevating the inlet-air temperature. The shaking device for the exhaust filter was activated several times during granulation and drying cycles to prevent accumulation of fine powder particles on the filter surface. The product was then transferred to compartment trays and dried in a tray drier at 45° to 50°C for 16 to 18 hours or until equilibrium moisture content was reached.

Particle size analysis

The granule size distribution was carried out by sieve analysis using a set of US standard sieves; and the size distribution was described by log-normal distribution

relationship. From the log-probability plots, geometric mean diameter, d_g, as well as geometric standard deviation, σ_g, defined by the slope of the log-normal curve were determined. In order to make the results more precise, each sieve analysis was carried out using a nest of minimum 12 sieves. Since it was not possible to accommodate the whole set of sieves on the sieve shaker at one time, the sieve analyses were carried out in two or more parts as required, however, with a fresh sample of granules taken every time. For each determination, a sample of 50 g of granules was subjected to vibrations on the sieve shaker for 5 minutes.

RESULTS AND DISCUSSION

Effect of binder concentration

Mean granule size as well as geometric standard deviation data obtained for formulation A and B using PVP, acacia and gelatin at various concentrations are given in Table 1 and 2, respectively. In general, an increase in binder concentration yielded larger granules. From the observations, it is apparent that granule size enlargement with respect to increase in binder concentration is more noticeable at lower binder concentrations. Beyond critical binder concentration, which varies with the binder, granule growth slows down and eventually attains almost a plateau.

The results show that there is a critical binder concentration at which granule growth changes during fluid-bed granulation. In the case of formulation A, there is a gradual increase in the mean granule size for 1 to 4% of PVP and acacia (Table 1). However, for both these binders, increase in granule growth from 4 to 5% is dramatic, and beyond 5% binder concentration granule growth is gradually reduced. In the case of gelatin, however, the gradual increase is observed for up to 2% of its concentration. At 3-4% concentration, the granule growth shows a dramatic increase which gradually reduces as gelatin concentration is increased further. Similar trend is observed for the granulation of formulation B (Table 2). A gradual increase in the mean granule size is observed for 2-3% PVP and acacia, and 1% gelatin. There is dramatic increase in the granule size for 4-5% PVP and acacia, and >1 to 4% gelatin. Beyond these binder concentrations, the granule growth is gradually decreased. Such observations indicate a change in the mechanism of granule formation with an increase in the binder concentration.

In a fluid-bed equipment, the initial gradual increase in granule size at lower binder concentrations may be attributed to the increase in penetration, covering or wetting

TABLE 1

Mean granule size, d_g, and geometric standard deviation, σ_g, of lactose (Formulation A) granulations using various binders and their concentrations.

Binder conc. (% w/w)	PVP		Acacia		Gelatin	
	d_g (μm)	σ_g	d_g (μm)	σ_g	d_g (μm)	σ_g
1	225	2.33	285	2.05	411	1.87
2	311	2.11	380	1.87	425	1.82
3	358	2.04	409	1.78	556	1.71
4	405	1.60	451	1.87	630	1.51
5	466	1.53	531	1.35	675	1.50
6	-	-	-	-	725	1.54
7	488	1.25	545	1.95	-	-
9	549	1.33	590	1.42	-	-
12	580	1.46	610	1.56	-	-
14	612	1.51	-	-	-	-

TABLE 2

Mean granule size, d_g, and geometric standard deviation, σ_g, of granulations of mixture of lactose and microcrystalline cellulose (1:1) (Formulation B) using various binders and their concentrations.

Binder conc. (% w/w)	PVP		Acacia		Gelatin	
	d_g (μm)	σ_g	d_g (μm)	σ_g	d_g (μm)	σ_g
1	-	-	-	-	497	1.63
2	455	1.39	502	1.57	671	2.28
3	516	1.61	573	1.71	794	2.41
4	575	1.70	660	2.01	916	2.01
5	636	2.03	720	1.81	931	1.82
6	-	-	-	-	1062	1.83
7	713	2.00	739	1.91	-	-
10	764	2.88	848	2.80	-	-
14	805	2.82	-	-	-	-

of excipient particles by the aqueous binder solution. This results in the formation of particle-binder-particle bond forming small granules by pendular bridging until all the particles are bonded on the surfaces of granules. The binder solution up to a critical concentration causes an increase in the number of bond formation. The particle-binder-particle bond strengthens with an increase in the binder concentration due to corresponding increase in binder adhesiveness resulting in an increase in granule size (2). This continues until an equilibrium granular state is reached (8). Further addition of the binder solution binds the granules together by capillary bridging without any granule growth. Until the breaking point, granules grow by pendular bridging; beyond which there is little or no growth, and the granules are held together by capillary bridges. The granules are uneven at the breaking point, and become smoother and spherical without any significant growth on further addition of the binder solution.

The initial rapid increase in the granule size indicates that the excipient powder in the form of loose fluffy aggregates is penetrated rapidly by the aqueous binder solution due to its large surface area to form nuclei which, subsequently, undergo nucleation to form primary granules. These granules grow by adhesion of other individual particles onto the surfaces of the nuclei or by direct agglomeration of the primary granules with each other.

The granule size data, however, show that beyond a critical binder concentration the granule growth is gradually reduced. This may result because of several reasons. Initially, due to a large number of prime particles, large number of nuclei are formed. As the nucleation and primary granule formation proceeds, the total number of nuclei decreases, and therefore further granule growth is also reduced. The reduction in granule growth may also be attributed to a change in the mechanism of granule formation in the process. It has been suggested by Capes (7) that at higher binder concentration, the granule size increases by layering and/or agglomeration. Stanley-Wood and Shubair (4) observed that at lower binder concentrations, the particles are coated with only a small proportion of binder solution which bonds powder particles together; while at higher binder concentrations, the cohesion of binder molecules to each other is such that powder particles are not bonded to each other by a binder bridge. Alkan and Yuksel (5) have reported that agglomeration and snow-balling are the main mechanisms responsible for granule growth in fluidized-bed, and that granule growth by agglomeration is faster than that by snow-balling. It may be postulated that up to a critical binder concentration the granules grow predominantly by agglomeration or coalescence, beyond which they grow

by snow-balling or layering. Since granule growth by snow-balling or layering is much slower than that by agglomeration (5), beyond critical binder concentration the granule growth gradually slows down. Also, at equilibrium granular state, weight of the granule exceeds the strength of particle-binder-particle bond. The gravitational force due to the weight of granules along with forces of shearing among the particles and between particles and fluidizing chamber, induced by the fluidizing air, causes the granules to break apart, consequently, further growth of the granules becomes negligible.

From the geometric standard deviation data, it can be inferred that, in the case of lactose (formulation A) granulation, the granule size distribution gets narrower as the binder concentration is increased from 1 to 7% w/w for PVP, 1 to 5% w/w for acacia, and 1 to 5% w/w of gelatin. Beyond these binder concentrations, a wider size distribution is observed (Table 1).

In the case of granulation of mixture of lactose and microcrystalline cellulose (formulation B), narrower size distribution was obtained at lower binder concentrations for the formulations containing PVP and acacia, however, granulation using gelatin exhibited narrower distribution as binder concentration was increased (Table 2).

Effect of type of binder

The effect of binders and their concentrations on the granule size distribution has been shown in Figs. 1 and 2. It is evident from the histograms that the specific activity of individual binder affected mean granule size and size distribution in a definitive fashion. In the case of formulation A (Fig. 1), at 1% concentration PVP yielded 87%, acacia 77%, and gelatin 38% of the total granules in the size range of 100 to 250 microns which was reduced to 26%, 9%, and 6%, respectively, at 5% concentration. In the size range of 250 to 450 microns, at 1% concentration PVP yielded 8%, acacia 11%, and gelatin over 19% of the total granules. This was increased to 50% and 60% for the granulation using PVP and acacia, respectively, at 5% concentration. However, granulation with 5% gelatin gave 14% granules in this size range. Whereas, at higher size level, i.e., >450 microns, gelatin yielded the highest total percentage, i.e., 43% of the granules at 1% concentration as compared to 6% and 12% for PVP and acacia, respectively. At 5% binder level, the percentage of granules in this size range increased to 24%, 31% and 79% for PVP, acacia and gelatin, respectively. Similar trend was observed for the granulation of mixture of lactose and microcrystalline cellulose (formulation B) (Fig. 2).

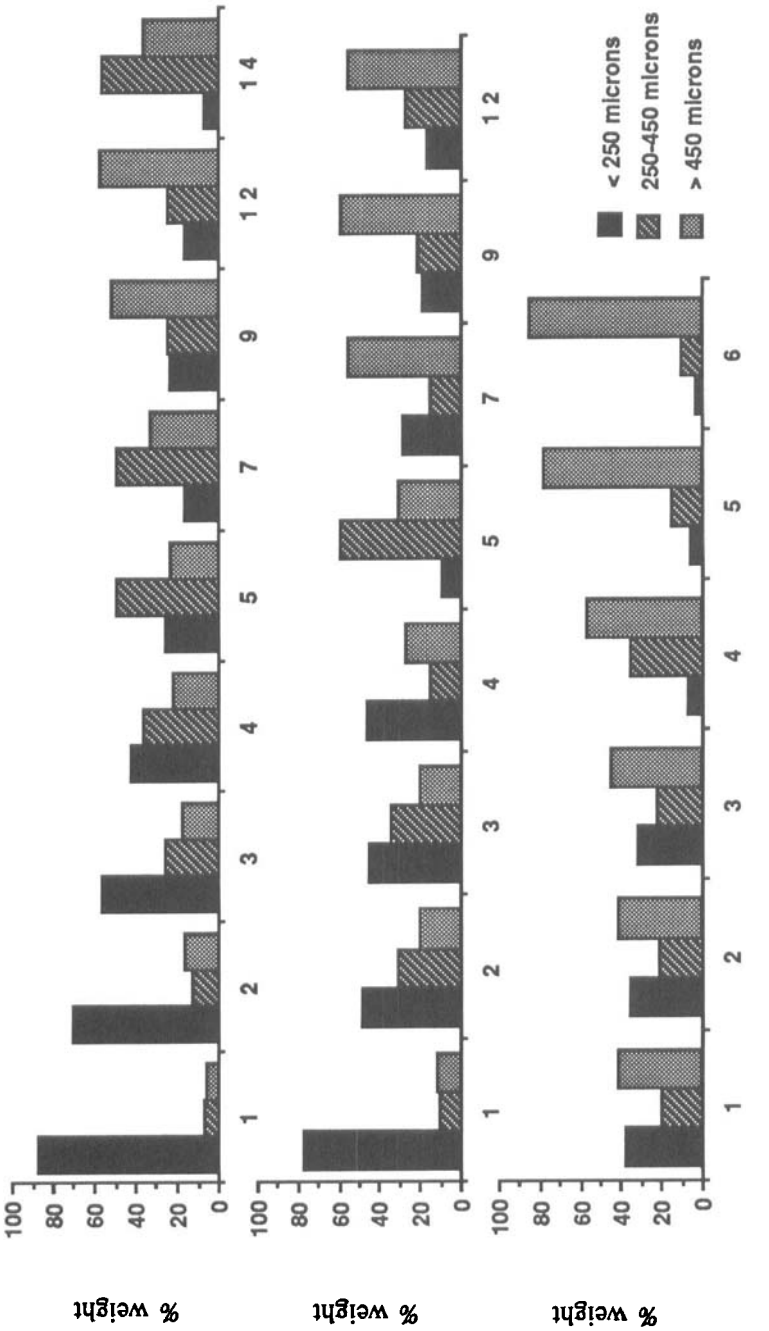

Figure 1 - Histograms representing granule size distributions for the granulation of lactose at various binder concentrations.

Top - PVP; Middle - Acacia; Bottom - Gelatin

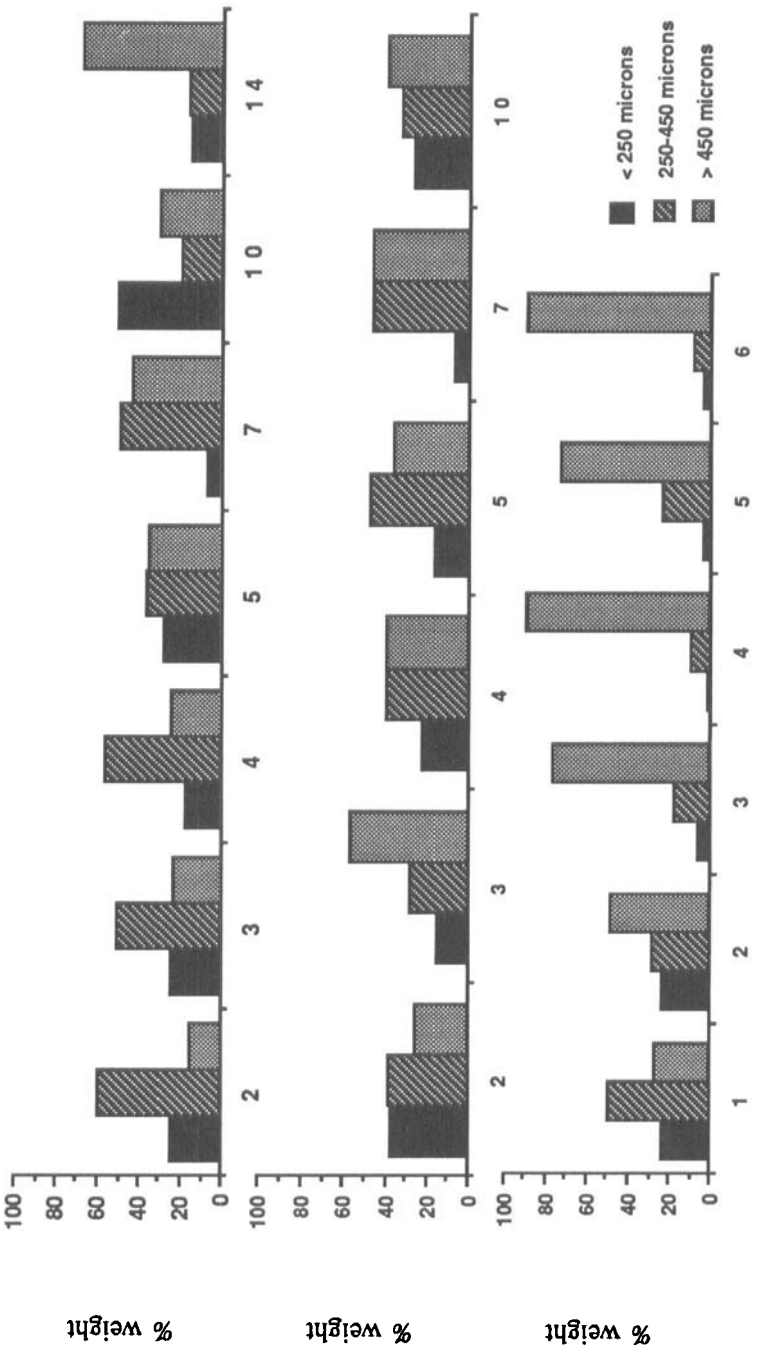

Figure 2 - Histograms representing granule size distributions for the granulation of mixture of lactose and microcrystalline cellulose at various binder concentrations.

Top - PVP; Middle - Acacia; Bottom - Gelatin

Such growth behavior may be attributed to the specific binder activity of the individual binder which determines the mechanism of granule growth. As mentioned earlier, nucleation and primary granule formation seems to be the predominant mechanism of granule size enlargement in the formulations containing PVP and acacia at concentrations between 1 to 5% w/w. Formulations granulated with gelatin show major part of granules in the size range of >450 microns even at lower binder concentration which indicates that in the formulations with gelatin, agglomeration of particles or primary granules with each other takes place simultaneously with the nucleation. The rapid growth in the granule size suggests that agglomeration predominates snow-balling at this stage of granule growth. The major factor that contributes to these changes seems to be the particle-binder-particle bond strength. The results show that the bond strength of the binders used is in the rank order of gelatin > acacia > PVP.

The size distribution and geometric standard deviation, σ_g, data show that at all binder concentrations, granulation with gelatin yielded the narrowest size distribution followed by those with acacia and PVP for formulation A (Table 1), and narrowest size distribution for PVP and widest for gelatin for formulation B (Table 2).

Although there are several factors which affect the binder activity, they can be correlated to represent overall binding efficiency of an individual binder. In order to assess relative activity of tablet binders, a new term binder coefficient, β, is proposed, and a numerical value which could help in the evaluation of relative binder activity is assigned to the binders.

Effect of excipient solubility and volume of granulation liquid

The observations show that the mean granule size for formulation B was comparatively larger than that for formulation A for all the binders and binder concentrations used (Table 1 and 2). These observations are in agreement with the findings of other studies (9-11). In the present studies, the high water-retention capacity and insolubility of microcrystalline cellulose in water required a higher volume of granulation liquid for adequate granulation of formulation B which resulted in larger granule sizes. This was possibly due to a number of factors. Firstly, as the volume of the granulation liquid was increased, so did the amount of lactose that dissolved during granulation which eventually acted as a secondary binder. Consequently, primary binder along with the secondary binder reduced the amount of fines, and yielded coarser granules resulting in an increase in the granule size. Secondly, as more solids went into solution,

the smaller soluble particles were dissolved preferentially thus reducing the surface area of the solids to be wetted during granulation.

It indicates that solubility of a part of the excipient in the granulation liquid is desirable for granule formation. The presence of a secondary binder was apparently also responsible for the narrower size distribution in the case of formulation B granulated using PVP and acacia as compared to formulation A granulation. However, in the case of formulation B granulated with gelatin, marginally wider granule size distribution was observed as compared to formulation A. This probably resulted because gelatin solution in less concentrated, and therefore less viscous state, was not as efficient in bond formation as it was in more concentrated and more viscous state resulting in relatively wider size distribution.

Granule growth pattern and mathematical relationship

The change in the mean granule size of formulation A and B as a function of binder concentration for PVP, acacia and gelatin has been presented in Figs. 3 and 4, respectively. These granule growth curves demonstrate that the mean granule size increases as the binder concentration is increased. However, beyond a critical binder concentration, when an equilibrium granular state is reached, the granule growth is reduced and eventually attains almost a plateau.

The observations indicate that the relative increase in the granule size with respect to an increase in the binder concentration, i.e., dX/dC, decreases at a constant rate proportional to the relative increase in binder concentration (Table 1 and 2). Mathematically, the relationship can be expressed as:

$$\frac{dX}{dC} \propto \frac{1}{C} \tag{1}$$

where X is mean granule size, and C is binder concentration.

However, since mean granule size is a function of various excipient powder properties, e.g., mean particle size, etc., deviation from the above equation may be observed while plotting granule size data as a function of binder concentration. In order to account for such deviation, a correction factor must be introduced in the above equation. Thus Eqn. (1) can be written as:

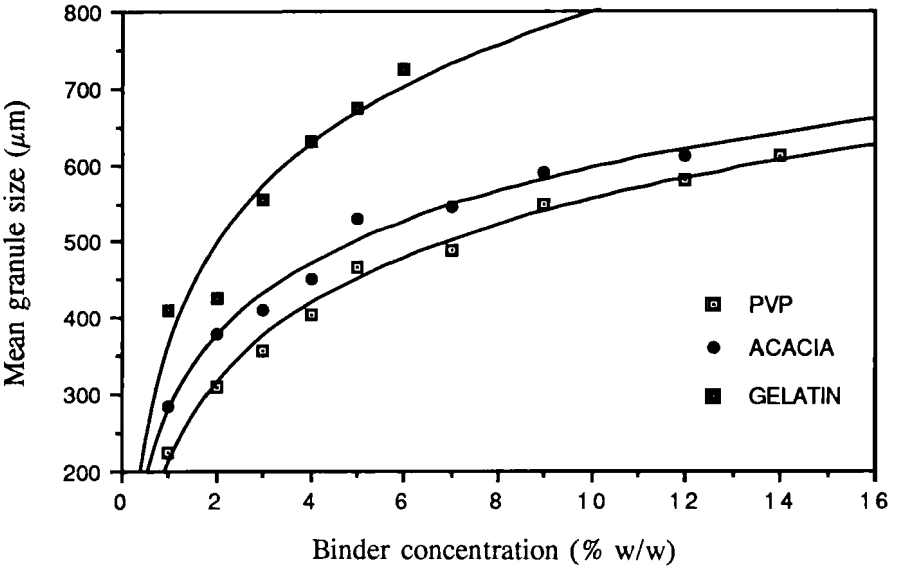

Figure 3 - Plot of the mean granule size as a function of binder concentration for the granulation of lactose.

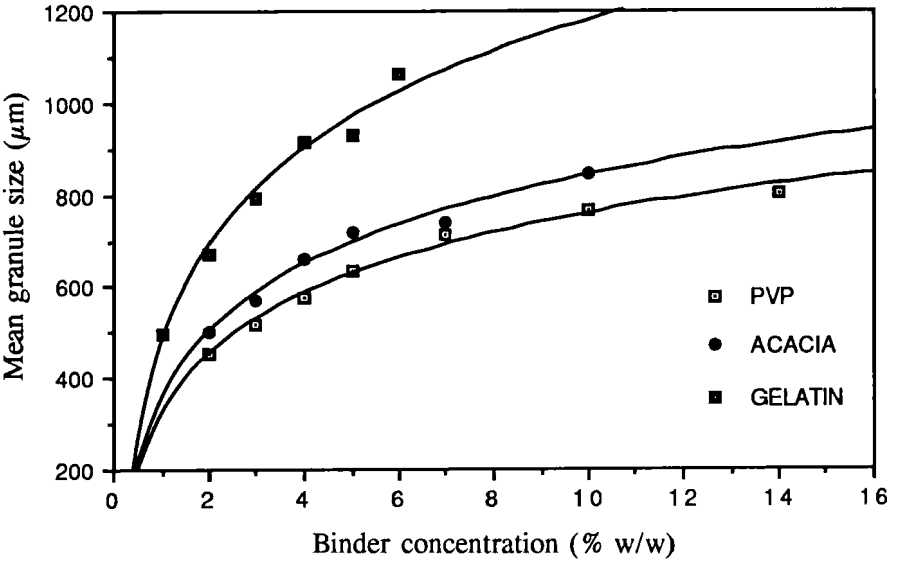

Figure 4 - Plot of the mean granule size as a function of binder concentration for the granulation of mixture of lactose and microcrystalline cellulose.

$$\frac{dX}{dC} \propto \frac{1}{C + f_c} \tag{2}$$

where f_c is the correction factor whose value is fixed by physical considerations to be ≥ 0, and accounts for any deviation of the process from Eqn. (1). The value of f_c is obtained from curve fitting, and has no physical meaning. The value of f_c during present studies was determined to be 0.5. Eqn. (2) can be rewritten as:

$$\frac{dX}{dC} = z \frac{1}{C + f_c} \tag{3}$$

where z is proportionality constant which represents granule growth behavior, and is a function of inherent binding activity or adhesiveness of the binder. The higher is the binding activity or adhesiveness of the binder, the higher is the relative increase in the mean granule size for each unit increase in the binder concentration and, consequently, higher is the value of granule growth constant, z. The value of z can be numerically determined from the mean granule size data at various binder concentrations.

Integrating Eqn. (3) in the following form:

$$\int dX = z \int \frac{dC}{C + f_c} \tag{4}$$

one obtains:

$$X = z \ln (C + f_c) + i \tag{5}$$

Using Eqn. (5), a straight line will be produced when X is plotted against ln $(C + f_c)$. The plot will have slope equal to z, and i as the intercept.

Since $X = f(C)$, theoretically at 0% binder concentration, the granule size will be equal to zero, thus:

$$X(0) = 0 = z \ln (0 + f_c) + i \tag{6}$$

or

$$i = - z \ln (f_c) \tag{7}$$

Combining Eqns. (5) and (7), one obtains:

$$X = z \ln (C + f_c) - z \ln (f_c) \tag{8}$$

or

$$X = z \ln \{(C + f_c) / f_c\} \tag{9}$$

Using Eqn. (9), the mean granule size for desired binder concentration can be predicted, provided value of granule growth constant or binder activity under the given experimental conditions is known.

Furthermore, Eqn. (9) can be modified to determine and compare the relative binding activity of two binders, and to predict mean granule size for a binder with respect to the other one. Assuming that two binders, e.g., binder 1 and 2, are independently used to granulate a given formulation at a binder concentration, C. For such a case, Eqn. (9) can be rewritten as:

$$X_1 = z_1 \ln \{(C + f_c) / f_c\} \tag{10}$$

and

$$X_2 = z_2 \ln \{(C + f_c) / f_c\} \tag{11}$$

where X_1 and X_2 are the mean granule sizes at binder concentration, C, for binders 1 and 2 with granule growth constant or binder activity z_1 and z_2, respectively. The ratio of Eqns. (10) and (11) may be written as:

$$\frac{X_1}{X_2} = \frac{z_1 \ln \{(C + f_c) / f_c\}}{z_2 \ln \{(C + f_c) / f_c\}} \tag{13}$$

If the value of granule growth constant or binder activity, z, of one of the binders is empirically assumed to be equal to 1, it will be possible to calculate the relative binder activity of another binder provided mean granule size for both binders at concentration, say C, is known. Alternatively, if relative binder activity of two binders, i.e., z_1 and z_2, is known, mean granule size, say X_1, for a binder at desired concentration compared to other, i.e., X_2, can be predicted.

Also, if mean granule size, X_1, at binder concentration, C_1, for a binder with binder activity, z_1, is known, mean granule size, X_2, at a different binder concentration, C_2, for another binder with binder activity, z_2, can be predicted from Eqn. (12) modified accordingly as follows:

$$\frac{X_1}{X_2} = \frac{z_1 \ln \{(C_1 + f_c) / f_c\}}{z_2 \ln \{(C_2 + f_c) / f_c\}} \quad (13)$$

In any event, the ratio of the binder activity of two binders, i.e., z_1 and z_2, will be constant. This ratio can be termed as binder coefficient, β.

In terms of binder coefficient, β, Eqn. (13) can be transformed to:

$$\frac{X_1}{X_2} = \frac{\beta_1 \ln \{(C_1 + f_c) / f_c\}}{\beta_2 \ln \{(C_2 + f_c) / f_c\}} \quad (14)$$

Eqn. (14) can be used to predict the mean granule size for a desired binder concentration. Alternatively, relative concentration of a binder needed for the desired granule size can be predicted. In either case, however, the value of the binder coefficient, β, must be known.

Predictive Ability

The proposed mathematical relationship was derived from the mean granule size data of lactose (formulation A) granulations using PVP, acacia and gelatin at various concentrations (Table 1). The applicability of the model was tested on the granule size data of mixture of lactose and microcrystalline cellulose (formulation B) granulation (Table 2), which followed the similar growth pattern and verified the validity of the proposed model. A comparison between the observed mean granule sizes and those predicted using Eqn. (14) for formulation A and B has been given in Table 3 and 4, respectively. An excellent agreement between the observed and the predicted values shows that the granule growth follows the trend defined by Eqn. (14) for both sets of formulations.

The numerical value of the binder coefficient, β, for the binders used was determined as the ratio of the slopes obtained by the regression of the mean granule size vs. binder concentration data for formulation A. PVP was empirically assigned the binder coefficient, β, value equal to 1.0. The value of binder coefficient, β, for acacia and

TABLE 3

Mean granule size data of lactose (Formulation A) granulation for various binders and their concentrations and the granule sizes predicted using Eqn. (14).

Binder conc. (% w/w)	Mean granule size (μm) PVP		Acacia		Gelatin	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1	225	202	285	222	411	313
2	311	296	380	326	425	459
3	358	358	409	394	556	555
4	405	404	451	445	630	626
5	466	441	531	485	675	684
6	-	-	-	-	725	731
7	488	498	545	548	-	-
9	549	542	590	596	-	-
12	580	592	610	651	-	-
14	612	619	-	-	-	-

TABLE 4

Mean granule size data of granulation of mixture of lactose and microcrystalline cellulose (1:1) (Formulation B) for various binders and their concentrations and the granule sizes predicted using Eqn. (14).

Binder conc. (% w/w)	Mean granule size (μm) PVP		Acacia		Gelatin	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1	-	-	-	-	497	451
2	455	426	502	469	671	660
3	516	516	573	568	794	800
4	575	583	660	641	916	903
5	636	636	720	699	931	985
6	-	-	-	-	1062	1054
7	713	718	739	790	-	-
10	764	807	848	888	-	-
14	805	892	-	-	-	-

TABLE 5

Mean granule size data of granulation of mixture of lactose and starch using various binders and their concentrations reported by Davies and Gloor (2) and the granule sizes predicted using Eqn. (14).

Binder conc. (% w/w)	Mean granule size (μm)					
	PVP		Acacia		Gelatin	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
2.00	200	181	219	190	249	259
2.75	211	211	225	224	299	302
3.50	223	234	248	248	328	335
4.25	250	254	263	269	369	363
5.00	276	270	283	286	-	-

gelatin relative to PVP was computed to be 1.10 and 1.55, respectively. This indicates the binder activity and effectiveness of acacia and gelatin to be 1.10 and 1.55 times, respectively, that of PVP. The same ratio was found to exist between the best fit points of the regression of granule size data for formulation B.

The predictive ability and the applicability of the proposed model was further tested on the data reported by Davies and Gloor (2). These authors have reported the granule size data at various binder concentrations from the granulation studies of mixture of lactose and starch using PVP, acacia and gelatin. Summary of the data reported by the authors and the values predicted using Eqn. (14) has been given in Table 5. A comparison between the reported and the predicted values shows an excellent agreement between the two which further supports the validity and the applicability of the proposed relationship.

From the analysis of data of Davies and Gloor (2), the value of correction factor, f_c, was determined to be 0.5, and that of binder coefficient, β, was computed to be 1.0, 1.05 and 1.43 for PVP, acacia and gelatin, respectively. These values are in close agreement with the values determined from the present studies, i.e., 1.0, 1.10 and 1.55 for PVP, acacia and gelatin, respectively.

This demonstrates that granule growth in a fluidized-bed follows the trend defined by Eqn. (14). The difference between the observed and the predicted values is seen only at lower binder concentrations. This is because of the fact that, at lower binder concentrations, granulation liquid plays an important role in the granule growth, and that this role becomes less significant for binders with higher adhesiveness or binder coefficient. That is why, even at lower binder concentrations, the observed mean granule sizes for gelatin did not differ significantly from the predicted values (Table 3 and 4).

CONCLUSIONS

Granule growth was observed as a function of binders, their concentrations, and volume of granulation liquid using two sets of formulations consisting of widely used tablet diluents with dissimilar affinity towards granulation liquid. It was observed that, in general, the mean granule size increased as the binder concentration was increased. From the granule size data, it is evident that at lower binder concentrations, any increase in the binder concentration causes a greater increase in the granule growth whereas at higher concentrations the granule growth is reduced, and beyond a critical concentration there is virtually little or no further granule growth. The mechanism of granule growth is dependent on the binding activity or adhesiveness of an individual binder.

It is clear that excipient solubility in the granulation liquid contributes significantly to the granule growth. The role of granulation liquid, in which the excipients are part soluble, is more prominent at lower binder concentrations because part soluble excipient acts as a secondary binder significantly adding to the binding activity of the primary binder. However, an optimal volume of granulation liquid must be used to obtain the desired granule size, size distribution, and other granule properties.

From the granule size data, a mathematical relationship between mean granule size and binder concentration is derived. In order to assess a single numerical value which could help in the evaluation of a specific binder activity, a new term, binder coefficient, β, which is indicative of the relative binder activity or adhesiveness is proposed. Numerical value of binder coefficient, β, based on binder activity is assigned to the binders used in the present investigations. PVP is empirically assigned the binder coefficient, β, value equal to 1.0. Relative binder coefficient value for acacia and gelatin were therefore computed to be 1.10 and 1.55, respectively.

The proposed relationship can be used to predict the relative mean granule size for the desired binder concentration. Alternatively, the concentration of a binder can be

predicted for the desired mean granule size. The proposed relationship and the concept of binder coefficient, β, can be used to obtain a batch of granules of more controlled and desired size.

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