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GRANULATION

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INTRODUCTION:

The pharmaceutical unit operation or unit process of granulation is the philosophical opposite of milling. Rather than particle size reduction one is interested in particle growth. Granulation can be defined as a process of agglomeration. A more descriptive definition, however, would be

> ...the build up of clusters from powder or powder/binder mixtures to produce a free flowing, cohesive material that can be further processed by compression or encapsulation.

Although the product of granulation should have the characteristics necessary for any subsequent processing, it should be pointed out that a granulation can serve, and does serve, as a marketable delivery system in some cultures (e.g., Japan, Italy.)

There are four general properties of a powder which are required to produce a good tablet or capsule dosage form (delivery system) with today's technology. They are

1. Compressibility
2. Flow
3. Wettability, and
4. Lubricity

The first two determine the requirements of manufacturing, while the latter two are usually obtained by the additives selected for a particular formulation.

If a material or mixture of materials exhibits both compressibility and flow, it can be prepared by direct compression. If a material exhibits compressibility but poor flow, it can be manufactured by dry granulation. If a material or material mixture exhibits neither flow nor compressibility, a wet granulation method is usually required. Although dry granulation is an important unit process, it is closely related to the operation of compaction and will not be discussed fully in this presentation; the emphasis will be on the wet granulation process and the effect of water.

The number of unit processes to be performed is based on the selection of the particular manufacturing method. A general flow chart for tablet preparation is shown in Figure 1, and it includes the steps from the most complicated process - that of wet granulation.

OBJECTIVES:

The objectives of granulation are summarized in the following list:

1. Increased particle size
2. Increased flow
3. Increased compressibility
4. Densification
5. Production of generally spherical, uniform-sized particles
6. Production of hydrophilic surfaces
7. Distribution of the active ingredient

Another phenomenon that might be considered an objective, but is truly an advantage of the wet granulation process, is the effect of covering raw material variations. This would be true for the excipients as well as the active ingredient(s).

THE PROCESS:

The operation of granulation is a very complicated one, and the reader should keep in mind that almost everything associated with this process becomes a variable which must be closely controlled if one is to have a reproducible product. The general categories one should consider as variables are (1) the materials selected, (2) material properties, (3) equipment, (4) the process, and (5) batch size. Because of the complicated nature of the process it is difficult to separate the unit operations when one considers the

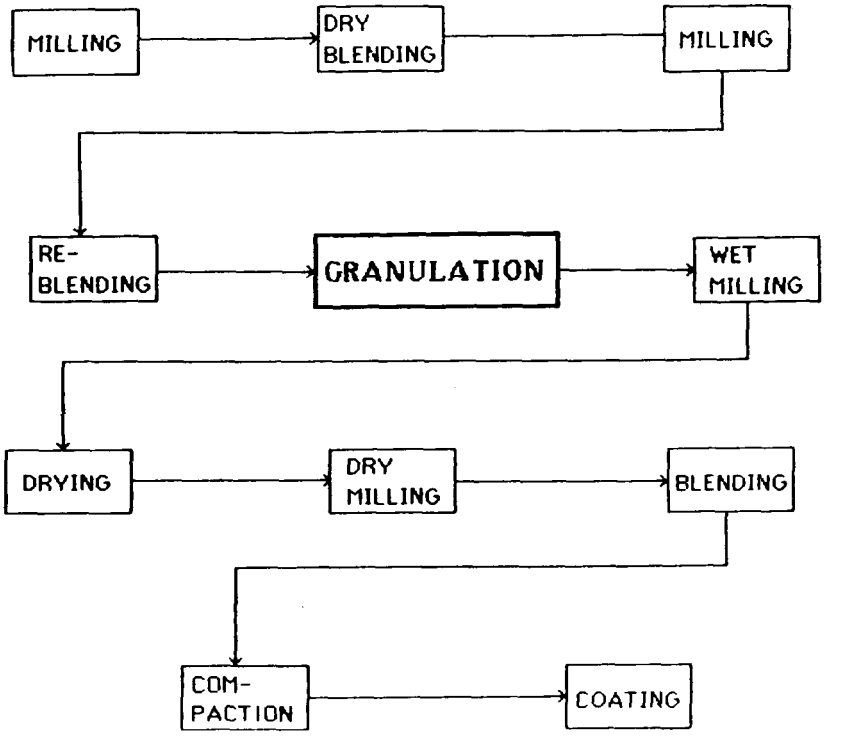

FIG. 1 - General flow chart for tablet manufacture

overall procedure of wet granulation, but in general, one considers the following steps in wet granulation:

1. Dry blend
2. Addition of granulating fluid
3. Kneading/mixing
4. Coarse milling
5. Drying
6. Dry milling

It should be pointed out that wet granulation is the only operation where step #3 (kneading) is required. This is especially true in the traditional type of granulation such as that performed in conventional planetary type mixers, but it is less applicable in the fluid bed granulation operation. With the current advances in technology and equipment (i.e., high-speed, high-shear mixers) one still obtains the shearing and kneading action, and because of the chopper blades, it is often possible to eliminate the coarse milling step as a separate operation.

STAGES OF THE PROCESS:

The stages of wet granulation as outlined by various authors include the following steps [1,2]:

1. Agglomeration
2. Agglomeration breakdown
3. Re-agglomeration, and
4. Paste formation

In general, if one proceeds to the fourth stage, one has passed the normal or conventional end-point for pharmaceutical granulations. It should be noted, however, that each case is unique; and that for certain materials, the fourth stage is required if one is to produce a compressible product which will perform adequately during manufacturing and yield a delivery system (tablet or capsule) with the appropriate activity.

GRANULATION END-POINT:

Various texts on granulation include several descriptive methods for determining the end-point of a granulation. These include the following:

> "A rough way of determining the end-point is to press a portion of the mass in the palm of a hand ... if the ball crumbles under moderate pressure, the mixture is ready for the next stage of processing, which is wet screening." [3]
>
> and
>
> "The end-point of which ... now easily a wet compaction (which would not reduce back to a powder) could be formed in the grip of the hand." [2]

There are several other such descriptions [1,4,5], but more scientific approaches to end-point determination have appeared recently in the literature. In general, these are based on the measurement of power draw in the various mixers or some related phenomenon. One of the earliest references by Travers [6] involved the determination of the torque on the mixer blade as a function of mixing time or liquid level (see Figure 2). Another involves a detailed analysis of power draw/liquid level or power draw/mixing time curves, such as that from Leuenberger (see Figure 3) [7].

COARSE MILLING:

At this point in the process, a wet milling step is usually included prior to drying. This is also called the coarse milling step, since

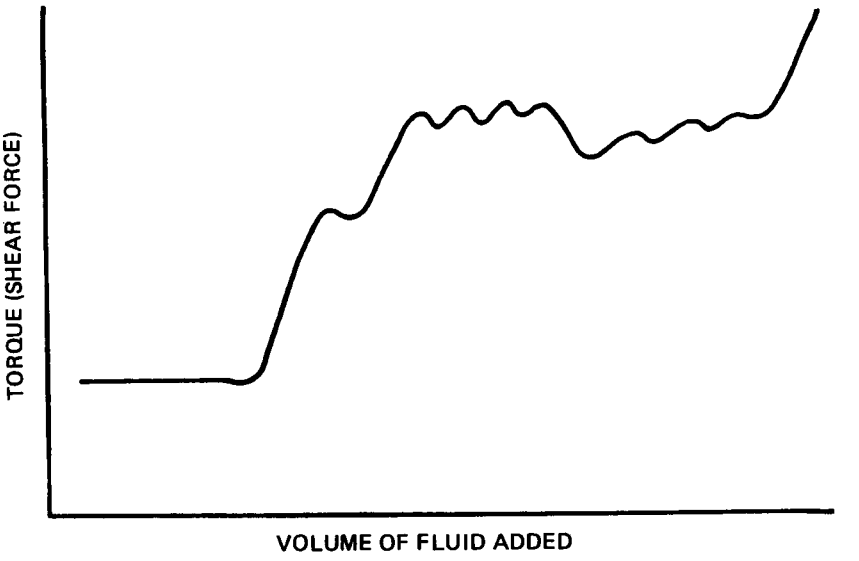

FIG. 2 - Shear force required during wetting in the granulation process (adapted from D.N. Travers, et.al., J. Pharm. Pharmacol., 27, Suppl., 3P (1975))

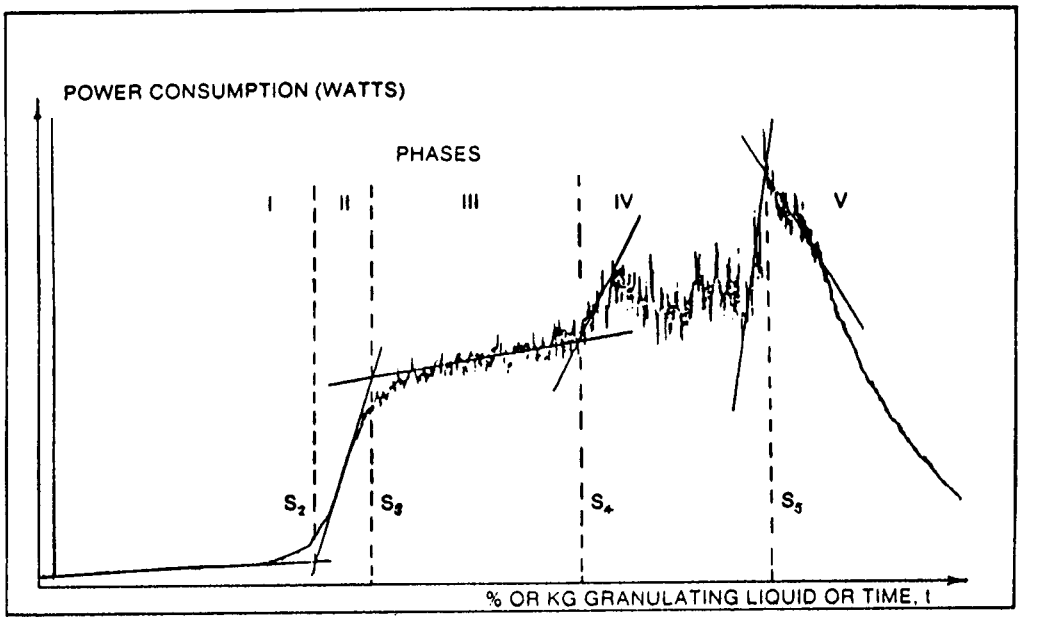

FIG. 3 - Shear force required during wetting in the granulation process (adapted from H.S. Leuenberger, et.al., Pharm. Tech., 3, 61 (1979)))

the equipment used has larger openings than that in the dry milling step. There are several reasons for wet milling; these objectives include:

1. To increase surface area for more efficient drying
2. To improve size uniformity
3. To prevent large particles which will shatter to "fines" on dry milling
4. Further blending
5. Granule formation

The first three, of course, constitute the primary objectives; and although step 5 might have been important at one time, it is not the usual situation today. Granule formation at this stage would almost be an extrusion step.

As mentioned above, the wet milling step as a separate operation can be eliminated in many cases with some of the equipment available today. Although the extrusion action provided by the wet milling step might have been necessary with simple mixers, the combination of high work input and the built in chopping mechanisms available with high-shear mixers can now produce a satisfactory end product; i.e., one which is ready for the drying step.

PARTICLE GROWTH:

In general, there are two major mechanisms for particle build-up [8]. They are identified as (1) Particle Agglomeration and (2) Particle Layering and are shown schematically in Figure 4.

The first type is representative of the process in the conventional planetary type mixer and the second, which one will recognize as a coating type process, is probably more representative of the fluid bed type granulation. The truth probably lies somewhere in between these two extremes, and the balance is heavily dependent on the type of equipment selected for the operation.

FORCES IN PARTICLE GROWTH:

According to Rumpf [8,9], there are four major forces in particle size enlargement. They are

1. Intermolecular Attracted Forces
2. Electrostatic Forces
3. Liquid Bridge Connections
4. Solid Bridge Connections

Although the first three can and do play important roles in various mechanisms of granule growth, any final bonds in pharmaceutical granulations will most probably be solid bridges. These, also

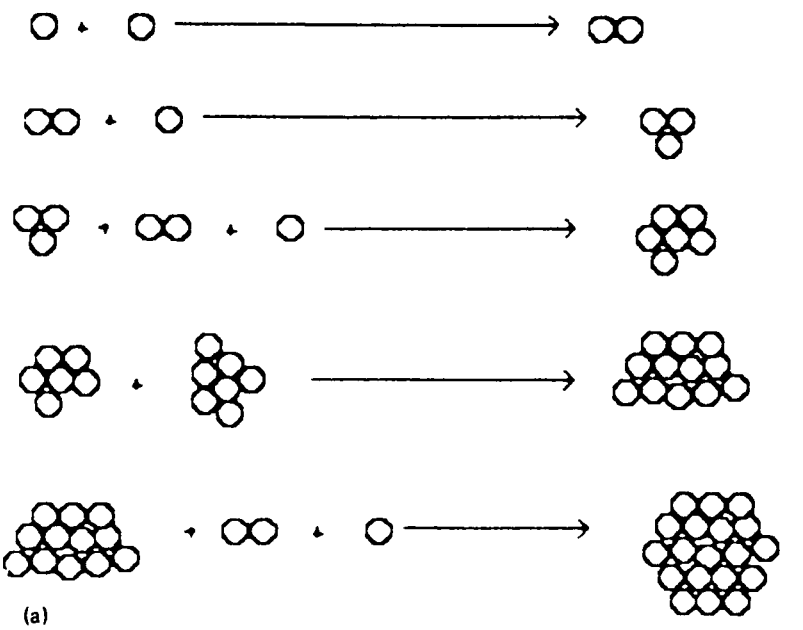

FIG. 4a - Schematic diagram of granule growth by agglomeration

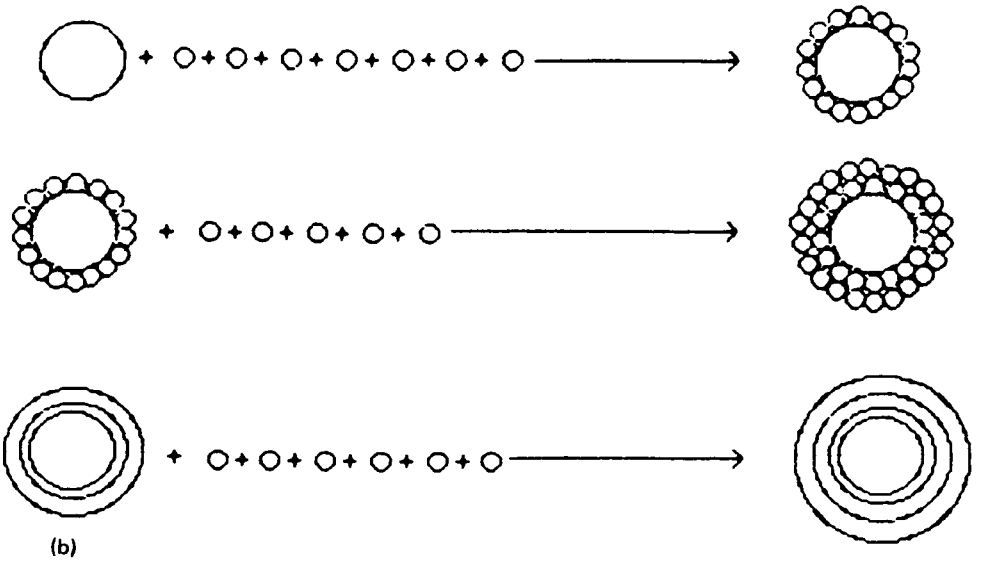

FIG. 4b - Schematic diagram of granule growth by layering (onion-skin effect)

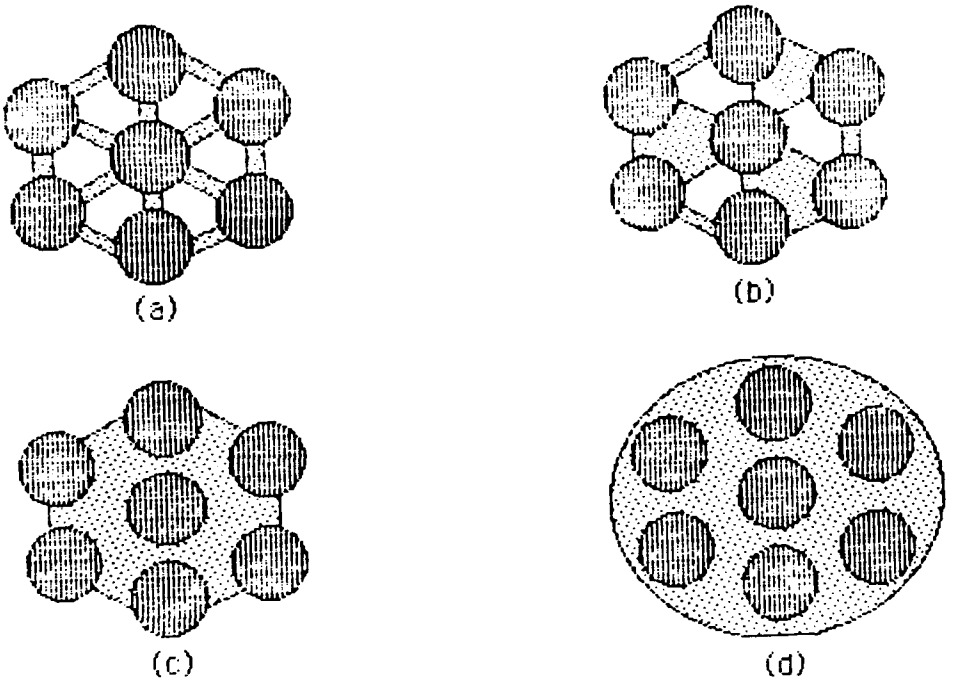

FIG. 5 - Schematic representation of the stages of powder wetting (liquid saturation) [Key: (a) pendular, (b) funicular, (c) capillary, (d) droplet]

according to Rumpf [8,9], can be formed by the mechanisms listed below:

1. Crystallization
2. Hardening of Binders
3. Local Fusion Welding
4. Particle Deformation and Sintering
5. Chemical Reaction

On a theoretical basis one can find in the literature equations describing the attractive forces between ideal, smooth, spherical particles, and the electrostatic forces in particulate systems. These relationships involve particle size, separation, distances between particles, and electrical charges. It is also possible to find equations describing the cohesive forces between particles due to adsorbed liquid layers on solid particles, liquid bridges, and viscous or adhesive binders. Calculations can be made regarding surface tension, contact angles, capillary forces, and radii of curvature [9].

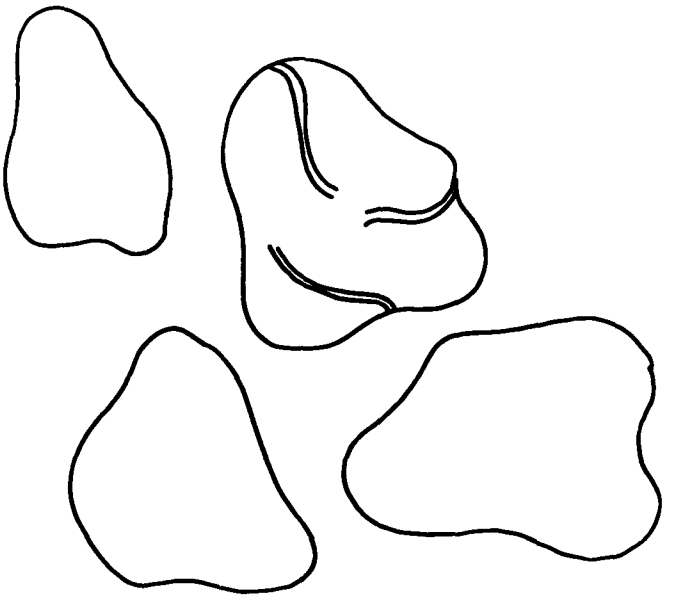

FIG. 6 - Schematic representation of hypothetical powder bed with intra- and inter-particulate pores

LIQUID SATURATION:

A more generalized explanation which is really a description of liquid-solid activity, was presented in a classic paper by Newitt and Conway-Jones in 1958 [10]. This is really the starting point for any practical discussions of granulation technology today. These workers describe three states of liquid saturation representing the stages of water distribution in a bed of solid particles. These are (1) the pendular, (2) the funicular, and (3) the capillary states, with the liquid saturation increasing in that order.

These states are shown schematically in Figure 5 along with a fourth state identified as the "droplet state," where the liquid now surrounds the solid particles. The appropriate end-point for conventional granulations lies somewhere near the capillary state, but as mentioned above, the droplet state may be required for certain formulations. It is the selection of this end-point which is one of the major problems facing those involved in granulation technology today.

In the pendular state, liquid is held at a point contact in the form of a bridge neck between individual particles. Contributing factors are the surface tension and negative suction pressure due to

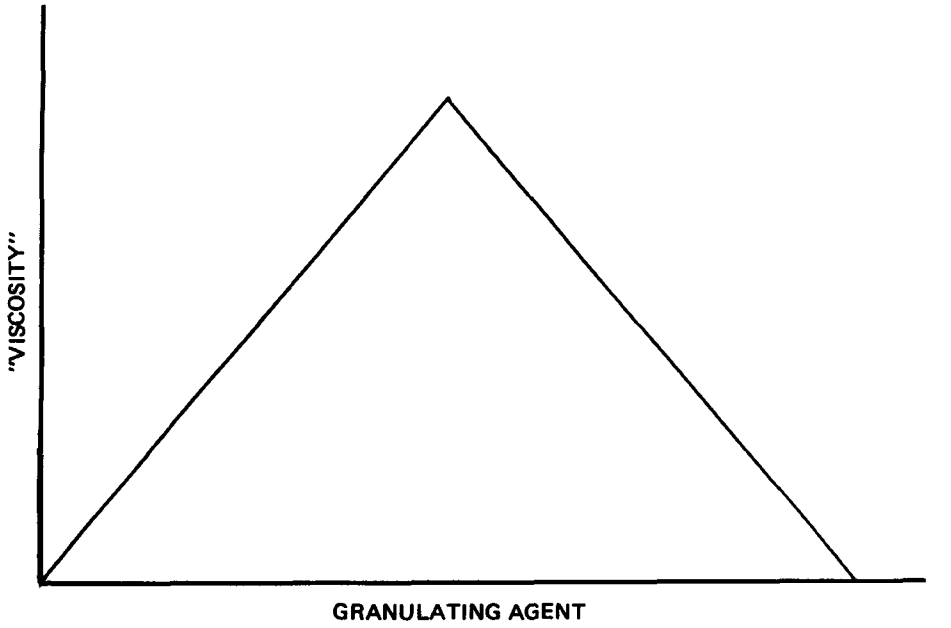

FIG. 7 - Hypothetical "viscosity" profile of a powder wetting procedure

curvature of the liquid (negative capillary pressure.) In the capillary state, the total pore space is filled by liquid. Interfacial forces and capillary pressure are again involved.

The funicular state is not as distinct a phase, but is somewhere between the other two. In addition to these stages, a fourth one, the droplet state, has been defined in Figure X. At this point, more liquid than the amount required to completely fill all the inter- and intra-particulate void space has been added to the mixture, and liquid now surrounds the solid. In general, if the droplet state is achieved, too much liquid has been added for the conventional granulation process. Although this analysis was presented on the basis of a simple two component system, these concepts should serve as a basis for more complicated systems with binders and other excipients.

The discussion above relates to the kneading or mixing step in the granulation process, and it is obvious that the quantity of granulating solution, as well as the type and time of mixing, can be critical.

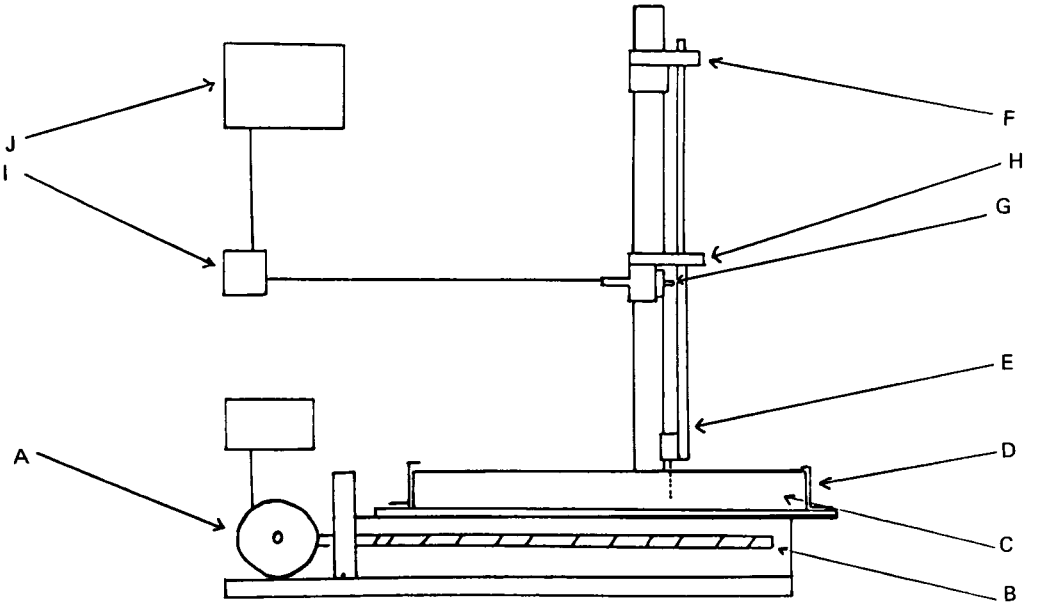

FIG. 8 - Diagram of the "granulation rheology" apparatus

GRANULATION RHEOLOGY:

The role of water in the unit process of granulation is addressed in some recent work completed in our laboratories relating to the type of measurement used in granulation end-point determination. If one begins with a powder bed schematically represented in Figure 6, one can add water to this system. If one considers the cohesiveness of the powder bed, it should increase during liquid addition. This hypothetical resistance to flow (or "viscosity") increases, as shown diagrammatically in Figure 7. As one continues to add the liquid (granulating solution) the available pore spaces between particles and within individual particles, are filled and a sharp reverse in direction of the curve occurs; i.e., the apparent viscosity of the wet powder decreases as a slurry is formed. An appropriate analogy can be found with dry sand and wet sand. It is more difficult to pull a shovel through the sand as the degree of wetness increases.

An apparatus to measure these changes was devised, and a schematic representation is shown in Figure 8 and a photograph in Figure 9. This apparatus was recently described in the literature [11]. Samples of the granulation can be removed from the mixer and measured

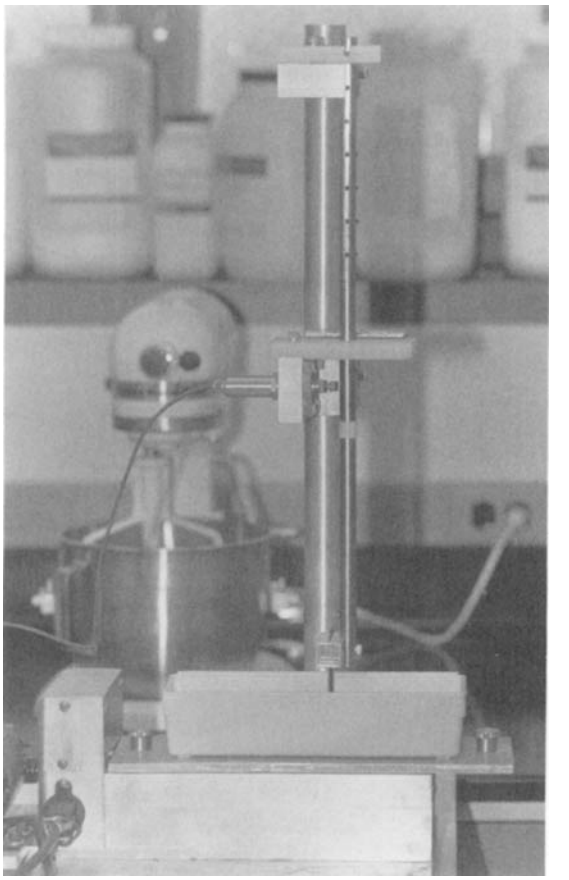

FIG. 9 - Photograph of "granulation rheology" apparatus

by this technique. The resulting characteristic curve (for microcrystalline cellulose) is shown in Figure 10; this is the experimental representation of the hypothetical curve in Figure 7, and an area which might represent a "good granulation" would occur at the lower area of the up-curve (in the region designated, A.) The profiles for three different materials are shown in Figure 11. They are microcrystalline cellulose, calcium phosphate, and lactose; and one can observe that they are quite different. A second type of plot resulting from this test apparatus is the curve shown in Figure 12, which represents the granulation viscosity (force) as a function of mixing time. In this case, a specific quantity of the granulating liquid was added initially and samples were analyzed as a function of

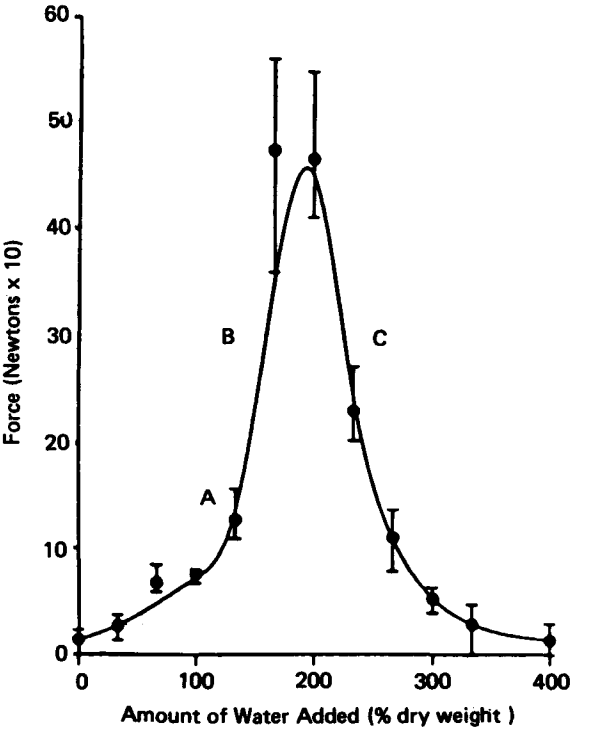

FIG. 10 - Solid/liquid profile for microcrystalline cellulose PH-101 [Key: A = 'good' granulation, B = overwet granulation, C = slurry]

mixing time rather than liquid level. In a separate experiment where the granulation was stopped and the material was dried at each of the time points, one can observe in Figure 13 that the force curve in Figure 12 appears to monitor the particle size changes; i.e., the curves are similar.

One can further analyze these results in a manner consistent with the analysis of Newitt and Conway-Jones discussed above and the stages of the process. One considers that initially particles agglomerate and are then broken down and reformed into a final capillary granule. This process is represented hypothetically in Figure 14 where curve "A" represents the disappearance of "fines", curve "C" represents the appearance of the final capillary granules, and curve "B" represents the growth and breakdown of the pendular granules during the process. It is apparent that curve "B" would be the major contributor to any particle size or force measurement [12,13].

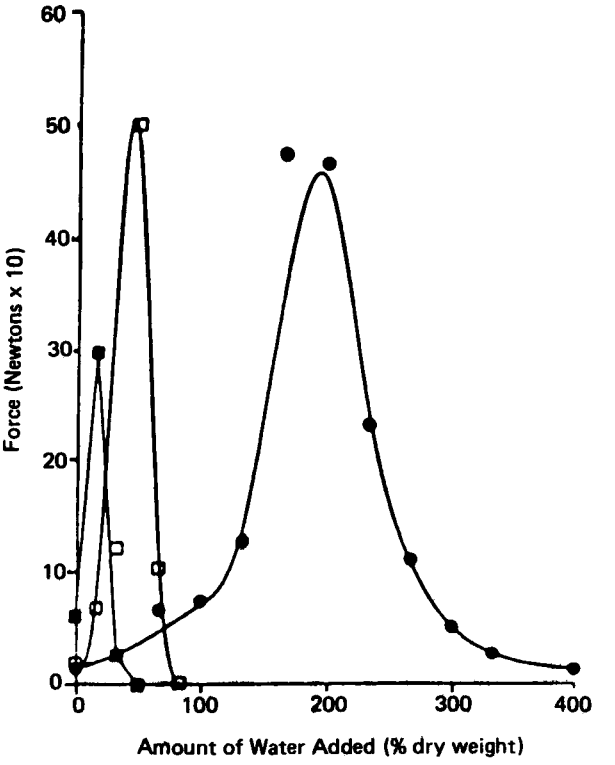

FIG. 11 - Solid/liquid profiles for three common tablet excipients [Key: micro-.crystalline cellulose PH-101, calcium phosphate, lactose USP, hydrous]

The forces related to the curves can be analyzed in the following manner. The resistance, F, contributed by the A component, the powdered material, can be described by equation 1.

$$F_A = A_o e^{-kt} \qquad \text{(Eq. 1)}$$

where:

A_o = the initial resistance offered by the dry powder
k = a constant depicting the rate at which the powdered material disappears, and
t = mixing time.

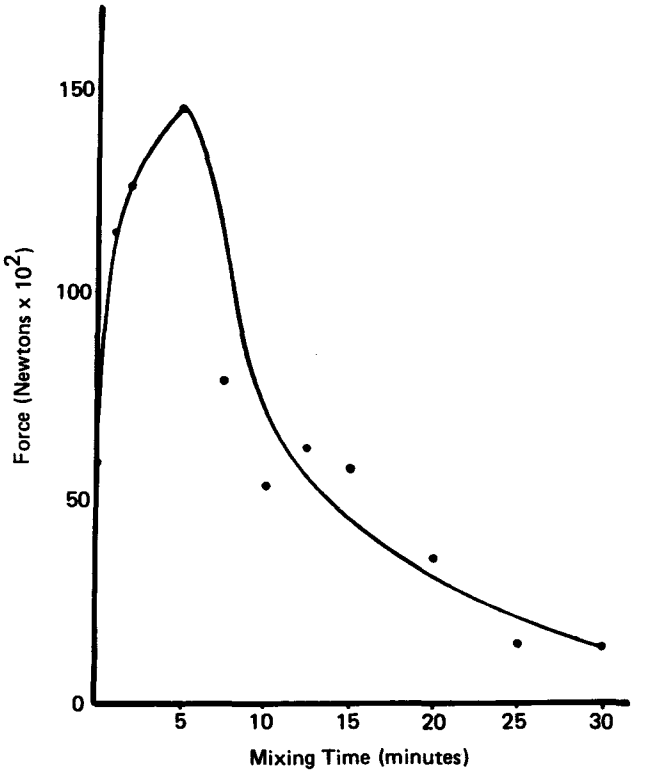

FIG. 12 - Force readings from the granulation rheology apparatus as a function of mixing time for microcrystalline cellulose PH-101

The resistance, F, contributed by the C component, the capillary granules, can be described by equation 2.

$$F_C = F_{eq} (1-e^{-k't}) \qquad \text{(Eq. 2)}$$

where:

F_{eq} = the resistance offered by the capillary granules when these granules comprise the entire system.
k' = a constant depicting the rate of capillary granule formation, and
t = mixing time

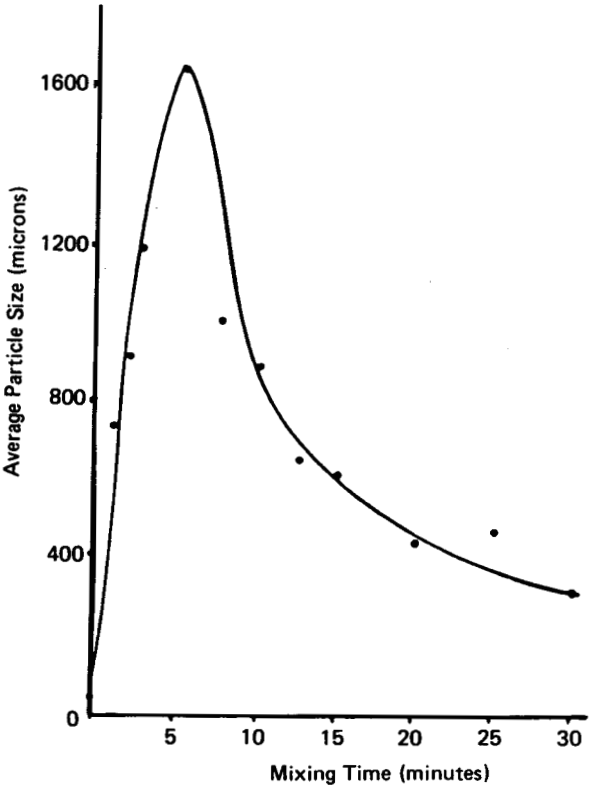

FIG. 13 - Particle size of the dried granulation as a function of increased mixing time for microcrystalline cellulose PH-101

The resistance, F, contributed by the build-up and breakdown of the large pendular aggregates as a function of mixing time can be given by the biexponential function in equation 3.

$$F_B = B(e^{-\alpha t} - e^{-\beta t}) \qquad \text{(Eq. 3)}$$

where:

F_B = the resistance contributed by the B component
α = the rate constant for pendular aggregate breakdown
β = the rate constant for pendular aggregate formation, and
B = a constant

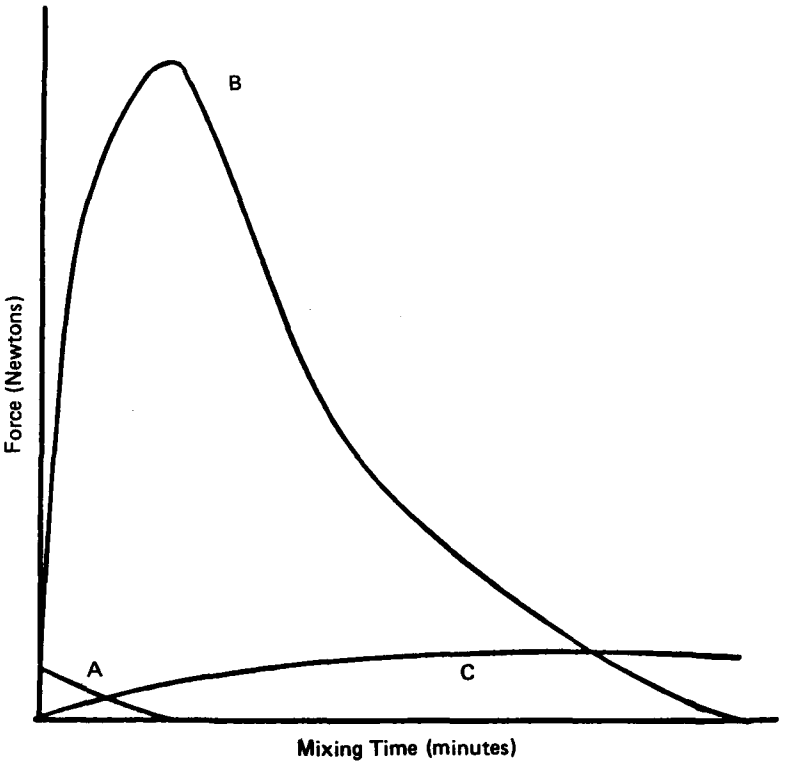

FIG. 14 - Hypothetical plot of individual forces responsible for the resistance readings obtained from the "granulation rheology" apparatus [Key: (A) powder, (B) build-up and breakdown of pendular granules, (C) build-up of capillary or equilibrium granules]

The total resistance of a granulation, F_T, can be calculated by combining the three forces as indicated in the following equation:

$$F_T = F_A + F_B + F_C \qquad \text{(Eq. 4)}$$

Appropriate data analysis results in Figure 15, which demonstrates the curve based on equation 4 (the solid line) and the experimental points.

Three different systems were tested and the rate constants for build-up and breakdown of agglomerates can be approximated to the wettability of the materials involved [13].

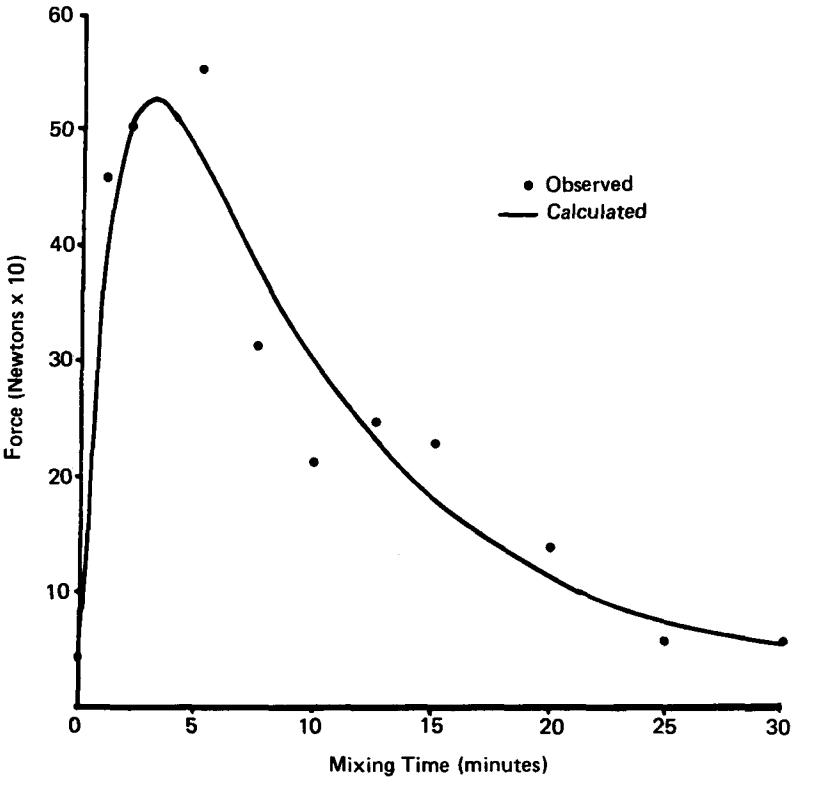

FIG. 15 - Calculated (curve) and experimental (points) values for force readings from the granulation rheology apparatus for microcrystalline cellulose PH-101

It is interesting to note that a curve with a similar shape was obtained when the same material was granulated in a high-speed, high-shear mixer (see Fig. 16.) This curve is based totally on particle size analysis, but can be analyzed in the same manner [14].

Conclusion:

It is apparent from the analysis presented above and from others available in the current pharmaceutical literature, that water plays an extremely important part in the granulation operation for pharmaceuticals and that appropriate analysis can begin to distinguish mechanisms and enable one to predict how materials will behave in this very important unit operation.

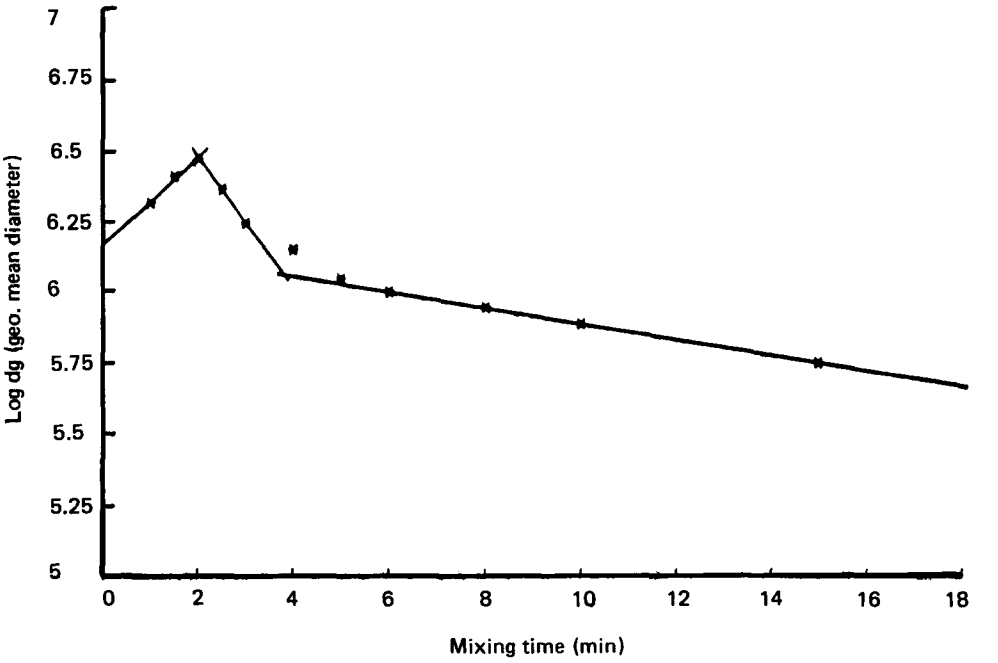

FIG. 16 - Plot of the (log) particle size as a function of granulation time for microcrystalline cellulose PH-101 in a high-shear mixer.

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