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GRANULATION RHEOLOGY I: EQUIPMENT DESIGN AND PRELIMINARY TESTING

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ABSTRACT

One of the most common pharmaceutical dosage forms is the compressed tablet, and of the several methods of preparing tablets, wet granulation remains widely used throughout the pharmaceutical industry. An apparatus was designed to follow the physical changes occurring in the granulation process. Its operation and preliminary results are presented.

As dry solid is wetted with granulating liquid, it passes through several stages, as it becomes wetter, it should exhibit a resistance to flow analagous to a viscous liquid. This resistance (force) can be measured. The test

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procedure follows the material from a dry powder through its maximum resistance and finally to a slurry. Such profiles could represent a characterization method for the solid and/or the liquid.

Materials tested included six common tablet excipients; these have been limited to single component granulations. Results indicate this apparatus is reproducible for these simple systems. Materials are shown to behave differently in the granulation process, and the apparatus appears capable of distinguishing between different materials.

INTRODUCTION

Compressed tablets remain the most widely used pharmaceutical dosage form. Of the three methods for tablet preparation, direct compression has received much attention for economic reasons, but as a process, it is not applicable to all formulations. Therefore, the wet granulation process still remains an important part of pharmaceutical technology. Many authors (1-5) have investigated wet granulations to assess the effects of changing process variables. Others (5-10) have studied the process in an attempt to determine a granulation endpoint, but these attempts are limited and represent work on a full production scale. The amount of fundamental work on the wet granulation

process is even more limited, and much of the basic work has been reported in engineering literature.

Wet granulation may be defined as a process of building up an optimum sized product which approaches a spherical shape from a starting material or starting mixture. For this work, we are most interested in the liquid-solid mixing step of the granulation process. We have defined completion of this liquid-solid mixing step to be the stage where no dry powder remains in the mixer bowl.

A mechanism by which granules are formed was proposed by Newitt and Conway-Jones (1). This method was based on the observation that in the granulation process, liquid progressively fills the void spaces in and between powder particles. It is this liquid which provides the bridges necessary for aggregation and the subsequent increase in particle size. As the granulating liquid becomes incorporated into the powder and fills the void spaces, the properties of the powder mixture change.

As a powder mixture becomes wetter, one would expect this system to exhibit increased cohesion and therefore, a resistance to flow. One would expect this resistance to

increase until all inter- and intraparticular pores are filled. Beyond this point, further addition of liquid should cause the mixture to change to a slurry and take on the characteristics of the granulating liquid.

If one considers the mixture or the slurry as different stages of a viscous liquid, then a profile such as the one shown in Figure 1 would be expected. As the granulating liquid is increased, the cohesion and resistance of the system would increase and this would be reflected as an increase in the 'apparent viscosity' of the material. The 'apparent viscosity' would increase until all the pores in the powder bed are filled. Past this point, the sharp break in the hypothetical curve would occur as the material changes to a slurry.

If this is true, as shown in Figure 1, it should be possible to obtain some measurement related to this 'apparent viscosity'. If the force a granulation exerts when it is stressed could be measured, this force might be able to be used as a means of characterizing the granulation. An apparatus has been designed to attempt to monitor this force.

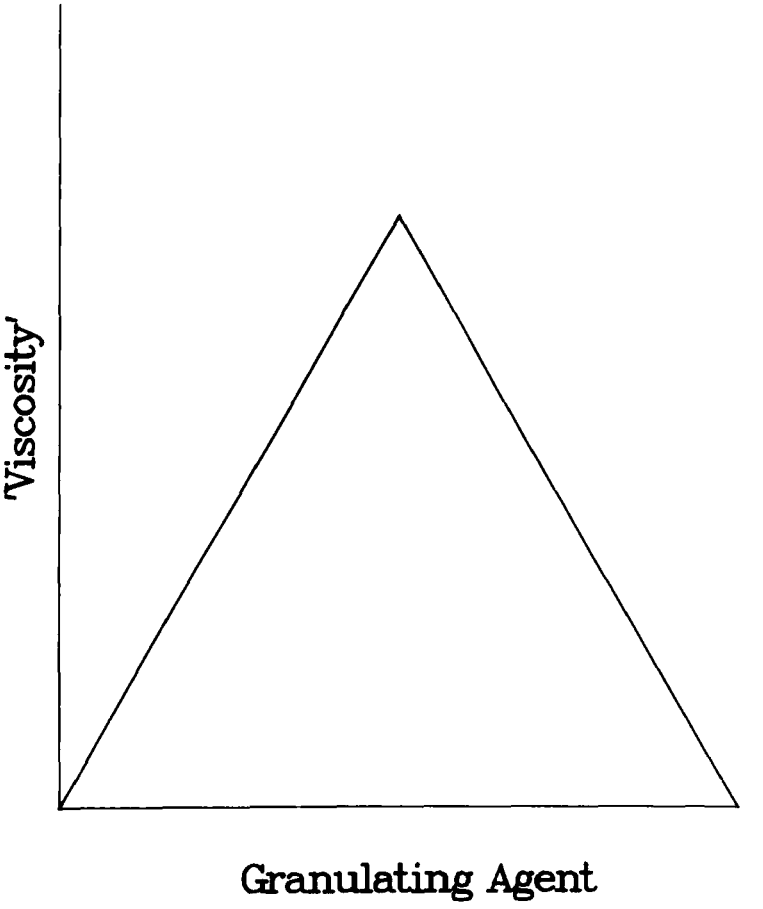

Figure 1. Hypothetical 'Viscosity' Profile of a Granulation Procedure

APPARATUS DESCRIPTION

An apparatus has been designed to follow the changes occurring in a granulation process. Its design is based on the observation that a material will exhibit an increased resistance to flow as it becomes wetter.

A schematic of the apparatus is shown in Figure 2. This apparatus consists of a motor (A) and screw-type drive shaft (B) which controls the movement of the sample tray (C) and platform. The plastic sample tray is removable, and when placed on the platform, is held in place by braces (D). To run a sample, the platform is moved to the right as far as possible. The sample tray is filled approximately 3/4 full and is attached to the platform by the braces. The measuring fork (E) which has 4 tines is suspended from the top platform (F) into the sample. When the apparatus is started, the platform and sample tray move to the left. If the sample offers resistance to the fork, the shaft will press against the load cell (G) attached to the middle platform (H), the signal amplified (I) and sent to a strip chart recorder (J). If the sample offers no resistance to the measuring form, there will be no movement of the measuring fork shaft and no displacement of the recorder.

CALIBRATION

Calibration of the appartus was achieved using a system of weights and a pulley. The weights were suspended from the middle of the measuring fork shaft just below the load cell. Calibration allowed construction of the curve shown in Figure

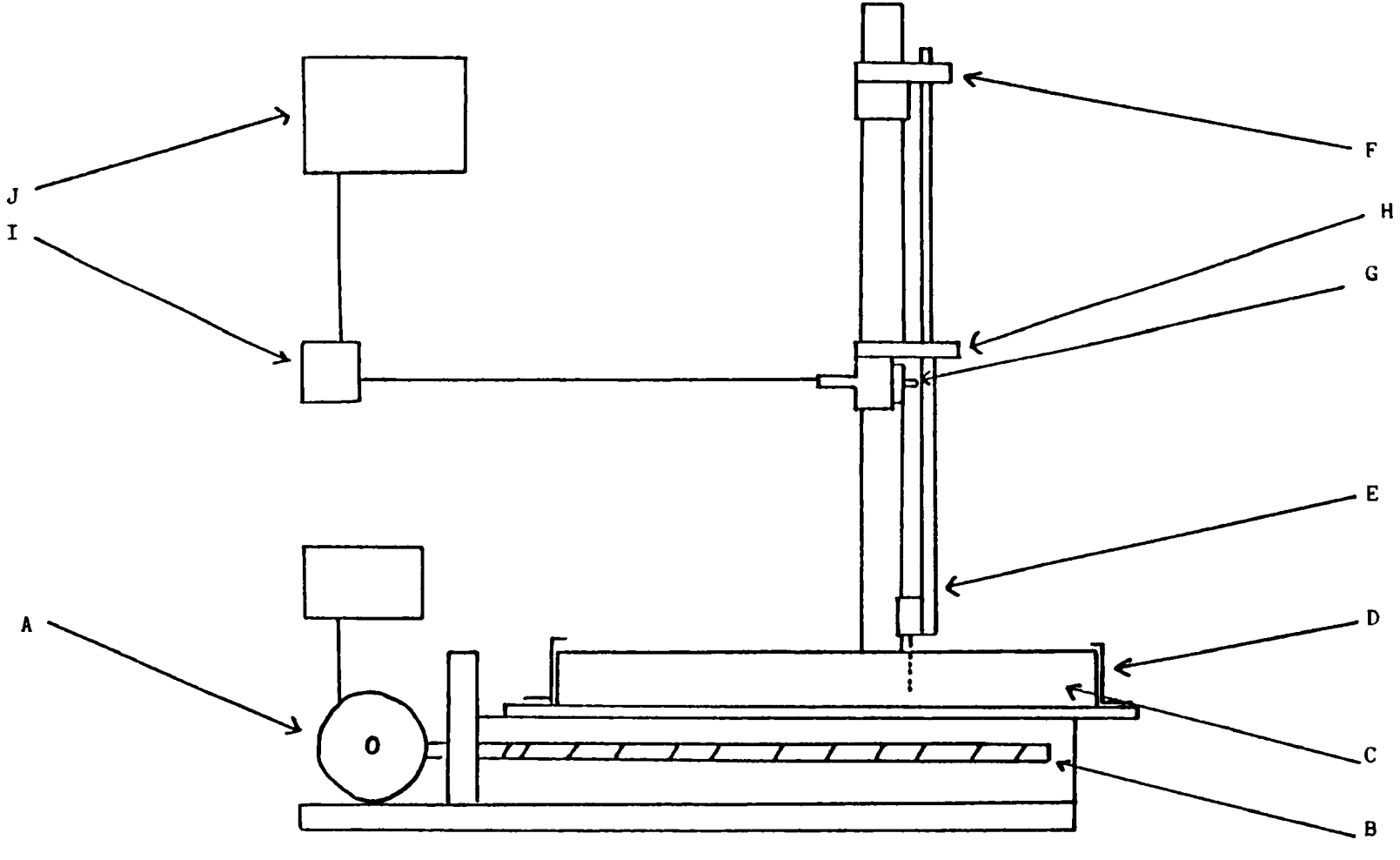

Fig. 2 Schematic Diagram of the Granulation Rheology Apparatus

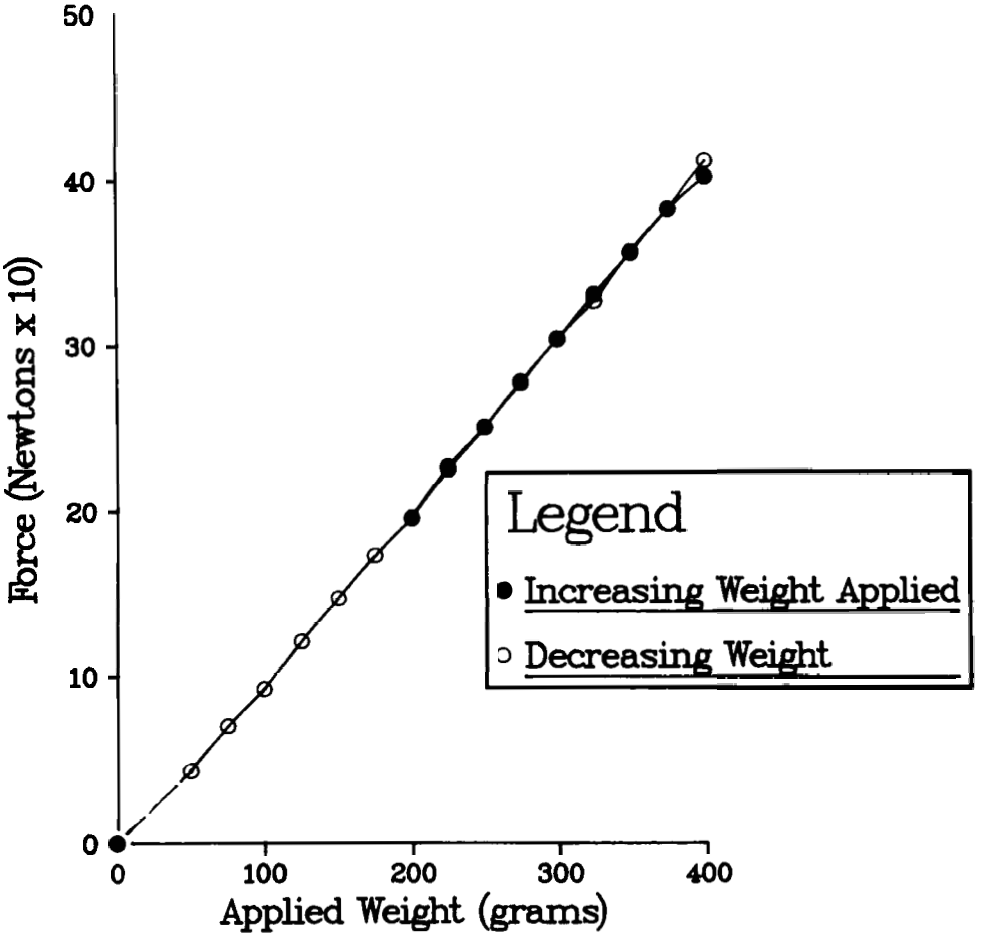

Figure 3. Calibration Curve for the Granulation Rheology Apparatus

3. From this, the weight, in grams, causing the recorder displacement can be determined, and this weight can then be converted to force readings in Newtons.

MATERIALS AND METHODS

The first test of the utility of the apparatus was to determine whether it could detect changes in a powder mixture

as liquid was added to the powder. This resulted in solid/liquid profiles of various materials.

MATERIALS

Several commonly used tablet excipients were investigated. These included microcrystalline cellulose (two grades), mannitol, calcium phosphate, and lactose.

GRANULATIONS

Granulations consisted of tablet excipients as single components with water as the granulating liquid. The granulations were prepared in a four quart capacity planetary mixer. The granulating liquid was added in one addition at the start of mixing. The mixer was set on the slowest speed which corresponded to 76 rpm.

Granulating liquid, in this case water, was added to either 50 or 100 ml increments to a known weight of dry powder. This was allowed to mix for 5 minutes. At the end of the mixing time, a sample subjectively chosen as representative of the mixture was tested using the apparatus described previously. This sample was then returned to the

mixer bowl and the process repeated until a slurry resulted. For this endpoint determination, a slurry was defined as generally a pourable mixture of powder and water which generated no resistance reading or one lower than the dry powder.

Solid/liquid profiles were also generated using ethanol as the granulating liquid for the two different batches of lactose USP.

RESULTS AND DISCUSSION

Solid/liquid profiles of the excipients chosen for study using water as the granulating liquid were examined. The solid/liquid profile for microcrystalline cellulose, Figure 4, is an example of the profiles generated by all excipients studied.

These solid/liquid profiles are the real version of the hypothetical curve shown in Figure 1 and represent the equilibrium situation illustrating resistance changes of a mixture as the amount of granulating liquid is increased. The vertical bars on this profile represent the range of 3 experiments. The up-curve illustrates the incorporation of

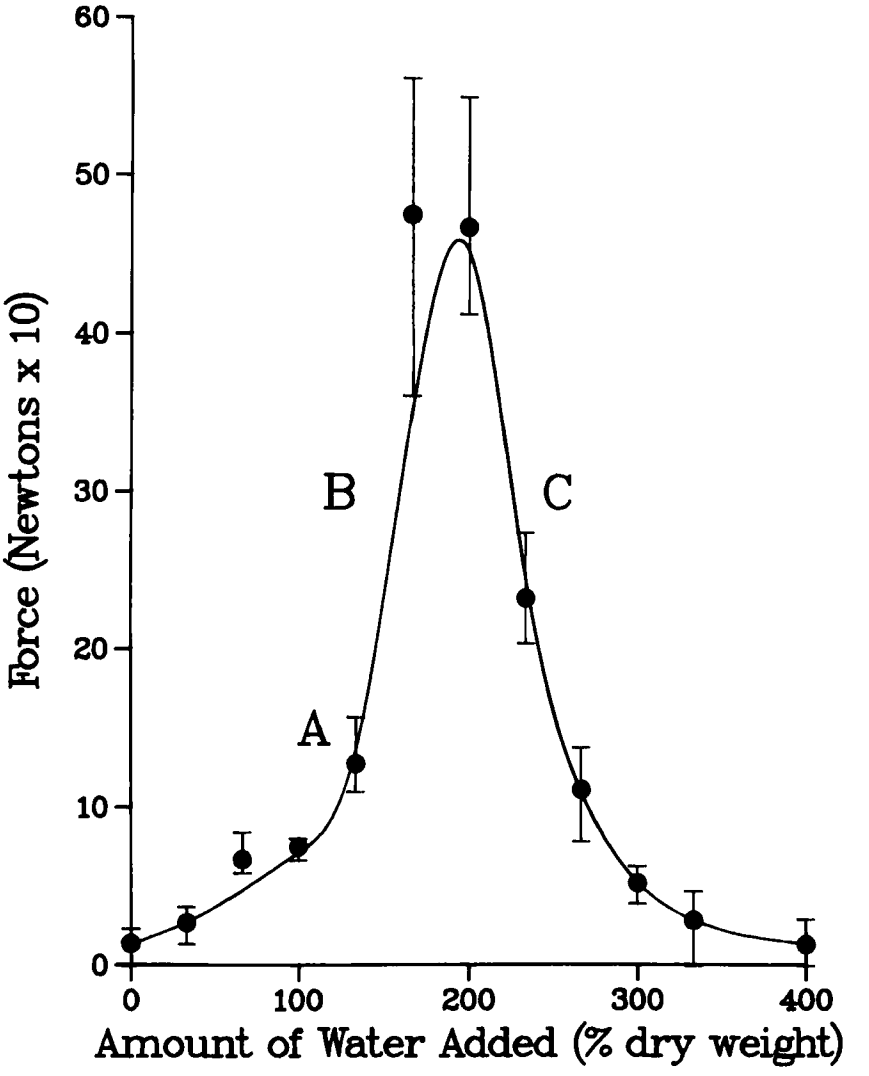

Figure 4. Solid/Liquid Profile of Microcrystalline Cellulose PH–101.

liquid into the powder bed and the down-curve represents the change from powder mixture to slurry.

A powder passes through several stages of liquid incorporation as this profile is generated. The pendular stage which occurs at low moisture levels is characterized by granulating liquid being held in the aggregate as discrete lens-shaped rings at points of contact of the powder particles. As the liquid level within the granule increases, the funicular stage is achieved where these rings coalesce and a continuous network of liquid interspersed with air is present. Further increases in liquid within the granule combined with mechanical agitation lead to the capillary stage when all the pore spaces in the aggregate are completely filled with granulating liquid. Past this capillary stage, one encounters the droplet stage where liquid is associated with the surface of the granule as well as the granule spaces being completely filled with granulating liquid. One would expect this stage to correspond to the slurry situation, and this would be represented as the down-curve of a solid/liquid profile. The other three stages would take place on the up-curve of a solid/liquid profile since these stages describe incorporation of liquid into the aggregate.

On all profiles, a conventional granulation appears only in Section A of Figure 4. The steepest section of the up-curve, Section B, is characterized by rather large aggregates. The maximum of a solid/liquid profile is generally represented by a solid mass of material. The down-curve, Section C, is a monitor of the change from powder mixture to a slurry.

The solid/liquid profiles of all the excipients chosen for study follow the general shape of the hypothetical curve. The only deviation from the theoretical shape is seen in the profile for mannitol. For mannitol, the dry powder offered more resistance than after water addition. This decrease in resistance following water addition could be explained as a lubrication effect.

This apparatus was also tested for its reproducibility on system shown to pack consistently in the sample tray. These results are given in Table I. The data indicate that this apparatus is capable of generating reproducible force readings for these samples.

Figure 5 shows the solid/liquid profiles of three of the excipients studied on the same graph. It is obvious from

TABLE I. REPRODUCIBILITY STUDY

Force Readings in Newtons for Ten Replicate Samples

SAMPLE *	MCC DRY	MCC 900ml	MCC 1000ml
1	0.638	0.809	0.196
2	0.785	0.883	0.221
3	0.834	0.834	0.196
4	0.858	0.760	0.196
5	0.834	0.834	0.172
6	0.736	0.981	0.221
7	0.711	0.932	0.196
8	0.834	0.883	0.172
9	0.785	0.858	0.221
10	0.883	0.883	0.196
MEAN	0.790	0.866	0.199
STD. DEV.	0.072	0.059	0.017

inspection of these profiles that different materials behave differently in the process of wetting and agglomeration. This may be due in part to their solubilities as well as other physico-chemical properties of the materials.

The two grades of microcrystalline cellulose generated similar solid/liquid profiles which is to be expected since

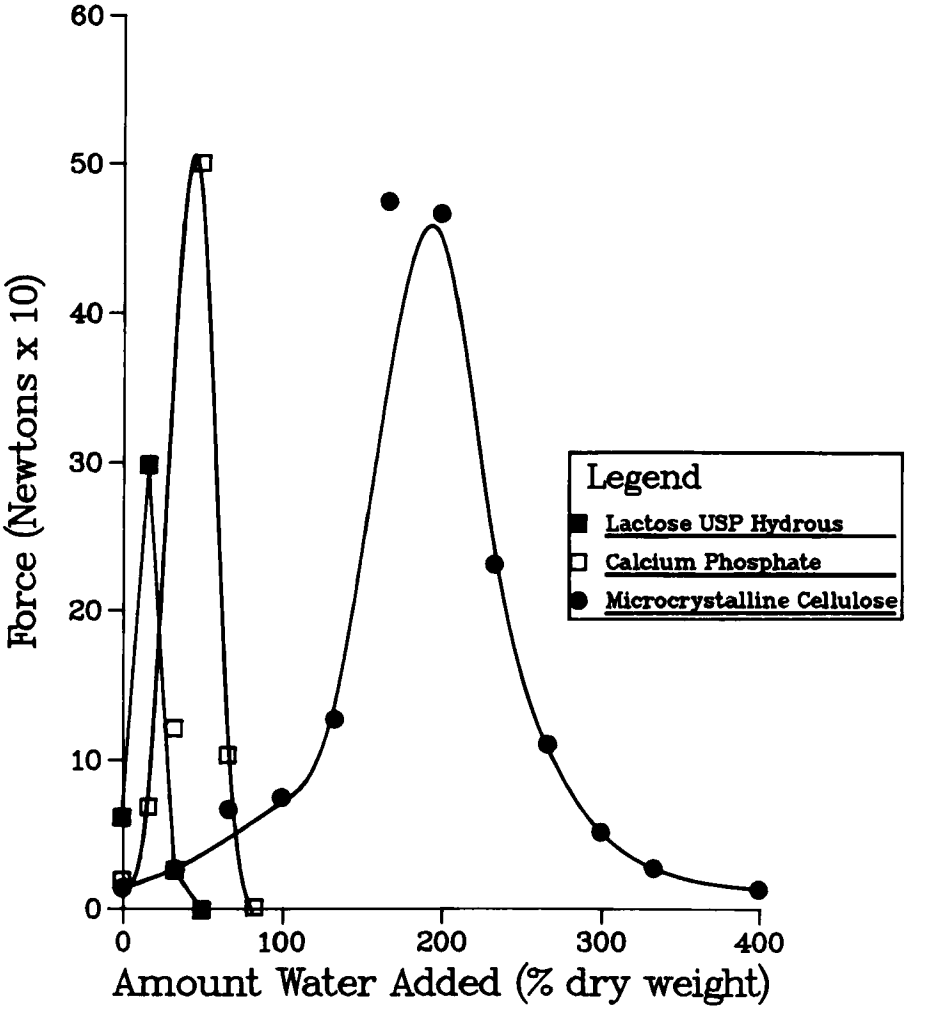

Figure 5. Solid/Liquid Profiles of Three Common Tablet Excipients

the only difference between these two materials is particle size. This is not the case for the lactose USP hydrous materials from two different suppliers. The profiles for these materials, Profile A in Figure 5 and Figure 6, are different and this supports the concern of formulators for

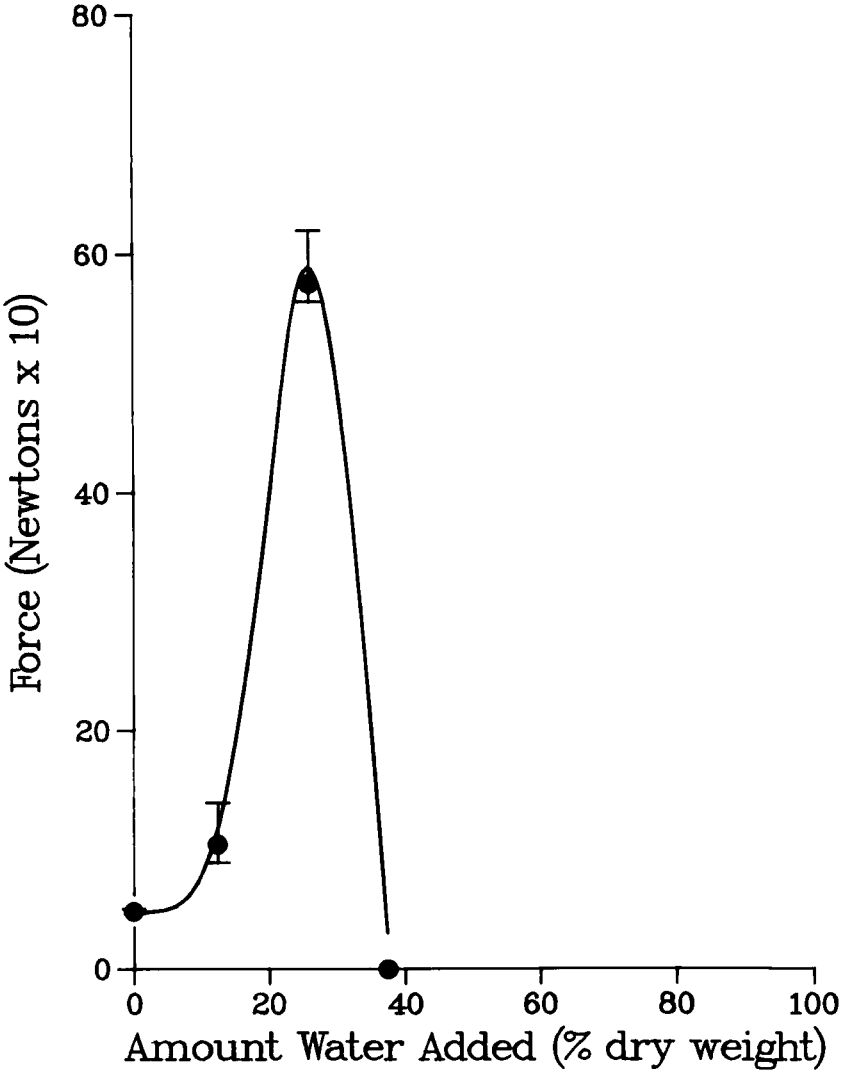

Figure 6. Solid/Liquid Profile of Lactose USP Hydrous

raw material variations. Solid/liquid profiles of both samples of lactose were also generated using ethanol as the granulating liquid. The shapes of the profiles generated using ethanol as the granulating liquid were the same as those generated using water. However, differences did exist between the lactose/water and the lactose/ethanol profiles. This is to be expected due to the difference in material solubility in the granulating liquid. Again, differences between the two lactose samples were evident.

CONCLUSIONS

These studies on commonly used tablet excipients have illustrated that this apparatus is capable of detecting differences between excipients. Also, the solid/liquid profiles have shown that all materials do not behave the same way in the processes of wetting and agglomeration. This apparatus is capable of detecting the physical changes taking place in a mixer bowl during wetting and agglomeration.

Studies are continuing to use this apparatus as a monitor of a granulation as processing variables are changed.