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RESEARCH PAPERS

Development of Agglomerated Talc. III. Comparisons of the Physical Properties of the Agglomerated Talc Prepared by Three Different Processing Methods

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ABSTRACT

Agglomerated talc was prepared by the wet granulation method using a fluidized-bed granulator, a planetary mixer, and a high-speed, high-shear mixer. It was found that agglomerated talc produced by a fluidized-bed granulator is more porous, has a more irregular shape, has a lower bulk density, and has more binder–talc contacts. This higher surface area of binder–talc interface and the highly porous and irregular shape of the agglomerated talc produced by the fluidized-bed granulator result in stronger intergranular bonding. The resultant compact was harder. The compression force–time curve also showed that the time required to increase the upper punch force from 10% to 90% was greater for the compaction of the fluidized-bed granulated talc. The longer exposure to shear forces would enhance plastic flow and facilitate the formation of stronger bonds. Phenylpropanolamine HCl tablets containing 77.5% agglomerated talc as the diluent were prepared. The properties of the tablet were found to be satisfactory. The agglomerated talc developed may be a promising direct compression diluent.

INTRODUCTION

Talc is an inexpensive, physiologically inert, and physicochemically inactive (1) substance. It fulfills all of the criteria of being a diluent. However, pharmaceutical talc is very fine and soft. Adding a large quantity of talc in a tablet dosage form will make the resultant tablet friable and unacceptable. To overcome the direct tableting capability of talc, the wet granulation approach can be applied to talc using the fluidized-bed granulation and mixing granulation method to modify the properties of talc. The resultant talc is called "agglomerated talc."

The development of agglomerated talc as a tableting diluent was conducted in three stages. The first stage of development focused on the production of agglomerated talc using a fluidized-bed granulator (2). The second phase of development was to optimize the planetary-mixing granulation and high-speed-mixing granulation process (3). In the last phase of development, the mechanism of the granulation processes for the fluidized-bed granulation, the planetary-mixing granulation, and the high-speed, high-shear-mixing granulation was identified by comparing the properties of the agglomerated talc produced. The diluent characteristic of the agglomerated talc was evaluated by formulating the agglomerated talc with an active ingredient (phenylpropanolamine HCl) and compared to a tablet prepared using the direct compression diluent—Ditab (unmilled dicalcium phosphate dihydrate).

EXPERIMENT

Physical Properties of Agglomerated Talc

Seven percent, 9%, and 11% PVP containing agglomerated talcs were prepared using the optimal granulation conditions of each granulation process determined through the previous experiments (2,3). In the fluidized-bed granulation, the atomizing air pressure was 0.8 bar, the amount of solvent was 150 ml, and the inlet air temperature was 80°C. In the planetary-mixing granulation, the amount of solvent was 144 ml and the granulation time was 5 min. In the high-speed-mixing granulation study, the speed of the agitator was kept at 600 rpm and the granulation time was 5 min, 29 sec. The agglomerated talc produced by the planetary mixer or high-speed mixer was wet screened through a number 12 sieve (1680 μ) and then dry screened through a number 40 sieve (420 μ) using an oscillating granulator (Erweka—GmbH, Germany). The bulk density, geometrical mean particle size, hopper flow rate, Brunauer, Emmett, and Teller (BET) surface area, and scanning electron photomicrography (SEM) of the agglomerated talc were obtained using the methods described previously (2,3). The hardness of the 800 mg agglomerated talc compact compressed by a Carver press and a 1/2 in., flat-faced punch and die set was determined by a Schleuniger hardness tester.

The compression force–time profile of the agglomerated talc compact was obtained using an instrumented Beta Press (Thomas Engineering Co., Inc.). The Beta Press was equipped with strain gauge based transducers to allow the measurement of the upper punch compression force, the lower punch compression force, and the ejection force for the compression cycle. A computer program (PC30, SMI Incorporated) was installed in the computer to analyze the data. Only 1 out of 16 stations of the Beta Press was installed with a 7/16-in. flat-faced punch and die set. Only one tablet was made for each revolution of the die table.

Agglomerated talc compacts, 600 ± 10 mg, were made using the instrumented Beta Press. The upper punch compression force was kept at 2000 lb and the compression speed was 51 rpm. The thickness and hardness of the resultant compact were examined.

Formulation and Properties of the Phenylpropanolamine HCl Tablet

In order to compare the diluent properties between the agglomerated talc and Ditab (unmilled dicalcium phosphate dihydrate, NF grade, Stauffer Chemical), a phenylpropanolamine HCl (Ruger Chemical Co., Inc.) tablet was made. The formulation for the phenylpropanolamine HCl tablets was as follows:

Phenylpropanolamine HCl	12.5%
Potato starch	10%
Diluent (agglomerated talc or Ditab)	77.5%

The powder mixture was mixed for 8 min. Tablets made from the powder mixture were compressed on a Carver press at a 2000-lb force, using a 7/16-in. cupped punch set. The tablet weight was maintained at 400 ± 10 mg. The hardness (Schleuniger hardness tester), friability (Erweka friabilator), and disintegration time (USP XX) of the formulated tablet were determined.

RESULTS AND DISCUSSION

Comparisons of the Properties of the Agglomerated Talcs Prepared by Different Granulation Methods

The bulk density and tap density of the agglomerated talcs prepared using different concentrations of PVP and different equipment are shown in Fig. 1 and Fig. 2. It is clearly shown that regardless of the amount of binder held in the agglomerated talc, the agglomerated talc prepared by the fluidized-bed granulator had the lowest bulk density and tap density; the one prepared by the planetary mixer had the median density, and the one prepared by the high-speed mixer had the highest bulk and tap density. The bulk density does not change sig-

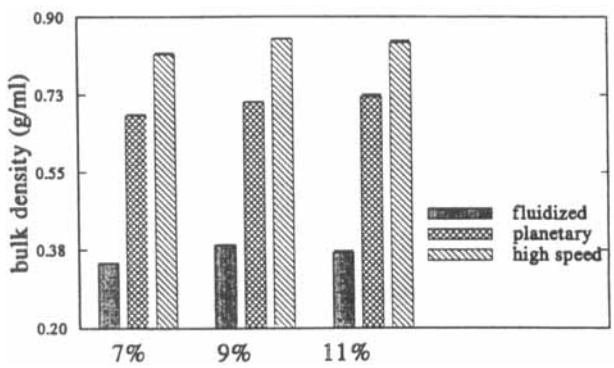

Figure 1. The bulk density of agglomerated talc prepared using different concentrations of PVP and different equipment.

nificantly with the changes in the concentration of binder. However, the tap density decreases slightly with the increase of binder concentration in all three different kinds of agglomerated talc.

The mean particle size of the agglomerated talcs prepared using different concentrations of PVP and different equipment is given in Fig. 3. It was found that the order of the mean particle size of the agglomerated talc is the same as that of the density; e.g., fluidized-bed granulated agglomerated talc << planetary mixer prepared agglomerated talc < high-speed mixer prepared agglomerated talc. Regardless of the method of preparation, the mean size of the agglomerated talc increases slightly with the increase in binder concentration. El-Gindy et al. (4) also reported the same observation. The greater binder effectiveness with higher concentrations may be attributed to the corresponding increase in the binder's adhesiveness.

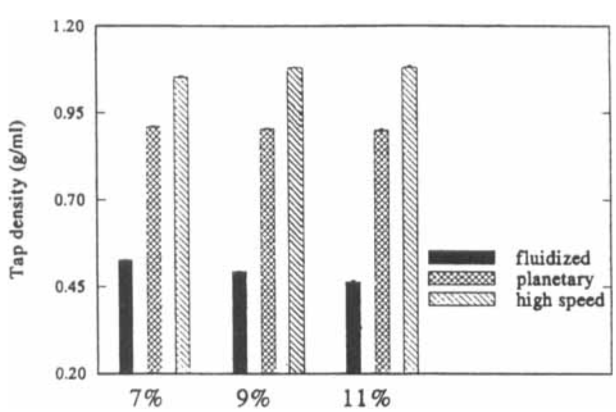

Figure 2. The tap density of agglomerated talc prepared using different concentrations of PVP and different equipment.

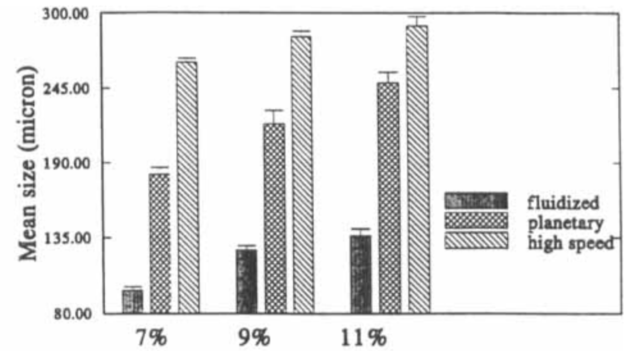

Figure 3. The geometrical mean particle size of agglomerated talc prepared using different concentrations of PVP and different equipment.

Flowability of the granules can be affected by the granule's surface properties, density, particle size distribution, and particle shape. As shown in Fig. 4, the flow rate of the agglomerated talcs prepared by different processing methods again follows the same order: fluidized-bed granulated << planetary mixer produced < high-speed mixer granulated. The highest value of density and the lowest value of fines of the agglomerated talc produced by high-speed mixer may be the reasons for its superior flowability.

The BET surface area (Fig. 5) of the 9% PVP containing agglomerated talcs prepared by three different methods shows that the fluidized-bed produced agglomerated talc has the highest surface area, and that the high-speed mixer produced agglomerated talc has the lowest surface area. In order to investigate the surface morphology of the agglomerated talc, SEM photomicrographs of the 9% PVP containing agglomerated talc pre-

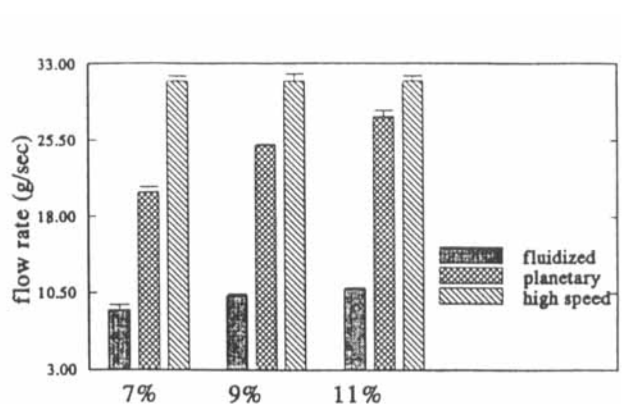

Figure 4. The flow rate of agglomerated talc prepared using different concentrations of PVP and different equipment.

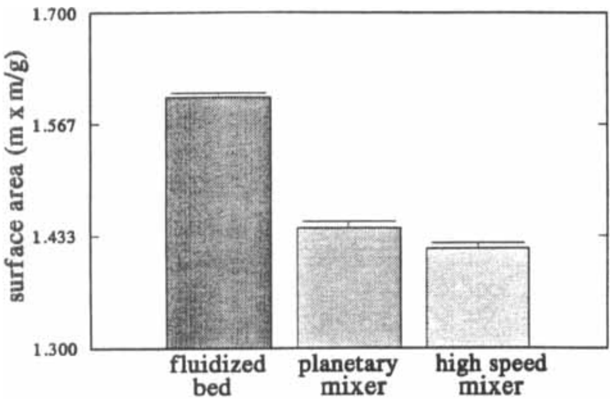

Figure 5. The BET surface area of agglomerated talc prepared using 9% PVP and different equipment.

pared by fluidized-bed granulator, planetary mixer, and high-speed mixer are presented in Figs. 6, 7, 8, respectively. It can be clearly seen that the fluidized-bed granulated agglomerated talc has a very irregular shape and a more porous structure than the other two kinds of agglomerated talc. The high-speed mixer produced agglomerated talc has a very dense and very spherical structure.

The bonding characteristic of the different kinds of agglomerated talc is elucidated by the hardness versus compact porosity plot as shown in Fig. 9. At the same compact porosity, the hardness of the fluidized-bed produced agglomerated talc compact is the highest, and the hardness of the high-speed mixer produced agglomerated talc compact is the lowest.

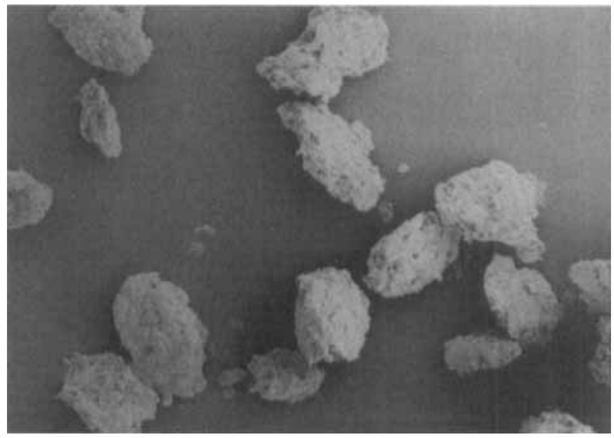

Figure 7. SEM photomicrograph of 9% PVP containing agglomerated talc prepared by planetary mixer.

The agglomeration mechanism and percentage of water applied during the process for the three granulation methods are summarized in Table 1. As shown in Table 1, since the drying process occurs at the same time as the granulation process, weight percentage of the water applied during the whole granulation process for fluidized-bed granulation is much higher than that for planetary mixer and high-speed mixer. Consequently, much higher binder and talc contacts occur in the fluidized-bed granulation process. Therefore, the product produced by fluidized-bed granulator is more porous; and has a more irregular shape, a lower bulk density, and more binder–talc contacts. Since the bonding

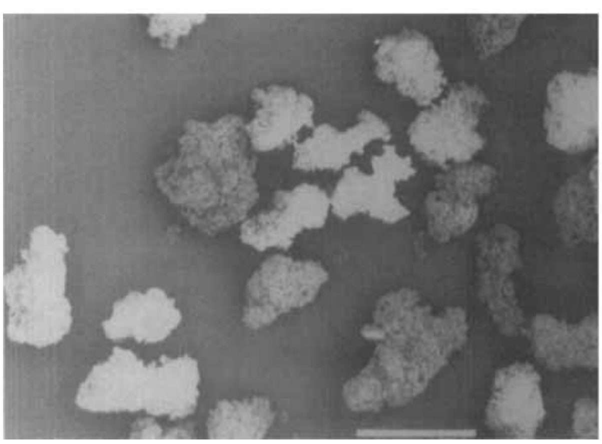

Figure 6. SEM photomicrograph of 9% PVP containing agglomerated talc prepared by fluidized-bed granulator.

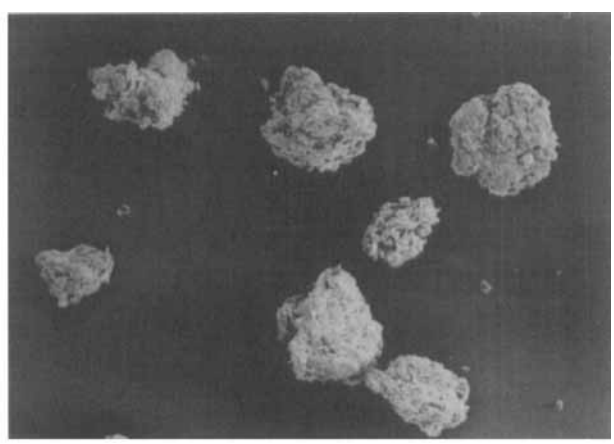

Figure 8. SEM photomicrograph of the 9% PVP containing agglomerated talc prepared by high-speed mixer.

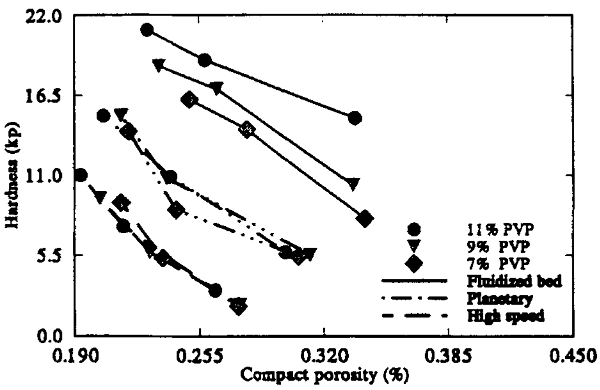

Figure 9. Hardness of the compacts of agglomerated talc prepared by three different wet granulation procedures.

strength between talc molecules is very weak, the strength of the agglomerated talc compact depends only on the binder–binder intermolecular force and the binder–talc intermolecular force. This higher surface area of binder–talc interface and the highly porous and irregular shape of the agglomerated talc produced by fluidized-bed granulator results in stronger intergranular bonding. The resultant compact is more porous and harder. Seager et al. (5) have also shown that the distribution of binder in granules is controlled by the process of manufacture.

The agglomerated talc produced by the high-speed mixer has a very dense structure and regular shape, as shown in Fig. 7. This is attributed to the fact that the agglomerates are extensively thrown against the wall by the centrifugal force of the agitator impeller during the granulation process. It has the best flowability among the three different kind of granules. Also, due to the highly efficient mixing of the apparatus, the amount of binder solvent (water) applied in the high-speed mixing is the lowest. This indicates that a lower binder–talc contact area has been created during the high-speed mixing process. When the granules are compressed, less binder–binder and less binder–talc contacts occur, and the subsequent compact is weaker (Fig. 9). The structure of the agglomerated talc prepared by planetary mixer is similar to that of the agglomerated talc prepared by high-speed mixer. However, due its lower shearing force of mixing, the subsequent granule is less dense, more porous, and has a lower packing density than the granule prepared by high-speed mixer.

Compaction of the agglomerated talc was performed using an instrumented Beta Press equipped with strain gauge based transducers to obtain the force–time curve of upper punch compression, lower punch compression, and ejection process for the compression cycle (PC30 system). Individual pulses which are generated by each transducer when a tablet is compacted can be analyzed and the parameters can be determined. As illustrated in Fig. 10, rise time is the time from 10% to 90% on the rise of the pulse; fall time is the time from 90% to 10% on the fall of the pulse; dwell time is the time from 90% point on the rise to the 90% point on the fall; pulse width is the time from the 50% point on the rise to the 50% point on the fall; and contact time is the time from the 10% point on the rise to the 10% time on the fall.

The upper punch compression data obtained from the force–time curve for the three different agglomerated talc compacts are summarized in Table 2. The rise time and contact time of the upper main compression of the fluidized-bed granulated agglomerated talc are greater than that of the planetary mixer prepared agglomerated talc and greater than that of the high-speed, high-shear mixer prepared agglomerated talc. The ranking of the total area under the curve also follows the same order.

Table 1

Major Agglomeration Mechanisms and Percentage of Water Applied During the Granulation Process for the Three Different Granulating Systems

Granulation Apparatus	Major Agglomeration Mechanism	Wt. of Water Applied / Wt. of Total Solid
Fluidized bed granulator	Nucleation, layering, consolidation, coalescence	55.7%
Planetary mixer	Nucleation, densification, consolidation, coalescence	22.3%
High-speed mixer	Nucleation, densification, consolidation, coalescence	20.5%

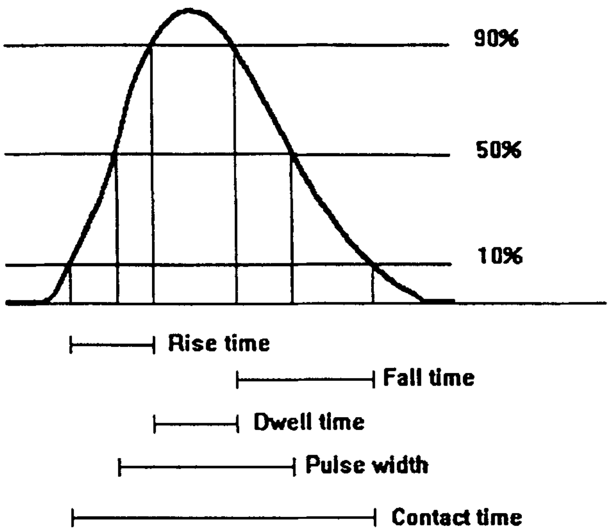

Figure 10. Pulse analysis of the force–time curve.

There is not a pronounced difference in the fall time and area from peak among the three different agglomerated talcs. The summary of the lower punch compression data obtained from the force–time curve is shown in Table 3. It can be seen that the value and tendency of the lower punch compression data are very similar to those of the upper punch compression data. From the results shown in Tables 2 and 3, the granulation method appears to influence the deformation resistance of the granules during compression. The lower bulk density (0.368 g/ml), higher tapped porosity (80.7%), and better binder distribution of the fluidized-bed granulated agglomerated talc give more resistance during the compression cycle. The bulk density and tapped porosity of the planetary mixer prepared agglomerated talc are 0.720 g/ml and 63.3%, and those of the high-speed, high-shear mixer prepared agglomerated talc are 0.842 g/ml and 56.0%, respectively (Fig. 1). The time required to increase the upper punch force from 10% to 90% was 23.5 msec for the fluidized-bed granulation, 20.1 msec for the planetary mixed granulation, and 15.3 msec for the high-speed-mixed granulation. The longer exposure to shear forces will probably enhance the plastic flow of the material and thus facilitate the formation of strong bonds.

The summary of the ejection data obtained from the force–time curve is shown in Table 4. The maximum ejection of the fluidized-bed granule is the highest, and that for the high-speed-mixed granule is the lowest. There are two possible reasons for the highest ejection force of the fluidized-bed granule. One may be the higher binder surface coverage of the fluidized-bed granule. Thus, the binder–die wall adhesion is greater. The other reason is that the fluidized-bed granulated agglomerated talc compact has the largest thickness. Since it has the largest contact area with the die wall, it needs more force to break the tablet–die wall adhesion.

Table 5 shows the density and hardness for different amounts of PVP containing agglomerated talc compacts compressed on the Beta Press. At the same binder concentration level, compacts of high-speed, high-shear mixer prepared agglomerated talc have the highest density and lowest hardness. However, compacts of the fluidized-bed granulated agglomerated talc have the lowest density and greatest hardness. As explained in the

Table 2

Summary of the Upper Punch Compression Data Obtained from the Force-Time Curve (11% PVP containing agglomerated talc)

	High-Speed Mixer	Planetary Mixer	Fluidized-Bed Granulator
Rise time (msec)	15.3 (4.6)	20.1 (0.1)	23.5 (0.2)
Fall time (msec)	12.8 (0.2)	12.9 (0.1)	12.9 (0.1)
Pulse width (msec)	32.2 (0.1)	33.1 (0.3)	34.1 (0.4)
Dwell time (msec)	15.7 (0.3)	16.0 (0.3)	16.6 (0.2)
Contact time (msec)	43.8 (4.7)	49.0 (0.4)	53.0 (0.1)
Max. force (lb)	1969.5 (67.2)	2033.0 (108.9)	1986.5 (40.3)
Area to peak (lb msec)	27.2 (4.2)	31.7 (0.5)	34.8 (1.8)
Area from peak (lb msec)	31.4 (0.2)	32.4 (3.6)	32.4 (3.6)
Total area (lb msec)	59.0 (4.2)	64.0 (4.2)	67.5 (2.1)

Table 3

Summary of the Lower Punch Compression Data Obtained from the Force–Time Curve (11% PVP containing agglomerated talc)

	High-Speed Mixer	Planetary Mixer	Fluidized-Bed Granulator
Rise time (msec)	15.3 (4.7)	20.4 (0.2)	23.9 (0.2)
Fall time (msec)	13.6 (0.1)	13.8 (0.1)	13.8 (0.1)
Pulse width (msec)	31.5 (0.2)	32.3 (0.2)	33.7 (0.1)
Dwell time (msec)	14.8 (0.1)	15.1 (0.4)	15.6 (0.3)
Contact time (msec)	43.7 (5.0)	49.1 (0.2)	53.5 (0.5)
Max. force (lb)	2001.0 (67.6)	2084.0 (108.9)	2071.0 (38.2)
Area to peak (lb msec)	27.5 (3.4)	31.1 (1.5)	37.6 (2.7)
Area from peak (lb msec)	31.8 (1.2)	34.3 (2.7)	31.9 (1.0)
Total area (lb msec)	59.5 (4.9)	65.5 (3.5)	69.5 (2.1)

Table 4

Summary of the Ejection Data Obtained from the Force–Time Curve (11% PVP containing agglomerated talc)

	High-Speed Mixer	Planetary Mixer	Fluidized-Bed Granulator
Rise time (msec)	9.8 (1.0)	10.1 (1.0)	7.5 (4.0)
Fall time (msec)	47.2 (0.2)	46.3 (0.1)	50.3 (22.1)
Pulse width (msec)	101.0 (0.1)	102.0 (0.1)	102.5 (4.9)
Dwell time (msec)	58.5 (2.1)	59.9 (1.1)	59.5 (27.6)
Contact time (msec)	115.5 (0.5)	116.0 (0.1)	117.0 (0.1)
Max. force (lb)	52.5 (1.0)	63.0 (1.0)	77.5 (0.7)
Area to peak (lb msec)	1.9 (0.1)	2.4 (0.1)	3.1 (0.1)
Area from peak (lb msec)	2.5 (0.1)	3.0 (0.1)	3.5 (0.1)
Total area (lb msec)	4.4 (0.1)	5.3 (0.1)	6.6 (0.1)

Table 5

Density and Hardness for Different Amount of PVP Containing Agglomerated Talc Compacts Compressed on a Beta Press

	Binder Concentration	Compact Density (g/ml)	Hardness (kp)
Fluidized-bed granulated agglomerated talc	11% PVP	1.86 (0.001)	11.1 (1.2)
	9% PVP	1.95 (0.001)	12.4 (1.4)
	7% PVP	1.99 (0.002)	11.1 (0.5)
Planetary mixer prepared agglomerated talc	11% PVP	1.93 (0.002)	9.8 (0.5)
	9% PVP	1.97 (0.003)	10.2 (0.3)
	7% PVP	1.99 (0.001)	6.9 (0.3)
High-speed mixer prepared agglomerated talc	11% PVP	1.97 (0.001)	7.3 (0.2)
	9% PVP	1.99 (0.001)	6.5 (0.6)
	7% PVP	2.02 (0.001)	5.6 (0.6)

Note. Compact weight: 600 mg, compression time: 0.04 to 0.06 sec per tablet, compression force: 2000 lb, tablet diameter: 7/16 in.

previous section, the greatest hardness of the fluidized-bed compact is due to its better binder distribution, which results in stronger intergranular bonding. Ragnarsson and Sjogren (6) reported that the tablet strength correlated well with the work required for compression. In this part of our study, it was found that the total area of the compression curve for the fluidized-bed granule is the highest. That indicates more work has been performed by the upper punch and the material has longer exposure to shear forces. All these factors contribute to the stronger bonding of the fluidized-bed agglomerated talc compact.

The compression processes of a semiautomatic hydraulic press and a automatic rotary press are very different. The compression speed was much slower and the dwell time of the tablet in the die was much longer in the hydraulic press than in the automatic rotary tableting machine. The die-filling method was also very different for these two presses. Table 6 shows the density and hardness for different amounts of PVP containing agglomerated talc compacts compressed on a semiautomatic hydraulic press. By comparing the data in Table 5 to the data in Table 6, it is noted that the difference in compact hardness among the three granulation methods is much more pronounced in the slow compression process (hydraulic press) than that in the fast compression process (Beta Press). The difference in the compression time between fluidized-bed granule and high-speed granule can be in about 1 or 2 sec using a hydraulic press. However, the difference in the compression time between these two granules is only 0.01 to 0.015 sec using a Beta Press. Since PVP is a plastic deformation material, plastic deformation is a time-dependent process. When the compression speed increases, the extend of the plastic deformation decreases (7). Substances which consolidated principally by fragmentation showed relatively little velocity dependence. The bonding strength of the agglomerated talc compact depends on the PVP–PVP and PVP-talc inermolecular bonding. The fluidized-bed agglomerated talc has much more surface area for PVP–PVP and PVP–talc contacts. Thus, its consolidation behavior is more speed dependent than the other two agglomerated talcs.

Properties of the Phenylpropanolamine HCl Tablets

The objective of this part of the study was to develop the agglomerated talc as a direct compression diluent. Therefore the nine different kinds of agglomerated talcs prepared with different concentrations of PVP and different apparatus were formulated with the active drug—phenylpropanolamine HCl. Starch was also incorporated in the tablet formulation to act as a disintegrant. The characteristics of the formulated tablet were investigated and compared to those of the tablet prepared with the same level of Ditab as the diluent.

Figure 11 shows the hardness of the 400 mg formulated tablets compressed under three different compression forces. The hardness of the tablet increases with the decrease of the tablet porosity or the increase of compression forces. The hardness of the formulated tablet using different substances as the diluent follows this order: fluidized-bed granulated agglomerated talc >

Table 6

Density and Hardness for Different Amount of PVP Containing Agglomerated Talc Compacts Compressed on a Semiautomatic Hydraulic Press

	Binder Concentration	Compact Density (g/ml)	Hardness (kp)
Fluidized-bed granulated agglomerated talc	11% PVP	1.81 (0.002)	18.9 (1.5)
	9% PVP	1.83 (0.001)	16.5 (1.4)
	7% PVP	1.84 (0.002)	14.1 (1.2)
Planetary mixer prepared agglomerated talc	11% PVP	1.85 (0.002)	10.9 (0.5)
	9% PVP	1.90 (0.003)	10.8 (0.4)
	7% PVP	1.93 (0.003)	8.6 (0.3)
High-speed mixer prepared agglomerated talc	11% PVP	1.91 (0.002)	7.5 (0.5)
	9% PVP	1.92 (0.003)	5.7 (0.3)
	7% PVP	1.95 (0.001)	5.3 (0.6)

Note. Compact weight: 800 mg, compression time: 3 to 5 sec per tablet, compression force: 2000 lb, tablet diameter: 1/2 in.

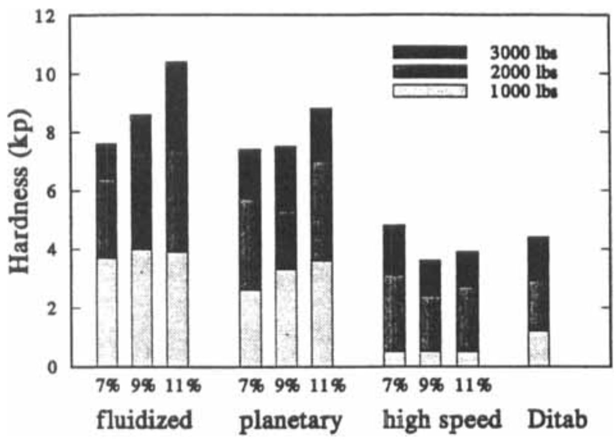

Figure 11. Hardness of phenylpropanolamine HCl tablets using different diluents.

planetary mixer prepared agglomerated talc > high-speed mixer prepared agglomerated talc ≅ Ditab. This order applied to all binder concentration levels. The fluidized-bed granulated agglomerated talc has more locations for surface binding, which results in more intergranular bonding and stronger tablets. The dense structure of the granule prepared by the high-speed mixer creates less intergranular bonding under compression.

The friability profile of the formulated tablet compressed at 2000-lb force is shown in Fig. 12. The tablets which used the high-speed mixer prepared agglomerated talc or Ditab as the diluent are not strong enough to withstand the mechanical force of the friabilator, and they break apart. The tablets which used fluidized-bed granulated agglomerated talc or planetary mixer granulated agglomerated talc as the diluent have acceptable friability value. However, the binder concentration in the agglomerated talc does not significantly affect the friability of the tablets.

The results of the disintegration test of the formulated tablets compressed at 2000 lb are shown in Fig. 13. Tablets using Ditab as the diluent disintegrate faster than the tablets made from the agglomerated talcs as the diluent. However, the disintegration time of the agglomerated talc containing tablets is still within acceptable range. In all agglomerated talc containing tablets, the disintegration time increases with the increase of the binder concentration.

CONCLUSION

Agglomerated talc produced by the fluidized-bed granulator was more porous, and had a more irregular shape, a lower bulk density, and more binder talc contacts. This higher surface area of binder–talc interface and the highly porous and irregular shape of the agglomerated talc produced by the fluidized-bed granulator resulted in stronger intergranular bonding. The resultant compact was more porous and harder. The lower bulk density, higher tapped porosity, and better binder distribution of the fluidized-bed granulated agglomerated talc provided more resistance in the compression cycle. The longer exposure to shear forces also enhanced the plastic flow of the material and thus facilitated the formation of strong bonds.

The phenylpropanolamine HCl tablets which used the fluidized-bed granulated agglomerated talc or planetary mixer prepared agglomerated talc as the diluent have acceptable hardness, friability, and disintegration profile. Also, the tablets which used agglomerated talc as the diluent have better mechanical properties than the tablets which used Ditab as the diluent. Therefore, through

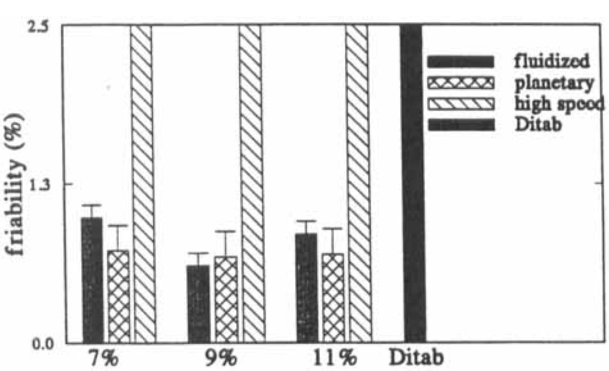

Figure 12. Friability of phenylpropanolamine HCl tablets using different diluents.

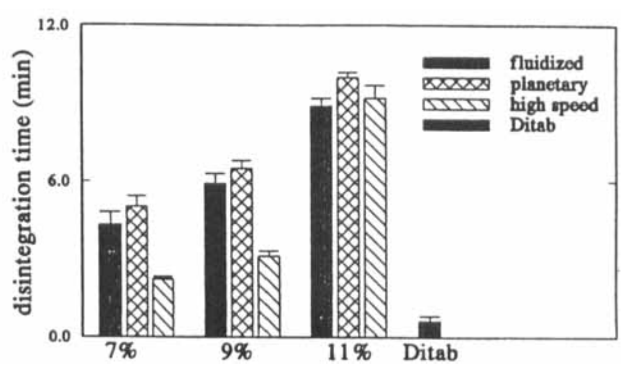

Figure 13. Disintegration time of phenylpropanolamine HCl tablets using different substances as the diluent.

the granulation process, some undesirable properties of talc as a diluent were successfully improved. Thus, agglomerated talc is a possible direct compression diluent.

REFERENCES

1. C. A. Discher, T. Medwick, and L. C. Bailey, *Modern Inorganic Pharmaceutical Chemistry*, 2nd ed., Waveland Press, Illinois, 1985.
2. K. Lin and G. E. Peck, Drug Dev. Ind. Pharm., 21(4), 447 (1995).
3. K. Lin and G. E. Peck, Drug Dev. Ind. Pharm., 21(2), 159 (1995).
4. N. A. El-Gindy, M. W. Samaha, and H. A. El-Maradny, Drug Dev. Ind. Pharm., 14(7), 977 (1988).
5. H. Seager, P. J. Rue, I. Burt, J. Ryder, and J. K. Warrack, Int. J. Pharm. Tech. Mfr., 2(2), 41 (1981).
6. G. Ragnarsson and J. Sjogren, Int. J. Pharm., 12, 163 (1982).
7. N. A. Armstrong and L. P. Palfrey, J. Pharm. Pharmacol., 41, 149 (1989).