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THE EFFECT OF MIXING TIME AND MIXER INTENSITY ON THE COMPRESSION PROPERTIES OF TABLETTOSE®

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ABSTRACT

The effect of mixer intensity on the compression properties of Tablettose® is considered. Changes are evidenced ranging from the negligible effects of a low intensity process such as roller mixing to a substantial physical alteration of the constituent particles when a high intensity process is used. It is suggested that in order to optimise the use of this component for direct compression formulation, a balance must be established between mixer efficiency and an acceptable level of particle damage.

INTRODUCTION

Tablettose® (Meggle, Germany) is a commercially available brand of α-lactose monohydrate that is specially processed to be of value as a direct compression tablet excipient (1). Recent studies have demonstrated that subjecting this material to a high intensity mixing process, as might be considered to satisfactorily disperse a low concentration of an active material prior to tableting, can have a profound effect on the mechanical and physical properties of the resulting powder blend (2).

In a production environment, variation of tableting performance with mixing can present significant problems particularly if it is desired to transfer manufacture from one piece of equipment to another. For this reason, the work described above has now been extended to consider the effect of mixer intensity on these same parameters for Tablettose®. The mode of operation of mixers commonly used within the pharmaceutical industry is well detailed in the literature (3). In this laboratory study the apparatus used ranged from a simple roller mixer to simulate a low intensity process such as a production scale V- or double cone blender, through an intermediate intensity planetary type mixer and finally the high speed mixer. Whereas the previous work utilised a high speed mix of 1000 rpm, this study has used a speed of 1800 rpm which is typical of the "slow speed" of many such mixers.

MATERIALS AND METHODS

Materials. Tablettose® (Hydrous α-Lactose, Meggle, Wasserburg, Germany) was received as a gift from the manufacturer and was used without modification.

Mixing. Suitably sized samples of Tablettose® were mixed for 2, 5, 15 and 30 minutes using the following mixers and conditions:

1) Roller Mixer - Approximately 250g of Tablettose® was placed in a 500ml amber glass bottle and subsequently mixed on rollers (Paulo Abbe Inc. New Jersey, USA) at 100rpm.

2) Planetary Mixer - Approximately 2kg of Tablettose® was placed in a 12 quart bowl of a planetary mixer (Hobart Manufacturing Company, Ohio, USA) and mixed at 225rpm.

3) High Speed Mixer - Approximately 2kg of Tablettose® was placed in a 10L capacity high speed mixer (TK Fielder, Eastleigh, England) and mixed at 1800 rpm.

Compression Testing. Samples of Tablettose® were lubricated with 1%w/w Magnesium Stearate in a roller mixer for two minutes and compressed on an

instrumented Manesty F tablet machine to a weight of 150mg using 7mm flat face tooling. Tablets were stored for 24 hours in sealed containers prior to being broken on a Schleuniger hardness tester.

Particle Size Analysis. The particle size distribution of representative samples from each mixing process and time interval together with an initial was determined by sieving to constant weight using sieves ranging from 63μm to 212μm.

Density Determination. The bulk density was determined by pouring 50g of the unlubricated material into a 100ml graduated cylinder and measuring the volume to the nearest ml after insertion and a single tap in an Engelsmann automatic compaction density unit. The tapped density was performed by measuring the constant volume attained after a further 2000 taps on the same unit. Where applicable the Hausner Ratio was subsequently calculated as the ratio of tapped to bulk density.

RESULTS AND DISCUSSION

The effect of laboratory scale roller mixing on the tableting properties of Tablettose® was negligible, with no changes apparent in compression profiles (Figure 1) or the particle size distribution (Figure 2) up to mixing times of 30 minutes. Similarly the changes in flow properties as described by the Hausner ratio (Table 1) were minor. These results bode well for scale-up and suggest that the mixing process might not be expected to alter the functionality of the excipient *per se*.

When Tablettose® was mixed for up to 30 minutes in a planetary mixer, small differences were detected between the compression profiles of the initial sample and those subjected to mixing which increased as the time extended (Figure 3). Since it is established that the consolidation of crystalline lactose is primarily by fragmentation (4), a reduction in mean particle size would be the most obvious explantion. Figure 4 suggests that while the changes in particle size distribution with planetary mixing were small there was a reduction of approximately 8% by

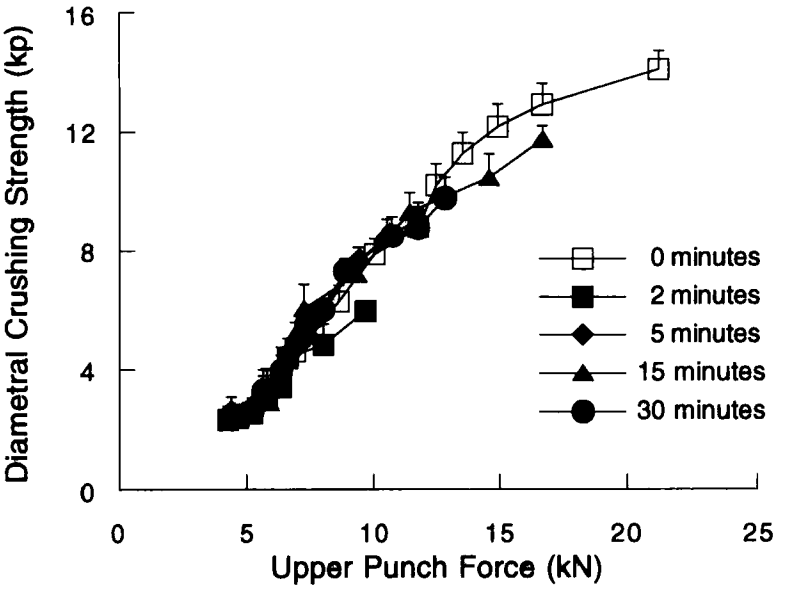

FIGURE 1

Diametral Crushing Strength as a Function of Upper Punch Force for Tablets Manufactured from Tablettose® After Roller Mixing from 0 to 30 Minutes.

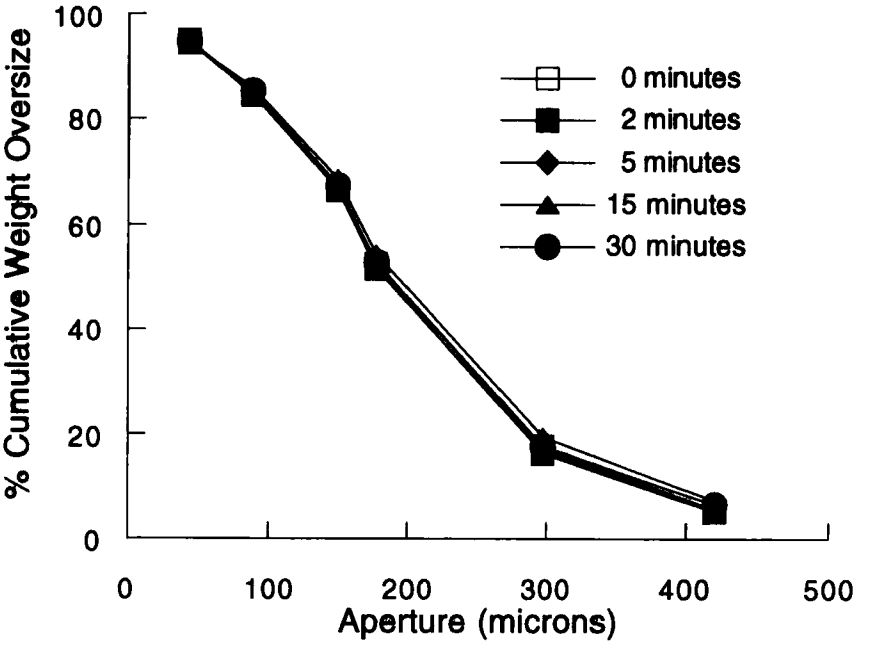

FIGURE 2

Percentage Cumulative Weight Oversize as a Function of Roller Mixing Time for Tablettose®

TABLE 1

The Hausner Ratio as a Function of Time for Samples of Tablettose® Subjected to Roller, Planetary and High Speed Mixing Operation.

Mixing Time Mins.	Hausner Ratio		
	Roller	**Planetary**	**High Speed**
0	1.14	1.14	1.14
2	1.15	1.16	No flow
5	1.18	1.17	No flow
15	1.18	1.17	No flow
30	1.19	1.17	No flow

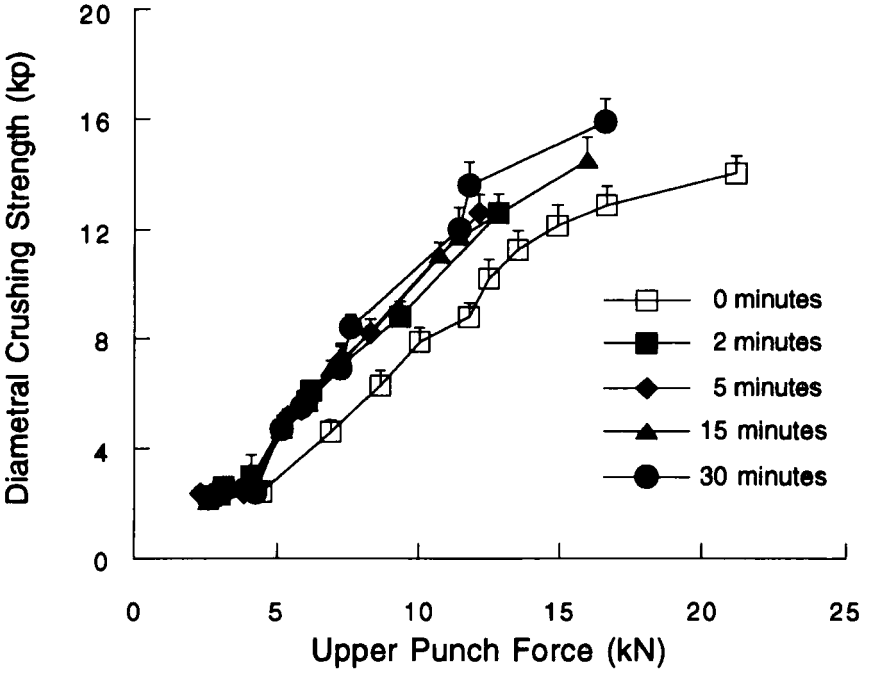

FIGURE 3

Diametral Crushing Strength as a Function of Upper Punch Force for Tablets Manufactured from Tablettose® After Planetary Mixing from 0 to 30 Minutes.

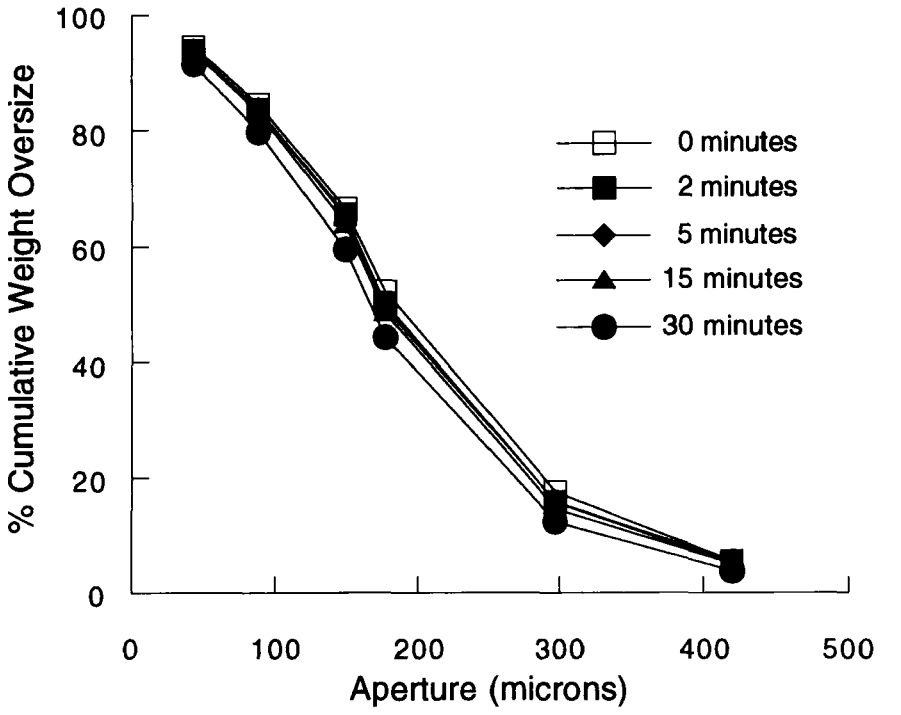

FIGURE 4

Percentage Cumulative Weight Oversize as a Function of Planetary Mixing Time for Tablettose®

weight in particles over 177μm and 7% in particles over 149μm over the 30 minute mixing period, which provides some support for this hypothesis. While the subsequent changes in particle size distribution due to mixing may have effected a change in the compression behaviour of the sample, they did not appear to have resulted in any adverse effect on the flow properties. The Hausner ratios detailed in Table 1 show comparatively little variance between 0 and 30 minutes. While this would appear to be most desirable for a production process, it should be remembered that, with the demonstrated propensity for particle size reduction with planetary mixing, different results might be apparent with higher beater speeds or alternative mixer geometry emphasising the need for rigorous process validation during scale-up.

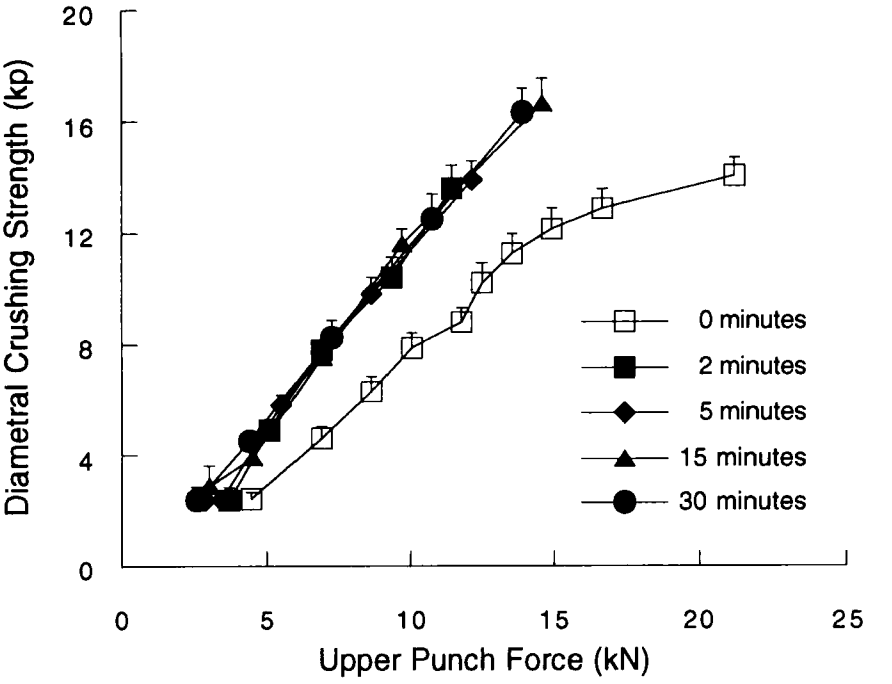

FIGURE 5

Diametral Crushing Strength as a Function of Upper Punch Force for Tablets Manufactured from Tablettose® After High Speed Mixing from 0 to 30 Minutes.

The most marked effects of mixing on Tablettose® were produced by the high speed process which in only two minutes rendered the material physically different from the initial sample. Tablets manufactured after 2 minutes mixing were approximately 50% stronger than initial samples. However, these changes did not continue with further mixing, indicating that whatever effect high speed mixing at 1800rpm induced in Tablettose®, it was complete at 2 minutes. In this instance the influence of reduced particle size on compression was unequivocal (Figure 6); between 0 and 2 minutes the weight of particles above 177μm decreased from 52.4% of the total to 29.6% and further declined to 21.3% at 30 minutes. While the effects of particle size reduction could be seen to be advantageous for the the tablet compression process, this benefit must be counterbalanced by the exhibited loss of flow characteristics (Table 1) making a Hausner ratio determination

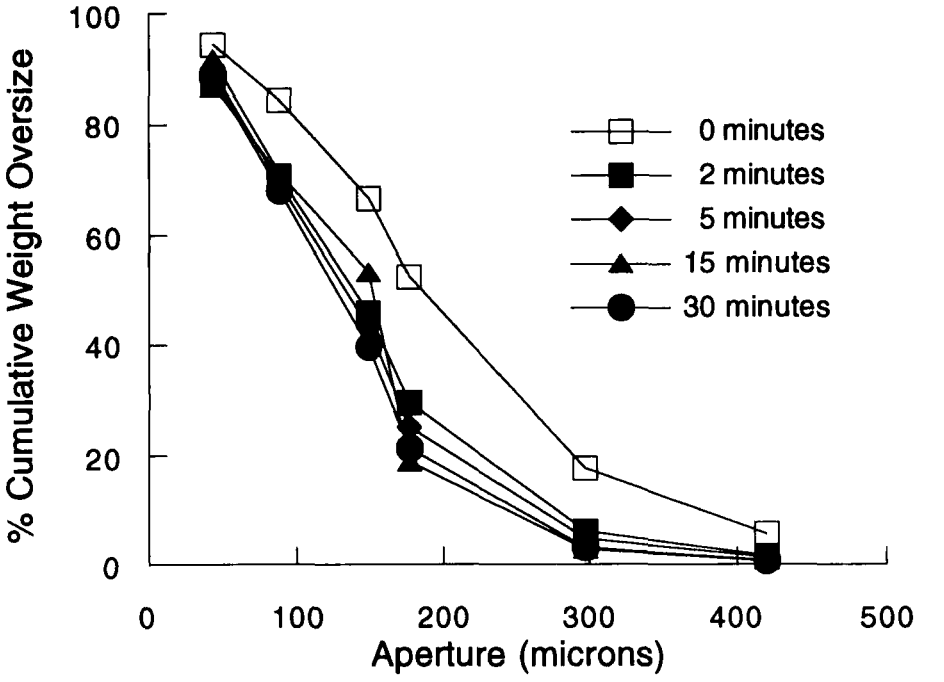

FIGURE 6

Percentage Cumulative Weight Oversize as a Function of High Speed Mixing Time for Tablettose®.

impossible. In addition, such changes in particle size distribution might also be associated with an alteration in the segregation behaviour of the mixed bulk powder with the subsequent implications for active content uniformity and weight uniformity.

Clearly the material is severely damaged by the high speed mixing operation. However, the fact that the Tablettose® samples could be lubricated and were able to flow in such a manner as to produce reproducible tablet weights for compression analysis, suggests one method by which the effects of these physical changes might be overcome. Alternatively, our earlier studies (2) indicated that the use of a lower mixer speed, 1000rpm, while resulting in a deterioration of powder flow did not reduce the Tablettose® to the point that it would not flow at all. Nonetheless, while any number of actions might be contemplated to limit the effect of damage to

Tablettose® on mixing, it would appear that the most appropriate way to avoid these potential problems would be to incorporate, during the development of a direct compression tablet process, an alternative lower intensity mixing step such as one of the methods described above.

CONCLUSION

The results presented above have served to demonstrate the significance of mixer intensity on the compression properties of Tablettose®. Low intensity processes such as roller mixing appear to have had little or no effect on the compression properties of this material even at mixing times of 30 minutes, whilst a high intensity process such as the high speed mixer altered the physical and mechanical properties of the powder after only 2 minutes. Clearly mixing processes of intensity intermediate between these two might be expected to have proportionate effects. In this instance, this has been shown using planetary mixing where small but significant changes in some parameters were demonstrated.

More importantly however, this work demonstrates the need to establish and validate a balance between the required efficiency of the mixing process and an acceptable level of damage to the excipients. By optimising the former and limiting the latter, the chances of obtaining the production goal of a reproducible process with limited inter-batch variation are increased. While this work has been directed towards characterising the effects of mixer intensity on Tablettose®, the principle is equally applicable to all such excipients that might be used in direct compression formulations.

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