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AN INVESTIGATION OF THE EFFECT OF HIGH SPEED MIXING ON THE MECHANICAL AND PHYSICAL PROPERTIES OF DIRECT COMPRESSION LACTOSE

P.M.Thwaites, A.B.Mashadi, W.D.Moore.

Development Laboratories, Merck Sharp and Dohme,
Hoddesdon, England.

ABSTRACT

The effect of high speed mixing on the mechanical and physical properties of four commercially available grades of direct compression lactose is considered. The changes that are evidenced in these properties are found to be specific to each grade of lactose and it is recommended that due consideration be given to the effects of incorporating such a process if inter-batch tablet variation is to be avoided.

INTRODUCTION

The advantages of direct compression tabletting techniques over other methods in certain specific circumstances are well documented (1). In particular it is not uncommon to consider direct compression when the required active dose is low or represents a small fraction of the total tablet weight.

Nonetheless in such an event obtaining satisfactory active content uniformity may present a significant challenge. This may often be solved by the employment of a high speed mixing stage but the concern will still remain that such a robust method may alter the physical characteristics of the powder and in particular the principal diluent.

Lactose is probably the most commonly used direct compression excipient (2). However it is well characterised as a brittle material (3-5) and it may be hypothesised that the use of such a high energy process may result in extensive particle fracture with subsequent alterations in both physical and mechanical properties.

We have investigated the effect of high speed mixing on four commercially available grades of direct compression lactose which were selected to reflect each of the stable crystal forms ie anhydrous α-lactose, hydrous α-lactose, anhydrous β-lactose and the presence of amorphous material in spray dried lactose. The preparation and properties of these materials are well detailed elsewhere (6,7).

MATERIALS AND METHODS

Materials. The following materials which are all marketed as direct compression grades of Lactose were used as received. Fastflo (Hydrous α-Lactose/Amorphous Lactose, Foremost Whey Products, Wisconsin, USA), Tablettose (Hydrous α-Lactose, Meggle, Wasserburg, West Germany), DCL-30 (Anhydrous α-Lactose, DMV, Veghel, The Netherlands), DCL-21 (Anhydrous β-Lactose, DMV, Veghel, The Netherlands).

High Speed Mixing. 1Kg samples of each Lactose were placed in a 10L Baker-Perkins high speed mixer and mixed for 2, 5, 15 and

30 minutes with both impeller and chopper blades rotating at 1000rpm. Each sample, together with initials was subjected to full mechanical and physical testing as outlined below.

Compression Testing. Samples of each Lactose were lubricated with 1%w/w Magnesium Stearate in a Turbula mixer for 2 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 of each Lactose at each mixing time together with an initial was determined by sieving to constant weight using sieves ranging in a $\sqrt{2}$ progression from 63μm to 212μm. The geometric median particle size was determined in each case from the log-normal size distribution.

Specific Surface Area. This was determined for each sample by the BET method (nitrogen adsorption) using a Quantasorb Surface Area Analyzer (Quantachrome Inc.).

Density Determination. The bulk density was determined by pouring 125g of material into a 250ml graduated cylinder and measuring the volume to the nearest ml after insertion and a single tap in a Radon automatic compaction density unit. The tapped density was performed by measuring the constant volume attained after a further 2000 taps on the same unit. Each measurement was repeated twice and averaged. The Hausner Ratio was subsequently calculated as the ratio of tapped to bulk density.

Differential Scanning Calorimetry DSC was carried out using a Mettler Model TA 3000 Thermal Analyzer. Samples of about 10mg,

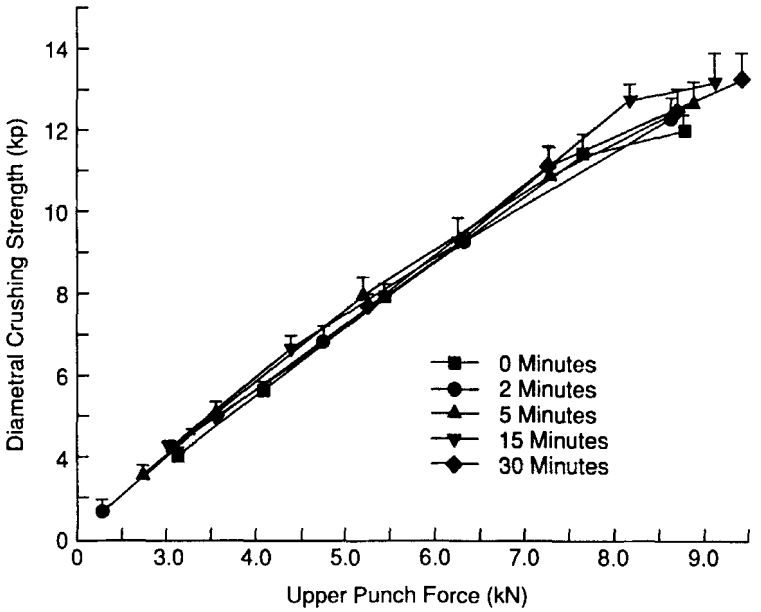

FIGURE 1

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

accurately weighed, were heated in sealed aluminium pans from 25°C to 220°C at 10°C per minute.

RESULTS AND DICUSSION

The results of mechanical analysis of the lactose samples indicate that the effect of mixing time on the compression properties of Fastflo (Figure 1) and DCL 21 (Figure 2) was minimal. For Tablettose (Figure 3) there was a gradual increase in crushing strength with mixing time; tablets manufactured after 30 minutes mixing were approximately 30% stronger than initial

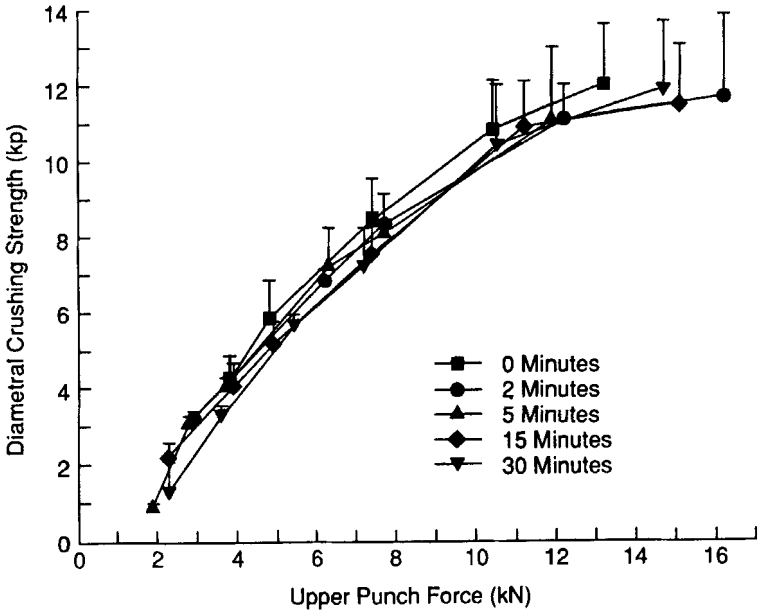

FIGURE 2

Diametral Crushing Strength as a Function of Upper Punch Force for Tablets Manufactured from DCL-21 Lactose After High Speed Mixing From 0 to 30 Minutes.

samples. For DCL 30 (Figure 4) the effect was marked and tablets manufactured after 30 minutes mixing were approximately twice as strong as initial samples at similar compaction pressures.

It might be hypothesised that the changes that occur in the mechanical properties on mixing for some of the samples of lactose may be attributed, at least in part, to an overall reduction in particle size. Reviewing the sieve analysis results; for DCL-30 (Figure 5) there was virtually no change in the initial narrow particle size distribution after 30 minutes mixing and specifically no increase in "fines" (particles <63μm). Fastflo

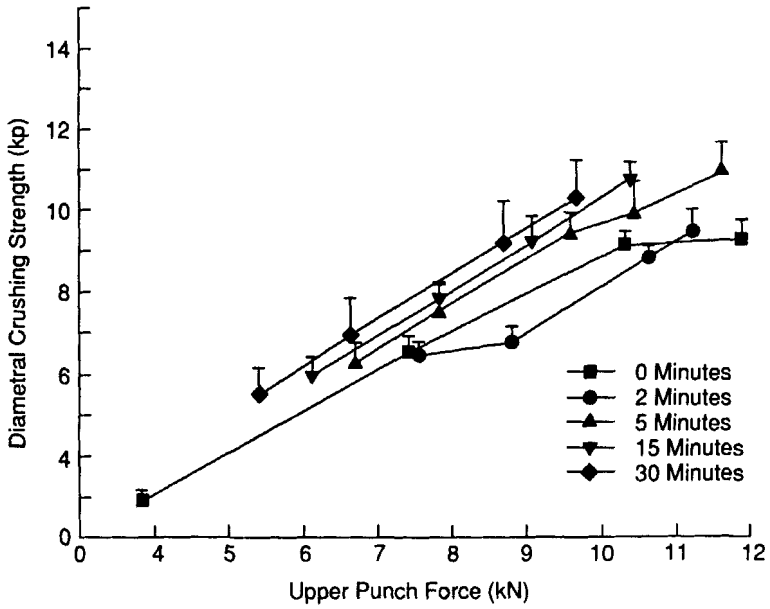

FIGURE 3

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

(Figure 6) and to a greater extent, DCL-21 (Figure 7) revealed a shift in the particle distribution to a smaller mean size with a moderate increase in "fines" (approximately 5% cumulative weight for Fastflo and 8% for DCL-21). The occurence of an increase in the weight of particles less than 63μm might reasonably be expected to account for changes in compression properties, however, as described above, the mechanical properties of Fastflo and DCL-21 are least effected by extended mixing time. By way of contrast, Tablettose (Figure 8), a granulated form of the alpha-monohydrate with a wide initial distribution exhibits a substantial reduction in particles over 200μm with no increase in

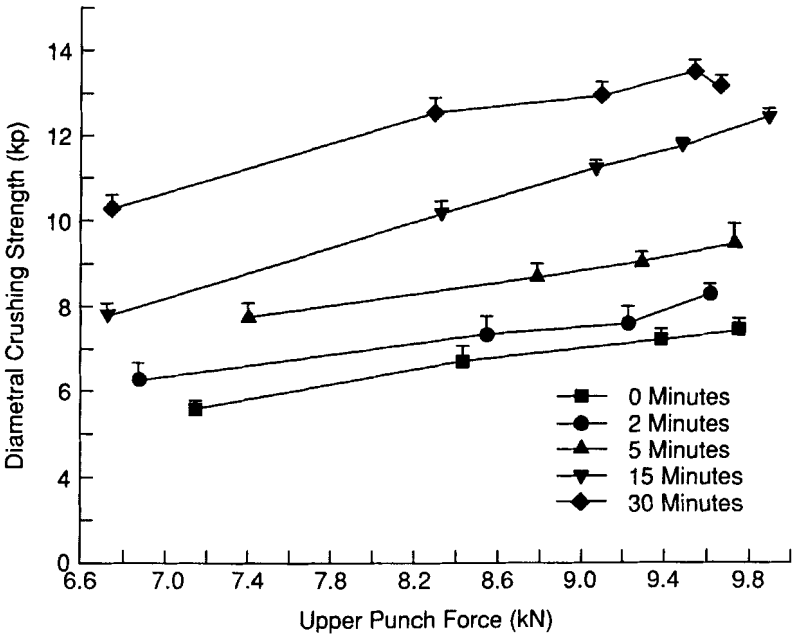

FIGURE 4

Diametral Crushing Strength as a Function of Upper Punch Force for Tablets Manufactured from DCL-30 Lactose After High Speed Mixing From 0 to 30 Minutes.

those less than 63μm. From Figure 9 where the geometric mean particle size is plotted as function of mixing time it is evident that the principal decrease in the Tablettose distribution occurs within the first two minutes of mixing. Clearly the granule structure of Tablettose is severely damaged after relatively short periods of high speed mixing.

The results of sieve analysis were confirmed by surface area measurements using nitrogen adsorption (Table 1). Although this

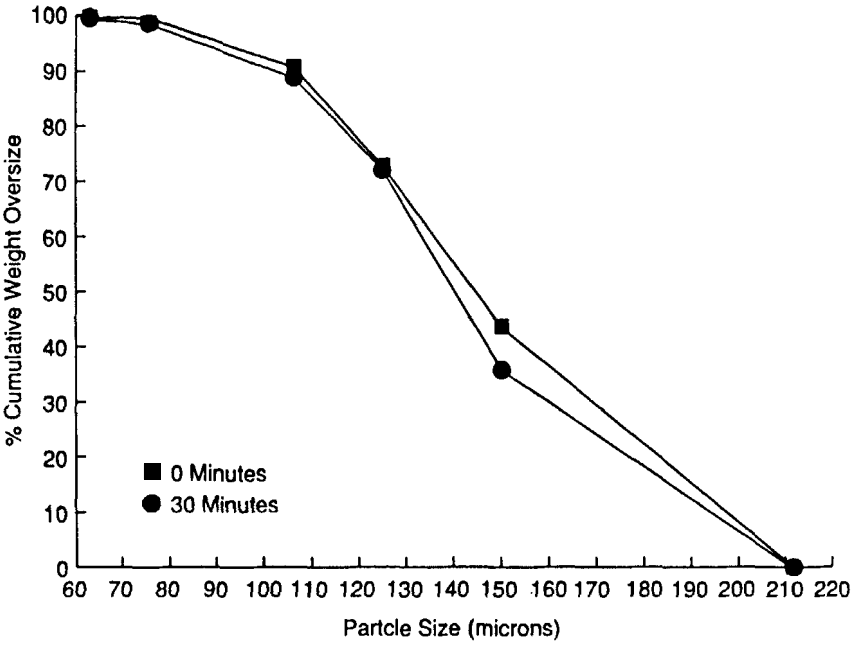

FIGURE 5

Percentage Cumulative Weight Oversize as a Function of High Speed Mixing Time for DCL-30 Lactose.

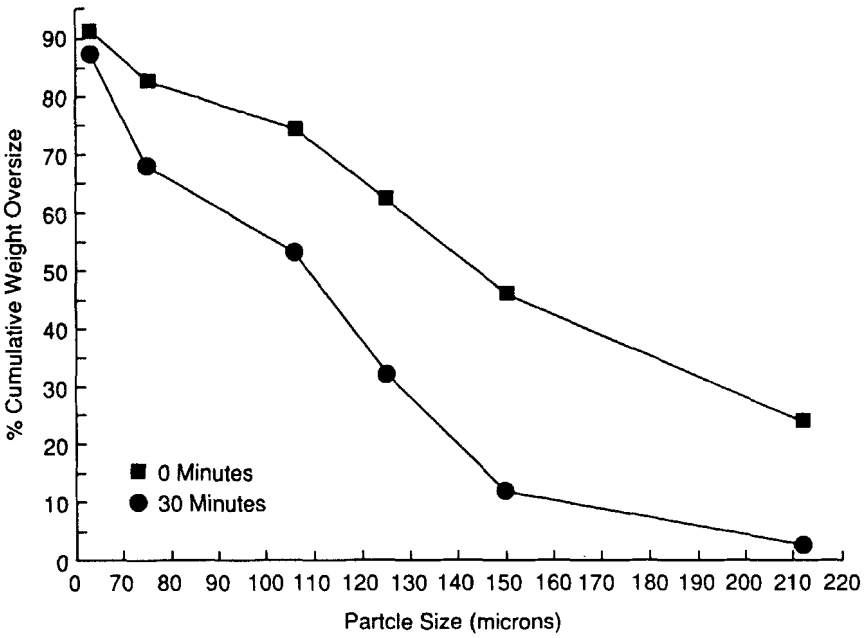

FIGURE 6

Percentage Cumulative Weight Oversize as a Function of High Speed Mixing Time for Fastflo Lactose.

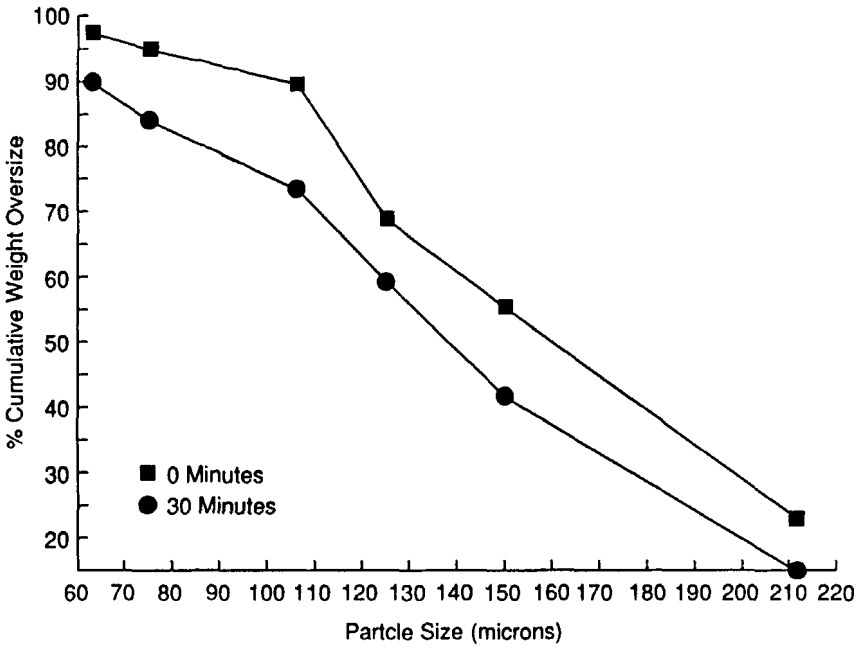

FIGURE 7

Percentage Cumulative Weight Oversize as a Function of High Speed Mixing Time for DCL-21 Lactose.

technique might be considered relatively insensitive at such low surface areas, it is seen that, with the possible exception of Tablettose, the increase in this parameter with mixing time is minimal. Once again, the small increase for Tablettose occurs within the first five minutes.

It is well established that crystalline lactose consolidates primarily by fragmentation (8). Thus for Tablettose the increase in surface area on mixing may partially account for the increase in crushing strength of the compacts. Fastflo, a spray dried lactose, contains a significant proportion of amorphous lactose

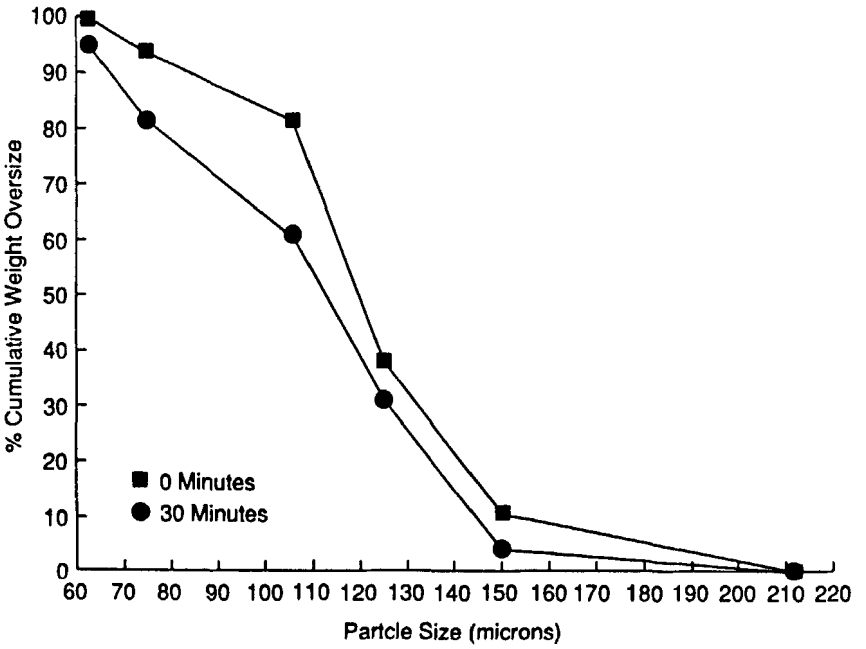

FIGURE 8

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

(approximately 15%) which is capable of plastic flow (9). This amorphous nature may provide resistance to fragmentation on high speed mixing as well as exerting a positive influence on particle binding and may account for the similarity of the compression profiles with mixing time. For both DCL-21 and DCL-30 which are anhydrous forms of β- and α-lactose respectively, particle fragmentation would be the expected mechanism of consolidation, however, only the compression profiles obtained on the former product are consistent with the small changes in particle size distribution. Such an explanation cannot be used to account for the large changes in compression properties evidenced for DCL-30.

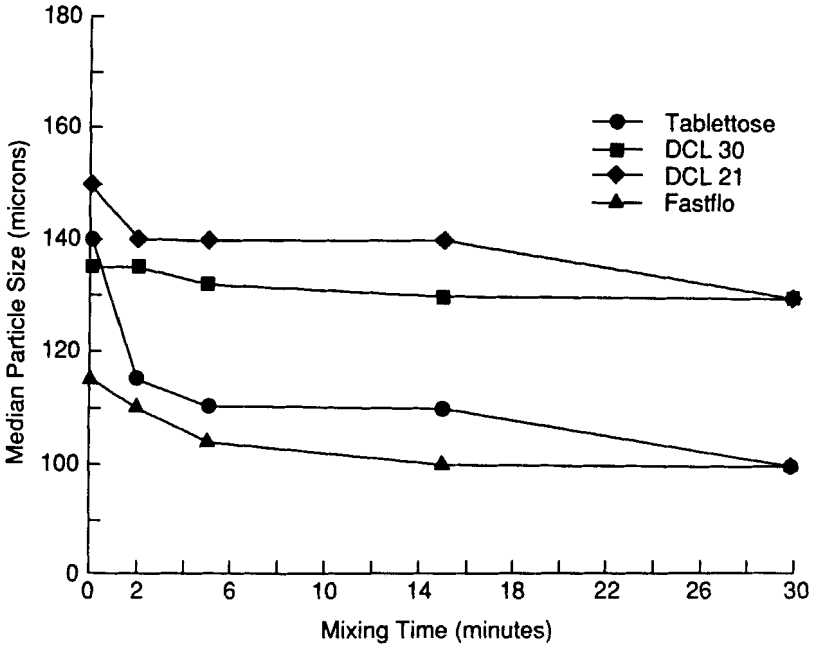

FIGURE 9

Geometric Mean Particle Size as a Function of Mixing Time

TABLE 1

Specific Surface Area as a Function of High Speed Mixing Time

Mixing Time Mins.	Specific Surface Area m^2g^{-1}			
	DCL-21	DCL-30	Tablettose	Fastflo
0	0.39	0.23	0.47	0.28
2	0.40	0.23	0.49	0.28
5	0.41	0.24	0.52	0.29
15	0.43	0.29	0.53	0.30
30	0.44	0.33	0.55	0.34

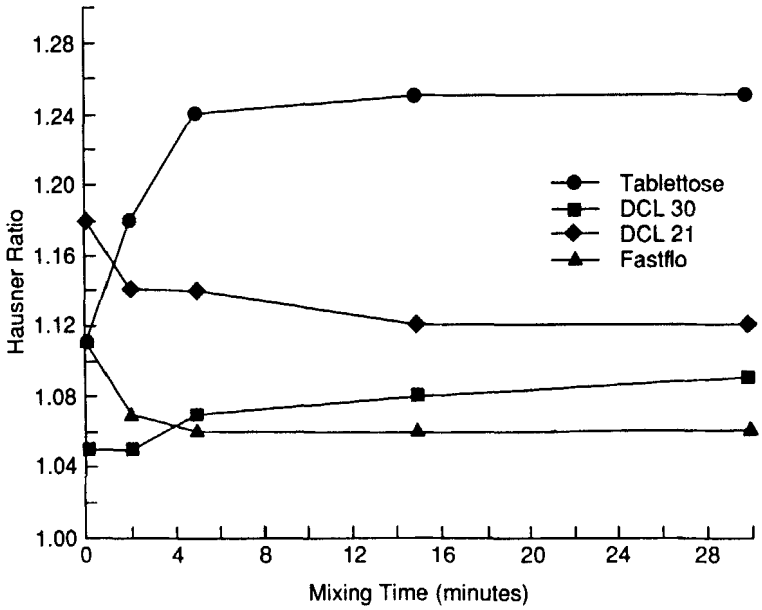

FIGURE 10

The Hausner Ratio as a Function of Mixing Time

It may be speculated that one of the effects of high speed mixing on DCL-30 is to increase the number of flaws in the particles, with a subsequent increase in the propensity to fragmentation on compaction, however as yet this remains unproven.

It has been reported that vigorous milling processes may result in polymorphic changes in crystalline lactose (10). To ascertain whether a polymorphic transistion was an underlying feature of some grades of lactose during high speed mixing which might influence compression, each sample was subjected to thermal analysis by differential scanning calorimetry. No changes were detected in any sample at any mixing time thus eliminating such an occurence as a possible explanation of the unexpected compression properties of DCL-30.

For each sample tested a Hausner ratio was determined experimentally, prior to lubrication, as a measure of powder flow. From the results in Figure 10 it will be noted that the early time reduction in particle size of Tablettose is accompanied by a deterioration in powder flow. Thus it may be concluded that while the breakdown of the granule structure of Tablettose might have a positive influence on the compression properties this effect is counterbalanced by a negative influence on the flow properties. Interestingly, for DCL-21 and Fastflo, high speed mixing may actually enhance the flow properties whereas for DCL-30 there is no change. These observations are consistent with the small changes in particle size distribution.

CONCLUSION

From the data presented above, it is apparent that the incorporation of a high speed mixing step into the processing of a direct compression grade of lactose may have a profound effect on the physical and mechanical properties of the resulting powder mix. Although in this study the mixing times have been deliberately extended from those generally used in practice, it is observed that for some grades of lactose, significant changes in tabletting properties occur at relatively short mixing times. The changes that occur do not necessarily contra-indicate the use of either a particular grade of lactose or the incorporation of high efficiency mixing as a processing step in a direct compression tablet formulation. They do however, suggest that a rigourous validation of the mixing process be performed with the desired excipients to prevent unneccesary inter-batch tablet variation.

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