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Time-dependent deformation of some direct compression excipients*

J. E. REES‡ AND P. J. RUE†

Department of Pharmacy, University of Aston in Birmingham, Gosta Green, Birmingham, B4 7ET, U.K.

Three techniques were used to compare the time-dependent deformation of microfine cellulose (Elcema G250), anhydrous lactose, dicalcium phosphate dihydrate (Emcompress), modified starch (Sta-Rx 1500) and sodium chloride. (1) In stress-relaxation experiments using a reciprocating tablet machine, none of the materials behaved as a Maxwell body in contrast to recent published work (David & Augsburger, 1977). Possible reasons for this disagreement are discussed. (2) Heckel plots showed that increasing the time for which a material was under compression (contact times of 0·17 and 10 s) had no effect on dicalcium phosphate compacts but increased the consolidation of other materials in the rank order sodium chloride < lactose < cellulose < starch. (3) Deformation tests on preformed compacts were carried out in diametral compression by loading compacts to 75% of their breaking force at four different strain rates between 0·05 and 6·5 mm min^{-1}. The deformation of Sta-Rx compacts was time-dependent. Sodium chloride compacts exhibited brittle behaviour in the diametral compression test and in the 10 s contact time experiment. This was apparently due to work-hardening, following the extensive plastic deformation of crystals during compaction as indicated by the stress relaxation results.

As early as 1950 the importance of plastic flow in the production of compacts by powder compression was recognized by Stewart who suggested that the more plastic a material, the more likely it is to form compacts.

Several investigators in particular Shlanta & Milosovich (1964) have used stress relaxation measurements to examine the plastic flow of pharmaceutical materials during compaction. More recently David & Augsburger (1977) analysed stress relaxation data using the Maxwell model of visco-elastic behaviour in an attempt to quantify the rate of plastic deformation of some direct compression agents. However, as we discuss in this paper, there are several problems associated with stress relaxation measurements which limit their usefulness in assessing the tableting characteristics of pharmaceutical materials.

Since plastic deformation is time-dependent, one parameter in tablet compaction is the time for which the particulate material is held under load. Jones (1977) has used the term "contact time" to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and decompression event, but excluding ejection.

We have examined the effects of time on the deformation of some direct compression agents using three parameters: stress relaxation during compaction; the effect of contact time on tablet density; and, for preformed tablets subjected to diametral compression tests, the effect of platten rate on tablet deformation.

MATERIALS AND METHODS

Materials

The following materials were used as received from the suppliers; Elcema G250—a granular form of microfine cellulose (Degussa, Frankfurt, West Germany), anhydrous lactose (KW—Revai Chemicals Ltd., London, U.K.), Emcompress—a direct compression form of dicalcium phosphate dihydrate (K.K. Greef Ltd, Croydon, U.K.), Sta-Rx 1500—a modified Starch U.S.P. (A.E. Staley Manufacturing Co., Illinois, U.S.A.), magnesium stearate (Hopkin and Williams Ltd., Essex, U.K.). Sodium chloride AR (Fisons Scientific Apparatus, Loughborough, U.K.) was milled using a ball mill and sieved to obtain a 150–300 μm size fraction. All materials and compressed tablets were stored at 50% R.H., 24° for 1 day before use.

Preparation of tablets

Sufficient material to produce a compact 2·5 mm thick at zero theoretical porosity was weighed to ±2 mg, poured into a 12·7 mm diameter die, and compressed between plane-faced punches using a

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† Present address Beecham Pharmaceuticals, Burgh Heath, Epsom, Surrey.

‡ Correspondence. Present address: I.D.D.C. Abbott Laboratories, Queenborough, Kent.

Wilkinson STD 1 reciprocating tablet machine. The die was previously lubricated by compressing a sample of the same material containing 50% w/w magnesium stearate. Applied compaction forces were monitored using an instrumented upper punch as described by Rees & Rue (1978).

Stress relaxation measurements

Stress relaxation experiments were performed during compaction of materials, using the reciprocating tablet machine described above. The tablet machine fly-wheel was turned by hand at a constant rate until the required peak force was reached, as indicated by an ultraviolet oscillograph (S.E. Laboratories Ltd., Feltham, U.K.) connected to the instrumented upper punch. To determine stress relaxation at virtually constant strain, the punches were then held at this fixed position while the decrease in punch force, due to relaxation of the compressed material, was monitored until no further decrease was observed. This was repeated using a total of three tablets of each material at one value of peak force of about 20 kN. Tablets produced in these stress relaxation studies were not used in the subsequent tests involving measurement of tablet properties.

Initial experiments were carried out using the various materials without additives, compressed in a lubricated die. However, to compare our results with those of David & Augsburger (1977) the stress relaxation experiments were also repeated using a mixture of the material with 0·3% w/w magnesium stearate, which was added by forcing sufficient of the lubricant through a 100 μm sieve aperture onto 50 g of the material spread on a metal tray. The powders were mixed for 5 min using a spatula, transferred to a polythene bag and shaken for a further 5 min.

Measurement of non-recoverable deformation

Batches of 30 tablets were made from each material at sufficient compaction force to produce tablets with a mean breaking force of about 78 N. Using a diametral compression testing instrument (Rees & Rue, 1978) at a rate of platten movement of 0·26 mm min^{-1}, the mean breaking force of 10 tablets from each batch was determined. Groups of 5 tablets were then tested individually by loading to 75% of the mean breaking force and rapidly removing the load by withdrawing the lower platten. The load was then reapplied without moving the tablet. The experiment was repeated using different tablets at each of four different rates of platten movement, the rates being 0·052, 0·26, 1·3 and 6·5 mm min^{-1}. Diametral load and platten displacement were monitored during each experiment using an X–Y recorder (Model 26000, Bryans Southern Instruments Ltd., Mitcham, U.K.). A typical trace is shown in Fig. 1 where total deformation of a tablet is given by $x_t - x_o$. The non-recoverable deformation (NRD) was calculated using equation 1.

$$NRD = x_1 - x_o \quad .. \quad .. \quad (1)$$

where x_o is the platten displacement when the recorded force rises from zero during the first loading; x_1 is the displacement when the force rises from zero on the second loading.

Construction of Heckel plots

The density of tablets prepared at a range of compaction forces was calculated from the thickness of each tablet measured by a micrometer immediately after ejection. Five tablets were prepared at each compaction force by one of two techniques. Firstly, tablets were compressed as described under "Preparation of tablets"; in this case the total time the material was under load during the compression event, excluding ejection, (i.e. the contact time) was 0·17 s. Secondly, tablets were loaded to the required peak compression force and the punch positions were held constant for 10 s before the compaction cycle was completed. The relative density of the tablet, D was calculated by dividing the density of the tablet by the true density of the material.

RESULTS AND DISCUSSION

The stress relaxation behaviour of the five materials after compression to a peak force of about 20 kN is

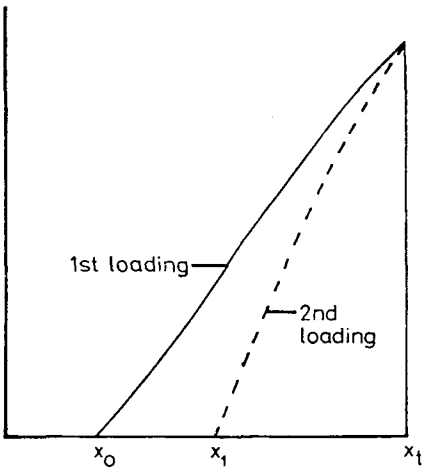

FIG. 1. Typical X–Y recording of the diametral loading of tablets to 75% of their breaking load. For definitions of symbols see text. Ordinate: Applied load. Abscissa: Platten displacement.

shown in Fig 2. As expected, materials such as lactose and Emcompress showed minimal stress relaxation; we found earlier (Rees & Rue, 1978) that tablets of these materials exhibited brittle failure during diametral compression. Conversely, a large total stress relaxation was observed for materials such as Sta-Rx and Elcema, tablets of which had shown considerable plastic deformation before failure in our previous studies. By means of a mathematical analysis similar to that used by David & Augsburger (1977), which tests for visco-elastic behaviour of the Maxwell type, a plot was drawn of force remaining in the visco-elastic region against time, as shown in Fig. 3. The force remaining refers to the difference between the recorded force at any given time and the asymptotic value of force once stress relaxation is complete. Each plot in Fig. 3 exhibits an initial curved section

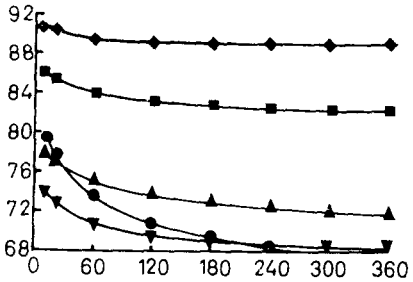

FIG. 2. Decay of the upper punch force (%) (ordinate) with time (s) (abscissa) at constant upper punch displacement after compaction to about 20 kN. Die wall lubrication only. ◆, Emcompress; ■, lactose; ●, sodium chloride; ▲, Elcema; ▼, Sta-Rx.

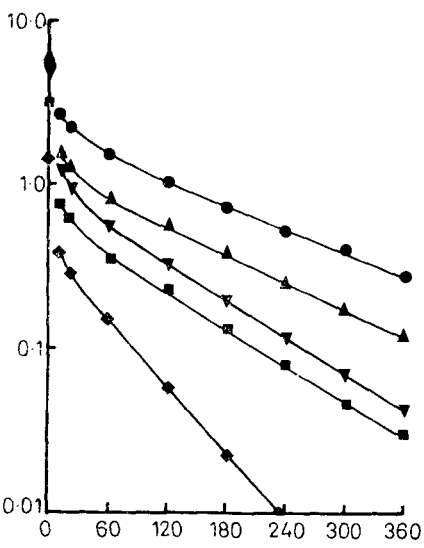

FIG. 3. Semi-logarithmic plot of the force remaining (kN) (ordinate) in the visco-elastic region with respect to time (s) (abscissa). Die wall lubrication only. Symbols as in Fig. 2.

which becomes linear after about 30 s. Thus the initial rapid rate of relaxation decreases until all materials assume the first order stress relaxation characteristic of a true Maxwell body. By using the Maxwell model the assumption is made that each material possesses a single relaxation time constant, the relaxation time being defined as the time required for the force to reach 1/e times the maximum force. However, since the data do not fit a Maxwell model, more than one relaxation time must be involved. The curved sections of the semilogarithmic plots shown in Fig. 3 indicate that the relaxation time is varying during the first 30 s after applying maximum force. It appears that, during this period, the relaxation time depends on the stress as discussed by Richardson (1957).

Our results contradict those of David & Augsburger (1977) who reported firstly that stress relaxation was complete after about 10 s and secondly that dicalcium phosphate dihydrate, Sta-Rx and Avicel (a brand of microcrystalline cellulose, chemically similar to Elcema) appeared to behave as true Maxwell solids. The materials used by David and Augsburger each contained 0·3% w/w magnesium stearate; we therefore repeated our stress relaxation experiments using a mixture of each material with 0·3% w/w magnesium stearate.

The main difference between the results for compacts with and without magnesium stearate was seen for sodium chloride; this material showed less total stress relaxation when the compacts contained lubricant. We suspect that lubricant present at interparticulate junctions ensured a more uniform stress distribution throughout the compact, thus minimizing localized high stress concentrations and reducing the amount of stress relaxation which occurred. Such an effect of lubricant would be large in an ionic crystalline solid in which the formation of strong interparticulate bonds in the absence of lubricant would oppose relative particle movement during consolidation and tend to produce high local stresses.

In other respects, lubricant appeared to have little effect on stress relaxation. The shapes of the semilogarithmic plots were similar for each material with or without magnesium stearate showing that the presence of this lubricant did not induce Maxwell type behaviour. A probable explanation for the difference between the results presented here and those of David & Augsburger (1977) is given by considering the strain conditions during the relaxation experiments. Stress relaxation must be measured at constant strain which, in this type of study, necessitates a constant distance between the upper

and lower punch faces. In the reciprocating tablet machine which we used, this distance is constant for a given upper punch displacement, assuming that elastic deformation of the punches and other machine components is negligible. However, in a rotary tableting machine such as that used by David & Augsburger (1977) a small downward movement of the lower pressure roll normally occurs during compression, due to movement in the overload spring mechanism (Deer & Finlay, 1973; Deer, 1975). This movement will reach a maximum at the time of maximum force. As the punch force decreases due to relaxation of the compact with the upper punch position fixed, the lower pressure roll will move upwards in an attempt to regain its equilibrium position. The effect of this movement will be to maintain a higher stress on the compact, and therefore on the upper punch, than that which would be found during relaxation under conditions of true constant strain. Thus, under the experimental conditions which apparently existed in David and Augsburger's study, pseudo-equilibrium values of residual punch force may be observed which are higher, at any given time, than under conditions of constant strain.

Another problem associated with stress relaxation measurements is that any plastic flow which occurs during the time required for initial force application is not represented by the relaxation curve. Stress relaxation measurements are normally continued for considerable periods of time. For example David & Augsburger (1977) continued relaxation measurements for 10 s and Cole, Rees & Hersey (1975) continued for 2 min. However, during the industrial pharmaceutical tableting process, the time available for plastic flow is usually of the order of only 0·1 s, more than half of this time corresponding to the rise in compaction force to a maximum.

Hiestand, Wells & others (1977) have used a different method for analysing stress relaxation data which involves plotting the stress, or upper punch force against the logarithm of time. A plot of this type for materials without magnesium stearate is shown in Fig. 4 where the upper punch force expressed as a percentage of the maximum applied force, is plotted against the logarithm of time for the first 10 s after peak force. Unlike the Maxwell model, the use of the log time plot assumes that the material exhibits several different relaxation times. The physical significance of the changes in slope of Fig. 4 are unknown and this causes difficulties in interpreting such relationships. Nevertheless a comparison of the log time plots reveals certain trends. The brittle

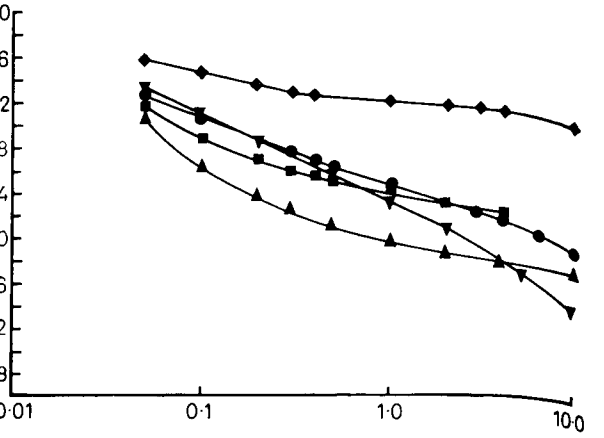

FIG. 4. Decay of the upper punch force (%) (ordinate) with log time (s) (abscissa) at constant upper punch displacement after compaction to about 20 kN. Die wall lubrication only. Symbols as in Fig. 2.

material Emcompress shows a slower relaxation and also less total relaxation than the plastic material Elcema which shows a relatively rapid and large relaxation. For Sta-Rx, the relaxation is initially slower than for the brittle lactose. After 10 s however, the total relaxation of Sta-Rx is much greater than for lactose; it is also greater than for the other plastic material Elcema and appears to be continuing at a relatively high rate. Although such plots are difficult to interpret, they facilitate comparison of the behaviour of different materials during the early stages of relaxation, by expanding the time scale immediately after peak force.

The relatively slow initial relaxation of Sta-Rx suggested that the consolidation of this material during compaction may be extremely time dependent. To confirm this hypothesis, the consolidation behaviour of each material was examined in terms of the relationship employed by Heckel (1961) and more recently by Hersey, Cole & Rees (1973). This involves plotting a function of the volume reduction during compaction, 1/(1-D) where D is the relative density of the tablet, against compaction force. We have found that by constructing these Heckel plots using compaction data obtained at two different contact times, the time-dependent nature of the consolidation process can be assessed. Studying the amount of non-recoverable plastic deformation by this method overcomes two problems associated with stress relaxation experiments which were discussed above. Firstly, any plastic deformation which occurs during force application is included in the term 1/(1-D). Secondly, for a given material compacted on a certain

machine at a certain peak force, elastic deformation of an overload mechanism or other machine components will have a virtually constant effect on all tablets produced at different contact times; thus, differences in the Heckel plots obtained at different contact times should be due only to plastic deformation.

The Heckel plots for each material using contact times of 0·17 and 10 s are shown in Fig. 5. Increases in tablet density, due to prolonging the time available for deformation, are in the rank order Sta-Rx > Elcema > lactose > sodium chloride > Emcompress. This rank order agrees with the finding of David & Augsburger (1977) that an increase in contact time increased the strength of Sta-Rx tablets by 135% Avicel tablets by 37% and lactose tablets by only 15%. Since plastic deformation of a material during compaction increases the area available for interparticulate bonding, one would expect materials such as Sta-Rx and Elcema, which show large increases in density with increasing contact time, to show similarly large increases in tensile strength.

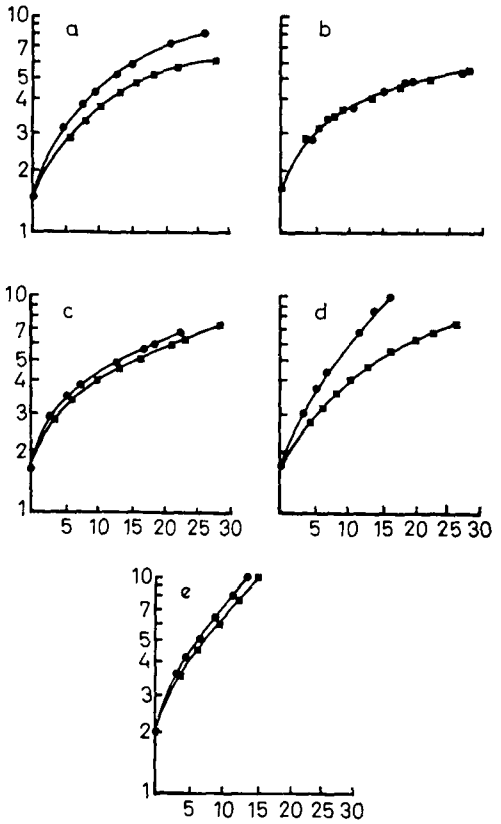

FIG. 5. The effect of contact time on the consolidation behaviour of five materials, shown as Heckel plots of 1/(1-D) on a log scale (ordinate) against compaction force in kN (abscissa). a: Elcema; b: Emcompress; c: anhydrous lactose; d: Sta - Rx; e: sodium chloride. Contact times: ■, 0·17 s; ●, 10 s.

The increases in density and tablet strength with contact time, discussed above, show the importance of knowing to what extent plastic deformation of a direct compression excipient is time-dependent and therefore strain rate sensitive. However, neither stress relaxation nor consolidation measurements allow quantification of the strain rate sensitivity of a material. We have shown previously (Rees & Rue, 1978) that during diametral compression testing, tablets of different materials deform by different amounts before failure. Part of this deformation is non-recoverable, due to plastic flow or possibly due to localized fracture in the region of loading, and part will be elastic and hence recoverable when the compressive load is removed. Any non-recoverable deformation (NRD) due to plastic flow of the material will be affected by the rate of loading. We therefore decided to investigate the effect of strain rate on the deformation behaviour of preformed compacts subjected to diametral compression. Fig. 6 shows the relation between the logarithm of platten rate and the logarithm of the non-recoverable deformation; in this case the NRD of each tablet was divided by the applied diametral force, to allow for slight differences in the forces applied to individual tablets. The brittle materials, lactose and Emcompress, which exhibited relatively little stress relaxation (Fig. 2) also showed no change in NRD with platten rate. However the visco-elastic materials Elcema and Sta-Rx, in which there is considerable

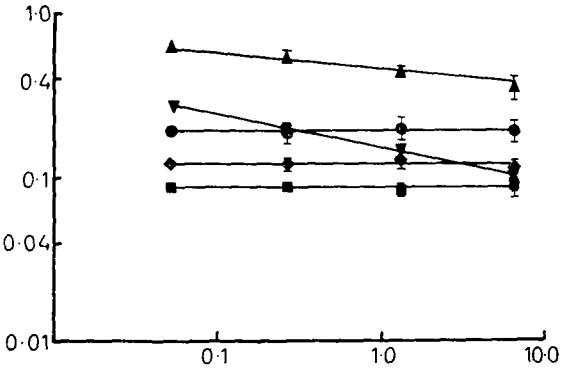

FIG. 6. Non-recoverable deformation (NRD) (ordinate) of compacts loaded to 75% of their breaking load in a diametral compression test plotted as a function of platten rate (mm min^{-1}) (abscissa). The NRD values are expressed per unit diametral force (mm kN^{-1}). Vertical bars indicate standard errors. Symbols as in Fig. 2.

time-dependent plastic flow, showed a decrease in NRD as the platten rate increased, indicating that with these materials at higher strain rates a greater proportion of the total deformation is elastic and therefore recoverable. Although sodium chloride has been shown to consolidate by plastic flow (Hardman & Lilley, 1973; Hersey & others, 1973) we observed no change in the NRD of this material with platten rate. This is probably due to work-hardening of the sodium chloride particles during compaction, especially under the influence of high shear forces at the die wall and at interparticulate junctions. Such work-hardening would form brittle regions which would not be capable of plastic deformation before brittle failure occurred. Failure properties would therefore be non-time-dependent. We have also found other evidence for brittle behaviour of sodium chloride compacts (Rees & Rue, 1978); in diametral compression tests, sodium chloride compacts showed relatively little deformation before failure occurred.

The gradients of the lines plotted in Fig. 6 are an indication of the strain rate sensitivity of the materials; the larger the negative gradient the higher the strain rate sensitivity. For Elcema the gradient is −0·090 and for Sta-Rx −0·191, showing that the deformation of Sta-Rx tablets is much more strain rate dependent than the deformation of Elcema tablets.

We found (Rees & Rue, 1978) that considerable deformation of Sta-Rx tablets occurred before failure in a diametral compression test. This observation and the fact that a large increase in consolidation of Sta-Rx occurred with contact time (Fig. 5) confirm that it is capable of extensive plastic deformation. Nevertheless, at any given compaction pressure the tablet strength is unexpectedly low (Rees & Rue, 1978) compared with the other plastic material Elcema and even compared with the brittle materials lactose and Emcompress. We consider that the low strength of Sta-Rx tablets is partly due to plastic deformation occurring too slowly for extensive areas of bonding to be produced during a high strain rate powder compaction event. Evidence for this highly time-dependent behaviour is given by the high negative gradient for Sta-Rx in Fig. 6 and its low initial rate of stress relaxation in Fig. 4. Attempts to predict the tableting properties of a material such as Sta-Rx on the basis of slow compaction studies, long-term stress relaxation measurements or a low strain rate diametral compression test should therefore be treated with caution. An additional factor contributing to the low strength of Sta-Rx tablets is that, during compaction at a high strain rate a large proportion of the total deformation of Sta-Rx will be elastic. During decompression and ejection the elastic deformation will recover, again at a high strain rate, causing extensive bond rupture and further reducing the tablet strength.

Small-scale studies of the effect of strain rate and contact time during compaction should help a formulation scientist to predict whether a specific drug, excipient or tablet formulation will be susceptible to changes in the compaction conditions during scale-up or when transferring from one type of tableting press to a higher strain rate machine.

CONCLUSIONS

1. The simple Maxwell model of visco-elastic deformation is inadequate to characterize the stress relaxation behaviour of the five directly-compressible materials studied.

2. Time-dependent consolidation behaviour can be assessed by comparing Heckel plots for tablets prepared at different contact times. This technique overcomes several limitations of stress relaxation measurements, in particular their failure to account for plastic deformation which occurs during initial application of compaction force.

3. Deformation measurements on preformed tablets can be used to quantify the relative strain rate sensitivity of materials. Those materials which showed no change in non-recoverable deformation of tablets with the rate of diametral loading also exhibited small or negligible changes in tablet density when the contact time was increased during compaction.

4. Although Sta-Rx is capable of extensive plastic deformation, this can only occur slowly. Changes in the contact time during powder compaction therefore have a marked effect on tablet properties.

5. For sodium chloride, studies on preformed tablets may lead to incorrect conclusions about the deformation of particles during compaction; stress relaxation results confirmed that sodium chloride crystals deform plastically during compaction but preformed compacts showed brittle properties, and contact time had little effect on tablet density, probably due to work-hardening during compaction.

6. Measurement of the strain rate sensitivity and time-dependent deformation behaviour using the techniques discussed in this paper should facilitate identification of particulate drugs, excipients and formulations which may be difficult to tablet on high speed rotary tableting machines.

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