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The Role of the Displacement-time Waveform in the Determination of Heckel Behaviour Under Dynamic Conditions in a Compaction Simulator and a Fully-instrumented Rotary Tablet Machine

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Abstract—The Heckel equation has been used widely to characterize the compression behaviour of pharmaceutical powders, yet very little attention has been paid to the role of the displacement-time profile used to generate this relationship. The objective of this study was to evaluate and compare selected standard waveforms with actual and theoretical tablet press waveforms in the Heckel analysis of representative formulations under dynamic conditions in a compaction simulator and to compare such data with that determined on the same formulation using an actual fully-instrumented rotary tablet press. Increased tableting rate and different programmed displacement-time waveforms with the same gross punch-speed changed the Heckel behaviour of all formulations. The results of this study suggest the pressure-volume relationship determined during powder-bed compression is affected by the instantaneous punch-speed profile of the displacement-time waveform for all materials studied, even though they deform by different mechanisms. It appears that the instantaneous punch-speed profile of the particular displacement-time waveform is a confounding factor of Heckel analysis. Compaction simulators programmed to deliver saw-toothed displacement-time traces have the advantage of constant punch-speed and may be a better choice for characterizing a formulation by Heckel indices and the strain-rate sensitivity index. On the other hand, they also carry the liability of not being a realistic representation of tableting on a rotary tablet press.

The Heckel equation has been used widely to study the compression behaviour of pharmaceutical powders. The equation takes the form:

$$\ln\left(\frac{1}{1-D}\right) = kP + A \tag{1}$$

where D is the ratio of the density of the powder mass at pressure P to the true density of the solid and k and A are regression constants (Heckel 1961a, b). k is determined by performing linear regression on the linear portion of the curve and its reciprocal is taken to be the mean yield pressure (P_y). A is the y-intercept of the extrapolated linear region and is a function of the densification that results from particle rearrangement before deformation.

The method described by Heckel differs greatly from its applications found in the recent literature. Heckel compressed powders under pseudo-static conditions in an isolated punch-and-die apparatus. Heckel found a linear relationship between $\ln(1/(1-D))$ and the peak compression stress which is indicative of a system where the loss of void volume in ejected tablets as a function of peak compression pressure is a first-order process. One tablet volume used in Heckel's experiments is the summation of volume lost during consolidation and the volume gained due to elastic recovery during both decompression and ejection. This procedure has been termed 'tablet out-of-die'. With the recent advent of fully-instrumented tablet presses, scientists have the ability to determine the volume of the powder bed at any time during the compression cycle. Heckel analysis of data acquired in this fashion has been termed 'tablet-in-die'. The major difference between the two methods is in the consideration of elastic recovery. The out-of-die method includes the volume gained during elastic recovery in the calculations, whereas, the in-die method only considers the volume lost during consolidation. Powders which have a large elastic component to their compaction behaviour do not always produce intact tablets and in this case, the in-die method may be used but not the out-of-die method. Celik & Marshall (1989) programmed a compaction simulator to mimic a rotary tablet press and concluded that all pharmaceutical materials studied exhibited essentially nonlinear Heckel behaviour. It can be questioned whether the simple relationship Heckel devised holds true for the dynamically acquired high-speed in-die data.

The derived Heckel indices have been shown by a number of researchers to be affected by punch speed. The first report of time-dependent Heckel behaviour was by Rees & Rue (1978). The tablets were produced on a reciprocating tablet machine at contact times of 0·17 and 10 s. They found that plastically deforming materials show time-dependent consolidation behaviour which manifested itself as increased mean yield pressures with decreased contact time. Using a compaction simulator, Roberts & Rowe (1985, 1986) produced evidence that increasing punch speed increases P_y values for materials exhibiting plastic flow, whereas, brittlely-deforming materials were largely unaffected by increasing punch speed. The authors defined a strain-rate sensitivity index, which is calculated using the following equation:

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$$\text{Strain rate sensitivity} = \frac{P_{y2} - P_{yl}}{P_{y2}} \times 100 \qquad (2)$$

where P_{yl} = the yield pressure at 0·033 mm s^{-1} and P_{y2} = the yield pressure at 300 mm s^{-1}. Using this equation, Roberts & Rowe (1985, 1986) ranked a series of pharmaceutical materials in terms of their strain-rate sensitivity. The experiments were performed using a saw-toothed displacement-time trace to ensure constant punch speed, and the compression was single-ended. The type of compression event that occurs during normal operation of a production rotary press is very different and features double-ended compression and non-constant punch speed. Using an instrumented eccentric press, Armstrong & Palfrey (1989) also showed that increasing tableting rate results in increasing Heckel mean yield pressures. In their study, they assumed the region between porosity values of 40 to 30% was linear and calculated P_y values based on these endpoints. The tablets they produced were made by single-ended compression with displacement-time traces different from those seen with rotary tablet presses.

Although compaction simulators have been designed to mimic the displacement time behaviour of any tablet machine, they rarely have been used in that fashion. More often, they are programmed with such standard waveforms as the saw-tooth or the sine wave. Furthermore, although actual compaction is done on rotary tablet presses that employ double-ended compaction, simulators often have been employed in the single-ended compaction mode. The objective of this study was to evaluate and compare selected standard waveforms with actual and theoretical tablet press waveforms in the Heckel analysis of representative formulations under dynamic conditions in a compaction simulator and to compare such data with that determined on the same formulation using an actual rotary tablet press.

Materials and Methods

Formulations

Four formulations were studied. Formulation I was dicalcium phosphate dihydrate (Di-Tab, Rhone-Poulenc, Chicago Heights, IL, USA) and 2% stearic acid (J. T. Baker Chemical Co., Phillipsburg, NJ, USA) which was blended for 15 min in a V-blender (Model #LB-8625, Patterson-Kelley Co., East Stroudsburg, PA, USA). Formulation II was anhydrous lactose (Sheffield Products, Norwich, NY, USA), 2% stearic acid, and 0·1% colloidal silicon dioxide (Cab-O-Sil, Cabot Corp., Tuscola, IL, USA) blended in a V-blender for 15 min. Formulation III was a commercially available 12/50 mesh aspirin/10% starch granulation (Monsanto Company, St Louis, MO, USA) which was passed dry through a 20 mesh screen. Formulation IV was microcrystalline cellulose (Avicel PH-102, FMC Corp., Philadelphia, PA, USA), 1% magnesium stearate (Ruger Chemical Co., Inc., Irvington on Hudson, NY, USA), and 0·2% colloidal silicon dioxide blended in a V-blender for 15 min.

Excluding formulation IV, the formulations were chosen for their varying deformational behaviour and a minimum of addititional excipients were added to each as needed to maintain tight control of fill weight and keep peak ejection forces below 800 N. Preliminary experiments performed under dynamic conditions illustrated that anhydrous lactose required both a glidant and a lubricant, whereas the aspirin granulation required no additional excipients. Di-Tab, with its excellent flow properties, only required a lubricant. Formulation IV, on the other hand, was designed to be a failing formulation which was prone to laminate. Preliminary experience in our laboratory showed that if microcrystalline cellulose is over-blended with 1% magnesium stearate, the resulting blend will tend to laminate. Also, to maintain a reproducible die fill with this formulation at higher production rates, a glidant was required.

True density determination

True densities were determined using a multi-volume pycnometer (Micro-Measurements, Model #1305, Norcross, GA, USA) and the mean of three determinations was recorded.

Tableting

One station of a Manesty Betapress (Beta-J1-1347, Manesty Machines Limited, Liverpool, UK) was instrumented to measure upper and lower punch force and displacement. Two pairs of 350-ohm, foil-type strain gauges (CEA-06-125UT-350, Micro-Measurements, Raleigh, NC, USA) were bonded to both punches in a Poisson arrangement in the manner described by Walter & Augsburger (1986). The gauges were then wired in a Wheatstone bridge circuit using shielded wire, and encapsulated in multiple layers of polyurethane. Punch movement was measured by placing linear variable displacement transducers (LVDTs) (Model #241-000, Transtek, Inc., Ellington, CT, USA) in the adjacent empty guides. In an effort to minimize errors in the measurement of punch movement, two LVDTs per instrumented punch were mounted in the trailing and preceding empty punch guides, as suggested by Ridgeway-Watt (1988). The voltage output of the two LVDTs was summed and recorded as the true mean punch face displacement. All displacement measurements were corrected for the elastic deformation of the punches.

The resolution of the force and displacement measurements was 18 N and 3·2 μm, respectively.

Signal conditioning and acquisition was performed with the aid of a modular radiotelemetric device. The strain gauge signals were amplified (Model#713-IA1-1-BPT, Metroplex Corp., Frederick, MD, USA), converted to a frequency-modulated signal via voltage controlled oscillators (VCOs, 32 and 40 kHz, Model#713-MV9-BPT, Metroplex Corp.), and mixed with a 400 MHz sub-carrier signal. The output from the displacement transducers required no amplification and was passed directly to the VCOs (16 and 24 kHz) and the mixer. The mixed signal was amplified and broadcast with a short-range transmitter (Model#SR-X, Metroplex Corp.) to a receiver (Model#SR-R, Metroplex Corp.). The transmitted signal was then demultiplexed and demodulated (Model#120, Metroplex Corp.) to reproduce the original output from the sensors.

The force and displacement data were simultaneously collected using a 4-channel, 12-bit digital oscilloscope (Model#420, Nicolet Instrument Corp., Madison, WI, USA). The data were down-loaded to a personal computer and analysed using the computer program IGOR (WaveMetrics, Lake Oswego, OR, USA).

To allow the press to be run under normal conditions, brackets were designed and constructed to affix the telemetry unit and transmitter to the underside of the upper turret.

The tablets were made in batches by first filling the feedframe with powder and adjusting fill weight and compression pressure. Upper-punch penetration was fixed by setting the control dial to a value of 5. Fill-weights were calculated so each material would compress to a height of 3·2 mm at zero porosity and these were adjusted as required under the dynamic die-fill conditions. The press was then allowed to run normally while capturing the data from the four sensors, until approximately 30 tablets were produced. The press was run over a range of pressures and speeds. Four to six replicates of the force-displacement waveforms were saved to disc for subsequent analysis. Ten tablets from each batch were weighed, measured for thickness and diameter, and tested for crushing strength.

Compaction simulation

An experiment was designed to assess the effect of the programmed displacement-time waveform on the consolidation behaviour of three formulations of varying deformation behaviour. A series of waveforms was devised with three major stipulations. First, all reach the same minimum distance between the punches. Second, the total time required for the punches to go from their start position to the minimum distance between the punches will be identical. Third, the total time required to travel from the minimum distance between the punches to the original start position will be identical. In this fashion, all waveforms will have the same gross punch speed, but varying instantaneous punch speed.

The compaction simulator (Mand Testing Machines Ltd, Stourbridge, UK) located at SmithKline Beecham Laboratories (King of Prussia, PA, USA) was equipped with 10 mm standard, flat-faced tooling and programmed with a series of displacement-time traces. The reference standard was a trace collected from the Betapress via the radiotelemetry link running at 1342 tablets min^{-1} while compressing a rubber plug to a peak compression force of 10 kN. There is no single displacement-time signature by which a press can be simulated. Clearly, displacement-time profiles are not independent of the compression force generated due to the deformations in the press and tooling (Walter & Augsburger 1986; Oates & Mitchell 1990). Another complicating factor is the alignment of the centres of the upper and lower rollers which is affected by the punch penetration and pressure setting. The degree of alignment affects the synchronicity of punch movement, the total compression time, and the dwell time. Finally, displacement-time traces can be expected to be influenced subtly by how the formulation responds to the rate and magnitude of the applied load. For the purposes of this study, a single reference 'real Betapress wave' to be used for all test formulations was generated to reflect representative conditions of force, punch penetration and roller alignment. To this end, a Neoprene rubber plug (Phelps Packing and Rubber Company, Baltimore, MD, USA) with a height of $\frac{1}{2}''$ and a diameter of $\frac{5}{16}''$ was compressed with $\frac{7}{16}''$ tooling at 1342 tablets min^{-1} to a peak compression force of 10 kN. It was important that the plug be smaller in diameter than the die to allow for deformation under pressure. For these runs, the feedframe was removed and the plug was placed in the empty die at the weight control cam. This approach accounts for the pressure-dependent deformations and other mechanical effects that occur in real presses, but ignores possible subtle effects due to the deformation characteristics of formulations. The second experimental condition was an ideal Betapress trace calculated by the equation of Charlton & Newton (1984) and based on a rate of output of 1342 tablets min^{-1}. The third trace was a single-ended compaction event in which only the upper punch moved. The loss of powder-bed height as a function of time was identical to the reference trace, but instead of being delivered by two punches as in the reference trace, powder consolidation was only performed by the upper punch. The instantaneous punch speed and the total in-die consolidation was equal to those seen in the reference standard. The next three waveforms are displacement-time traces which are increasingly dissimilar to the original reference standard. The fourth trace is a sine wave which was chosen to descend into the die at the same moment as the third waveform, reach the same peak displacement at the same time, and return to the die surface at the same moment. Here the instantaneous punch speeds are different from the third waveform, but the gross punch movement is identical. The fifth waveform was the much used saw-toothed wave which delivers a constant speed. As with the sine wave, its descent into the die starts at the same time, it reaches the same peak displacement at the

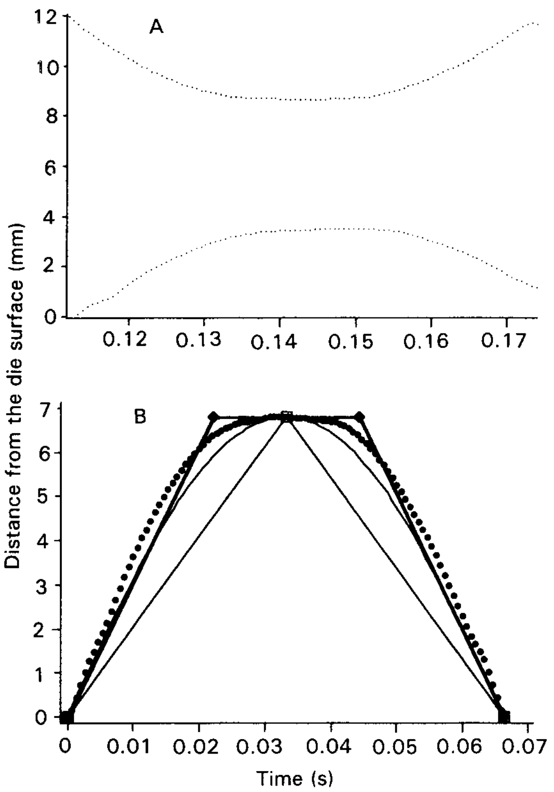

FIG. 1. A plot of the waveforms used to program the compaction simulator at SmithKline Beecham Laboratories. A. A real Betapress trace collected by the compression of a rubber plug to 10 kN. B. A series of single-ended displacement-time waveforms with equal gross punch speed. ◆ Trapezoid wave, □ saw-toothed wave, — sine wave, ● single-ended real wave.

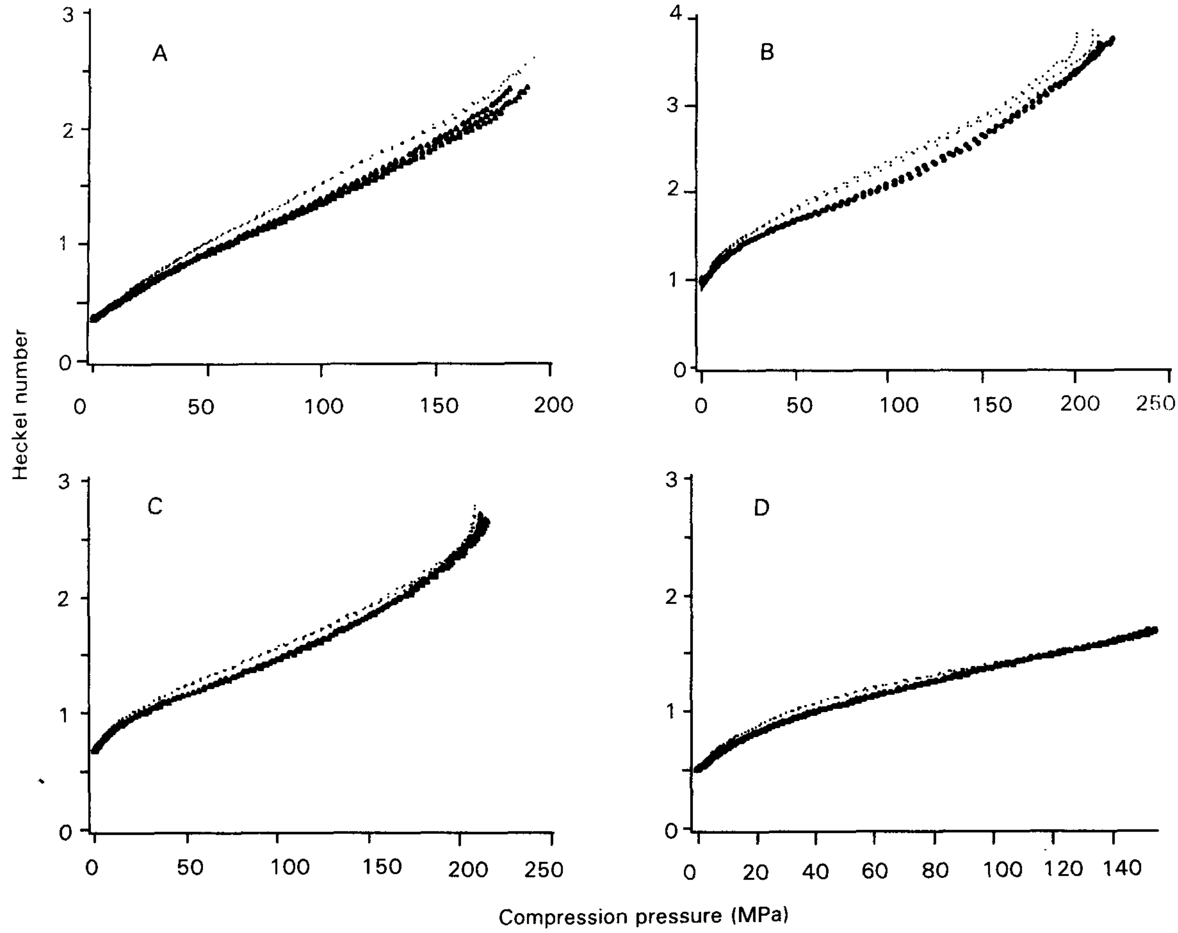

FIG. 2. Representative Heckel plots of the four formulations at two tableting rates shown in triplicate. A. Avicel PH-102 formulation. B. Aspirin/10% starch granulation. C. Anhydrous lactose formulation. D. Dicalcium formulation. Approximately 750 tablets min^{-1} (·) and approximately 1300 tablets min^{-1} (●).

same time, and returns the die surface at the same time. The sixth wave form was a trapezoid wave with the same stipulations as the sine and saw-toothed wave, except this trace provided 23 ms of dwell time. Shown in Fig. 1 are the waveforms programmed into the compaction simulator.

Formulations I, II and IV were studied. The tablets were produced by filling the empty die with a sample after it had been weighed on an electronic balance. The fill weights used were 400, 380 and 540 mg for the Avicel PH-102 (IV), anhydrous lactose (II), and dicalcium phosphate (I) formulation, respectively. Each formulation was compressed to the peak compression force of approximately 20 kN and six replicates of each programmed waveform were performed. Heckel analysis was performed on the force-displacement data after a correction for elastic punch deformation. The mean yield pressure was estimated by linear regression of the consolidation phase of the Heckel plot between 70 and 160 MPa.

Results and Discussion

Tableting

Heckel analysis (eqn 1) was applied to the force-height data for the four formulations run on the Betapress. Shown in Fig. 2 are the Heckel plots for these formulations at two different rates of output. Shown in Table 1 are the P_y values calculated by linear regression of the region of the curve between 50 and 150 MPa.

The Heckel plots of all four formulations show differences between the two curves at different production rates. These differences are greatest early on in the compression event and decrease as the event continues toward the peak pressure. These early stages of compression are characterized by greater available porosity and large differences in punch speed, whereas, later on in the event, the punch speeds become less disparate and porosity becomes less available for permanent deformation to occur. Due to the difference between the curves at different production rates, the mean yield pressures (P_y) present a very muddled picture.

The dicalcium phosphate formulation showed a decrease in P_y as a result of increased production rate. This unexpected result can be explained after considering the work of others. Roberts & Rowe (1985, 1986) found in their study that dicalcium phosphate showed no rise in P_y as a result of increased punch speed, whereas Armstrong & Palfrey (1989)

Table 1. A summary of the Heckel mean yield pressure values for the four formulations at three rates of output, tableted on the instrumented Betapress.

Main formulation excipient	Tablet production rate (tablets min^{-1})	Mean yield pressure (MPa)	95% Confidence, limit
Microcrystalline cellulose	744	96·7	1·221
	1083	98·9	2·695
	1354	103	3·015
Anhydrous lactose	756	142	2·283
	1108	134	3·907
	1375	137	12·05
Dicalcium phosphate dihydrate	756	217	5·52
	1128	198	4·49
	1276	180	6·7
Aspirin/10% starch granulation	755	90·5	4·363
	1051	78·2	1·646
	1374	84	15·2

did find a rise in P_y as a result of increased tableting rate. In the present study, typical Heckel values (ln (1/(1 − D))) for 756 and 1276 tablets min^{-1} at 50 MPa are 1·1478 and 1·0792, respectively, which is consistent with the observations of Armstrong & Palfrey (1989). Faster production rates require a greater amount of pressure to reach the same state of densification. Typical Heckel values for the same two speeds at 150 MPa were 1·6666 and 1·6663, respectively. At this point in the compression event, there is no longer any disparity in the Heckel behaviour. This observation is consistent with the fact that the punch speeds are converging. In our analysis, the net result when lower production rates are compared with higher production rates is that at greater production rates the porosity is greater at low pressures and essentially equal at high pressures. As a result, the mean yield pressures are lower for higher production rates than for lower production rates. At the higher press speed, particles do not have as much time to rearrange and repack as the pressure begins to develop, thus resulting in higher porosities at lower pressures. This difference is lost at higher pressures, where consolidation is more complete.

The Avicel PH-102 formulation showed a small increase in P_y as a result of increased tableting rate. In this case, the differences that were seen early in the compression event were still evident at the end of consolidation as the porosity progressed toward a minimum. At 50 MPa, corresponding typical Heckel values for 744 and 1374 tablets min^{-1} were 1·0218 and 0·9257, respectively, and at 150 MPa they were 2·0601 and 1·946, respectively.

The aspirin/10% starch granulation and the anhydrous lactose formulation showed similar behaviour. The P_y values for the faster speeds were modestly lower than the values calculated for the slowest speed. Curiously, the lowest value was found at the middle speed.

The results of the mean yield pressure regressions of the four formulations raise some very interesting points. Dicalcium phosphate has been shown to deform by brittle fracture, and exhibit no strain-rate sensitivity (Roberts & Rowe 1985, 1986). On the other hand, David & Augsburger (1977) demonstrated that this material exhibits a small degree of stress relaxation and Dwivedi et al (1991) reported that dicalcium phosphate will show peak offset times at low peak pressures. When all these characteristics are taken into consideration, it can be theorized that at high porosities dicalcium phosphate is acting as a visco-elastic material with some degree of strain-rate sensitivity, but as porosity decreases it behaves brittlely and exhibits no apparent strain-rate sensitivity. The net effect will be a decrease in mean yield pressure as a function of tableting rate on a high speed rotary tablet press. To the contrary, Avicel PH-102 has been shown to deform by plastic flow (Reir & Shangraw 1966), exhibit stress relaxation (David & Augsburger 1977) and be highly strain-rate sensitive (Roberts & Rowe 1985). With this material, even though the punch speed is decreasing throughout the compression event and converging with the punch speed at a lower tableting rate, the material is so sensitive that these small differences in punch speed still result in Heckel behaviour changes. Anhydrous lactose has been shown to deform primarily by fragmentation but it is also capable of exhibiting plastic deformation. Roberts & Rowe (1985) also showed it to be moderately strain-rate sensitive. The present data suggest its behaviour to be between those of dicalcium phosphate and Avicel. Like the former, anhydrous lactose showed a decrease in P_y, albeit a small one. Interestingly, as production rate is increased, the mean yield pressure does not continue to decrease, which suggests behaviour similar to Avicel. Even though the punch speeds are becoming more comparable, the small differences are sufficient to cause changes in Heckel behaviour. The aspirin/10% starch granulation behaved similarly to the anhydrous lactose formulation which suggests moderate strain-rate sensitivity.

Compaction simulation

The results of the Heckel analysis on the compaction simulator using different waveforms provides some interesting contrasts to the real tableting data. Shown in Fig. 3 are the Heckel plots from the compression of the Avicel PH-102 formulation with the six displacement-time waveforms. For comparison, each is plotted with the results from the saw-toothed wave. The saw-toothed wave features constant punch speed, whereas, all the other waveforms feature a complex, non-constant punch speed profile. By comparing the results from the saw-toothed wave with those of the other waveforms, any punch-speed-dependent changes in consolidation behaviour can easily be discerned.

All the plots in Fig. 3 A, B show similar behaviour. Early in

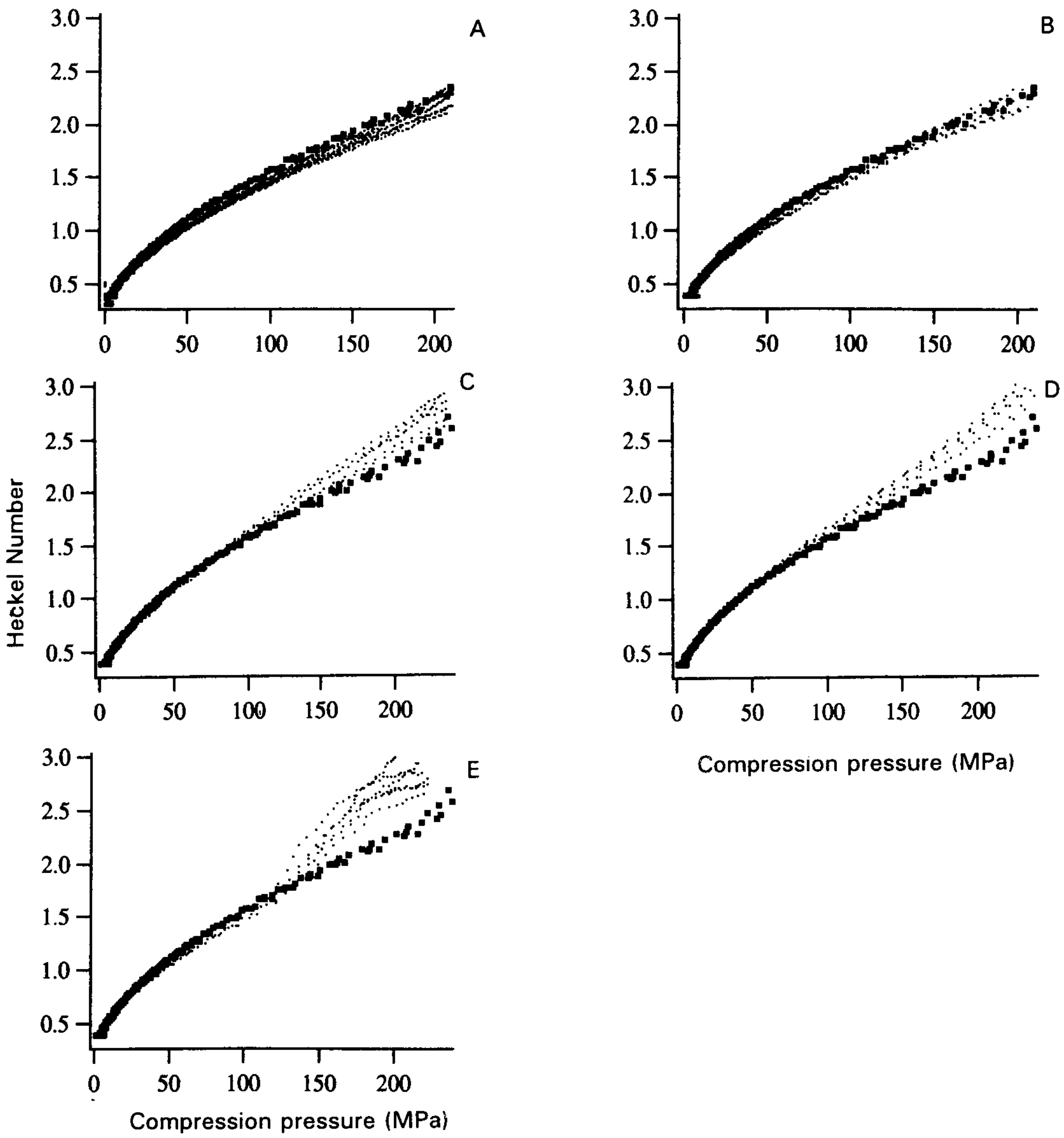

FIG. 3. Comparison of the Heckel plots of the Avicel PH-102 formulation compressed by the various displacement-time waveforms with the Heckel plots of the saw-toothed wave (■). Six replicates of the Heckel plots are shown. A. Ideal Betapress wave (·). B. Real Betapress wave (·). C. Single-ended real Betapress wave (·). D. Sine wave (·). E. Trapezoid wave (·).

the compression event, both show less powder bed consolidation, but as the compression event continues, the differences diminish. Eventually, the curves become superimposable at high pressures. Both Fig. 3A and 3B feature double-ended compaction and a punch speed profile where the peak speed occurs early in the compression event and decreases throughout the compression event. The plots in Fig. 3 C, D, and E all show similar behaviour which was slightly different from 3A and Fig. 3B. Early in the compression event, all three show slightly less consolidation than the saw-toothed wave, but as the compression event continues toward peak compression pressure, the three waveforms show a greater consolidation as a function of pressure. The sine wave and the single-ended real wave produced smooth curves which gradually showed greater consolidation. The trapezoid wave, on the other hand, demonstrated an abrupt increase in consolidation at approximately 125 MPa, which reflects the point where the upper punch was rapidly decelerated as it obtained its dwell position.

The consolidation behaviour of each formulation was affected by the instantaneous punch speed of the displacement-time waveform used to compress it, even though the gross punch speed was equal for all the materials. Also, the waveforms which used double-ended compression appear to cause the material to exhibit relatively more resistance to deformation. In an effort to examine further the consolidation behaviour of the three formulations, a mean yield pressure was estimated by regression of the linear portion of the Heckel plot for all the waveforms (Table 2). All P_y values for the waveforms were compared with the results for the most realistic waveform, the real Betapress wave, using Dunnett's *t*-test. The degrees of freedom were calculated

Table 2. A summary of the Heckel mean yield pressure regression P_y for the three formulations compressed by the various displacement-time waveforms. All P_y values are compared with the real Betapress wave using Dunnett's *t*-test. $n = 6$; d.f. $= 30$; 95%, two-sided; critical value $= 2·66$.

	Mean yield pressure (MPa)	%CV	95% CI	Dunnett's *t*-test
Avicel formulation				
Saw-toothed wave	140	4·37	6·39	3·286*
Sine wave	138	3·73	5·38	2·788*
Trapezoid wave	80·4	9·23	7·78	11·813*
Single-ended real wave	109	6·56	7·53	4·433*
Double-ended real wave	127	6·04	8·03	
Double-ended ideal wave	138	5·58	8·08	2·931*
Anhydrous lactose formulation				
Saw-toothed wave	215	6·97	15·7	6·247*
Sine wave	156	3·68	6·05	0·331
Trapezoid wave	135	5·28	7·48	2·767*
Single-ended real wave	151	10·8	17	0·996
Double-ended real wave	159	7·10	11·9	
Double-ended ideal wave	220	11·2	25·9	6·811*
Di-Tab formulation				
Saw-toothed wave	358	5·32	20	5·13*
Sine wave	306	3·05	9·8	1·099
Trapezoid wave	212	6·24	13·9	12·563*
Single-ended real wave	280	2·98	8·77	4·26*
Double-ended real wave	316	5·23	17·3	
Double-ended ideal wave	284	5·33	15·9	3·873*

* $P < 0·05$.

using the standard formula: d.f. $= (n - 1) + k(n - 1)$, where n is the number of observations per treatment and k is the number of treatments. The critical value for a two-tailed, 95% confidence level was 2·66.

The comparison of the P_y values for the three formulations showed some interesting results. The Avicel PH-102 formulation showed values which ranged from 80 to 140 MPa and all waveforms resulted in statistically different P_y results. Earlier studies have pointed out that the Avicel PH-102 formulation was the most rate-sensitive material of the three and it appears to be the most affected by changes in instantaneous punch speed. The anhydrous lactose formulation showed values with ranged from 135 to 220 MPa and only three of the waveforms resulted in statistically different P_y results. The sine wave and the single-ended Betapress wave both showed no significant difference from the result of the real Betapress wave. Anhydrous lactose has been characterized as having intermediate strain-rate sensitivity and appears to be less sensitive to changes in instantaneous punch speed. The dicalcium phosphate formulation showed values which ranged from 212 to 358 MPa and four of the waveforms resulted in statistically different P_y results. Like the lactose formulation, the sine wave was found not to be significantly different. In previous studies, dicalcium phosphate has been characterized as having the least rate-sensitive behaviour of the three formulations, yet it still shows consolidation behaviour changes as a result of changes in instantaneous punch speed.

Conclusion

The results of the experiment examining the effect of the programmed displacement-time waveform on the Heckel behaviour of pharmaceutical material offer some interesting insights. In general, the pressure-volume relationship determined during powder bed compression is linked to the punch speed profile of the displacement-time waveform for all materials studied, even though they deform by different mechanisms. It is remarkable that differences were elicited from the powders in spite of the fact that the gross punch speed was equal for all waveforms. It appears that the instantaneous punch speed profile of the particular displacement-time waveform is a confounding factor of Heckel analysis and may explain the differences in results among different laboratories. Another interesting point was the different behaviour exhibited by the waveforms which used double-ended compaction. Unlike the single-ended compaction wave which showed less resistance to deformation than the saw-toothed wave at higher pressures, the double-ended compaction wave showed slightly more or equal resistance to deformation than the saw-toothed wave at higher pressures. This suggests that the method used to compact the powder bed (single- vs double-ended compaction) may also affect the consolidation behaviour of the compact. Thus, to compare the Heckel analysis results of different laboratories, the entire dynamics of the compression must be matched. It is clear that in addition to P_y, many other compaction parameters may be affected by the displacement-time profile used to program a compaction simulator. Walter & Augsburger (1986) and Oates & Mitchell (1990) have pointed out the importance of programming a compaction simulator with relevant displacement-time data.

The results of this study question the appropriateness of performing Heckel analysis on compaction data gathered from high-speed rotary tablet presses or compaction simulators programmed to mimic high-speed rotary tablet presses. During the consolidation of the powder bed, the material is exposed to punch speeds which can range from 350 to 0 mm s^{-1}. Roberts & Rowe (1985) have already shown that changes in derived Heckel indices can occur as a result of increasing constant punch. On a high-speed rotary press, the large range in speed which occurs during each compression event confounds the use of the Heckel model. Mean yield pressures for the studied materials really do not appear constant after particle rearrangement, and the practice of assigning a single value to it appears to be inappropriate. Compaction simulators programmed to deliver saw-toothed displacement-time traces have the advantage of constant punch-speed and may be a better choice for characterizing a formulation by Heckel indices and the strain-rate sensitivity index. On the other hand, they also carry the liability of not being a realistic representation of tableting on a rotary tablet press and may not be predictive of scale-up behaviour.

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References

Armstrong, N. A., Palfrey, L. P. (1989) The effect of machine speed on the consolidation of four directly compressible tablet diluents. J. Pharm. Pharmacol. 41: 149–151

Celik, M., Marshall, K. (1989) Use of a compaction simulator system in tabletting research. Drug Dev. Ind. Pharm. 15: 759–800

Charlton, B., Newton, J. M. (1984) Theoretical estimation of punch velocities and displacements of single-punch and rotary tablet machines. J. Pharm. Pharmacol. 36: 645–651

David, S. T., Augsburger, L. L. (1977) Plastic flow during compression of directly compressible fillers and its effect on tablet strength. J. Pharm. Sci. 66: 155–160

Dwivedi, S. K., Oates, R. J., Mitchell, A. G. (1991) Peak offset times as an indication of stress relaxation during tableting on a rotary tablet press. J. Pharm. Pharmacol. 43: 673–678

Heckel, R. W. (1961a) Density-pressure relationships in powder compaction. Trans. Metall. Soc. A.I.M.E. 221: 671–675

Heckel, R. W. (1961b) An analysis of powder compaction phenomena. Trans. Metall. Soc. A.I.M.E. 221: 1001–1008

Oates, R. J., Mitchell, A. G. (1990) Comparison of calculated and experimentally determined punch displacement on a rotary tablet press using both Manesty and IPT punches. J. Pharm. Pharmacol. 42: 388–396

Rees, J. E., Rue, P. J. (1978) Time-dependent deformation of some direct compression excipients. J. Pharm. Pharmacol. 30: 601–607

Reir, G. E., Shangraw, R. (1966) Microcrystalline cellulose in tableting. J. Pharm. Sci. 55: 510–514

Ridgeway-Watt, P. (1988) Tablet Machine Instrumentation in Pharmaceutics. Ellis Horwood Ltd, Chichester, pp 305–306

Roberts, R. J., Rowe, R. C. (1985) The effect of punch velocity on the compaction of a variety of materials. J. Pharm. Pharmacol. 37: 377–384

Roberts, R. J., Rowe, R. C. (1986) The effect of the relationship between punch velocity and particle size on the compaction behaviour of materials with varying deformation mechanisms. J. Pharm. Pharmacol. 38: 567–571

Walter, J. T., Augsburger, L. L. (1986) A computerized force/displacement instrumentation system for a rotary tablet press. Pharm. Tech. 10: 26–34