RESEARCH ARTICLE

Effect of repeated compaction of tablets on tablet properties and work of compaction using an instrumented laboratory tablet press

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Abstract

The repeated compaction of Avicel PH101, dicalcium phosphate dihydrate (DCP) powder, 50:50 DCP/Avicel PH101 and Starch 1500 was studied using an instrumented laboratory tablet press which measures upper punch force, punch displacement and ejection force and operates using a V-shaped compression profile. The measurement of work compaction was demonstrated, and the test materials were ranked in order of compaction behaviour Avicel PH101 > DCP/Avicel PH101 > Starch > DCP. The behaviour of the DCP/Avicel PH101 mixture was distinctly non-linear compared with the pure components. Repeated compaction and precompresion had no effect on the tensile fracture strength of Avicel PH101 tablets, although small effects on friability and disintegration time were seen. Repeated compaction and precompresion reduced the tensile strength and the increased disintegration time of the DCP tablets, but improved the strength and friability of Starch 1500 tablets. Based on the data reported, routine laboratory measurement of tablet work of compaction may have potential as a critical quality attribute of a powder blend for compression. The instrumented press was suitable for student use with minimal supervisor input.

Introduction

Tablets account for >70% of all administered pharmaceutical solid dosage forms, based on low cost and ease of manufacture. Despite extensive study, the cause of many observed manufacturing problems remains hard to identify and key relationships between compression mixture and excipient properties, and tablet Critical Quality Attributes, remain hard to identify. The objective of this research was to investigate the effects of repeated compaction and precompresion on tablet “work of compaction” measurements, and to determine the impact of precompresion on tablet properties, using an instrumented laboratory tablet press.

The ability of a material to absorb work during the compaction process has a significant impact on tablet properties; in general the more work done on a material during compaction, the more compressible it is. Measurement of the work of compaction requires an accurate system for recording both punch position and punch force. The measurement of punch position on a tablet press was first reported by the group of Higuchi¹ ². Use of punch position measurements to calculate work of compaction and characterize compressibility was first proposed by de Blaey³ ⁴ who undertook a series of calculations to arrive at the net work of compaction for the tablets produced. This was done by compacting each tablet twice, and deducting the work done during the second compression from the work done in the first compression in an attempt to take into account the elastic properties of the tablet. A number of subsequent studies of the impact of compression force and material properties on work of compation have since been reported, but the study of work of compaction has been limited as result of the technical difficulties of the technique and the complexities of understanding the data.

Single punch tablet machines cannot be used to study precompresion. Most modern production rotary tablet presses have the capability to deaerate the powder bed and extend the duration of the compaction event using precompresion, but the use of rotary press for research purposes is expensive in terms of lost production time, and materials. Precompresion is widely believed to improve tablet strength and reduce the incidence of capping – a major manufacturing problem, although it is also known to cause capping in some products. Vezin et al.⁶ used an instrumented modified rotary press to measure the dependence of tablet tensile strength on lubricant mixing time, pre- and main compression pressure. Vezin et al.⁶ evaluated pre-compression of Avicel® and Emcompress® and also a paracetamol granulation at pre-compression pressures of 13 and 26 MPa, using a variety of tablet toolings. Repeated compaction on a single punch tablet machine was studied by Armstrong et al.⁷, who measured upper punch force during 13 successive compactions at constant upper punch position on Avicel, compressible starch, magnesium carbonate, lactose and phenacetin. The interval between compactions ranged from 1.3 s to 5 min. The compaction pressures used were 17–109 MPa.

Farber et al.⁸ proposed a “unified theory of compaction” based on study of the effect of repeated compaction...
(dry granulation) on tablet strength following roller compaction. This suggests that the work performed on a material during roller compaction is irreversible, and that the first compaction event (dry granulation or roller compaction) reduces tablet compaction capacity available for the main compaction event.

The simple design and capability of the instrumented laboratory tablet press make it straightforward to generate and capture work of compaction measurements, including precompaction. The purpose of this study was to determine the effect of precompensation and repeated compaction on tablet properties and tablet work of compaction as part of a student project. Compaction profiles using up to three compaction events were used to evaluate the effect of pre-compensation (1/3 main force) and repeated compaction (1, 2 and 3 times) on tablet tensile strength, friability and disintegration time for four materials – Avicel PH101®, dicalcium phosphate dihydrate (DCP) fine powder, a 50/50 mixture of Avicel PH101 and DCP, and Starch 1500®.

Materials and methods

Microcrystalline cellulose, (Avicel® PH101) (FMC), dicalcium phosphate dihydrate (DCP) (Calipharm PH970E, Albright & Wilson Ltd., West Midlands, UK), and Starch 1500® (Colorcon, Dartford, UK) were used as received. The Avicel PH101/DCP binary mixture was prepared by mixing equal amounts of each component in a Copley Cone Mixer (Type AR400 Serial NR. 39407) for 3 min.

Compaction experiments were conducted using the instrumented laboratory tablet press (Model GTP-1, Gamlen Tableting Ltd, Nottingham, UK), a portable computer-controlled laboratory tablet press with a tablet breaking strength function. All compaction studies were performed under force control in the "fixed load" mode of the tablet press, using a displacement speed of 60 mm/s and a tablet die diameter of 6 mm, in which the compaction force selected by the user is applied using the standard V-shaped compression profile at 1 mm/s. The maximum punch force is 5 kN, with continuous monitoring of punch position to a resolution of 1–2 μm. The data collection frequency range available to the user is between 50 and 2000 Hz; in this work a data collection frequency of 200 Hz was used.

A powder sample of 100 mg or 130 mg in the case of dicalcium phosphate dihydrate (to maintain a tablet thickness of ~3 mm) was weighed directly into the die which was placed into the tablet press. The target compression load was selected (100–500 kg, at 100 kg intervals), and the tablet was compacted. About 6 mm, flat-faced cylindrical compacts were produced using the press’s standard V-shaped compaction profile. Pre-compensation using different compression loads was achieved using the ‘‘single compaction’’ setting, followed by ejection. Measurements of ejection stress were recorded but are not reported here. The interval between the precompensation event and the main compaction was 1 min. After a preliminary study, a precompensation pressure of one-third of the main compaction pressure was adopted for the pre-compensation studies.

For repeated compactions the number of compactions mode was set to two for a double compaction event and to three for three compactions. The interval between repeated compactions is ~1.5 s. The GTP-1 generates a real-time force–displacement graph with a data record of the maximum compression load and subsequent ejection force measurements for each compaction; all data are exported into Excel® for subsequent analysis. In addition, individual tablet thickness and weights were measured. A minimum of six tablets each were produced for each study condition.

Based on the work of de Blaey a short study of the effect of recompaction at constant compaction pressure was undertaken. The purpose of this was to check de Blaey’s assumptions about the need for a second compaction (which has not been universally adopted by other workers), and the conclusions he drew from his results. Use of the repeated force function at high loads on the GTP-1 results in a small overshoot of the compaction force set point caused by the rigidity of the tablet during the second or subsequent compaction. To better understand the impact of repeat compaction, a further set of second compactions was performed in which the force setting was adjusted to ensure that force applied was exactly the same as used for the first compaction. At a force level of 500 kg, the compaction force set point selected for the second compaction was 460 kg; this had been determined empirically to give the same peak force for the second compaction as the first compaction at a set point of 500 kg.

De Blaey’s data analysis states that the work done on the second compaction should be deducted from the work done on the first compaction. The reasons for this are not entirely clear from the text. However, the data generated in this study clearly show (see Results) that the work done on the second compaction only generates elastic deformation on the formed tablet, and results in very little, if any, irrecoverable work on the tablet. As a result, in this study the work of elastic recovery during decompression of the tablet in the die was calculated and deducted from the total area under the triangle formed by dropping a perpendicular from the peak compression force (Figure 1). The work done on the compaction system itself (punch, load cell and drive system) was measured using a steel tablet and included in the displacement calculation but no other corrections to the work of compaction were made.

Tablet fracture strength was measured at a test speed of 1 mm/min using the fracture test mode of the GTP-1. The fracture stress values were converted to tensile fracture stresses using Equation (1) from Fell and Newton where σ1 represented the tensile fracture strength of the tablet, P is the breaking load and D and t are diameter and thickness, respectively.

\[ \sigma_1 = \frac{2P}{\pi Dt} \]  

(1)

Tablet friability was measured on samples of six tablets compacted at target compression pressures of 35, 105 and 165 MPa according to British Pharmacopoeia standards using an Erweka Gmbh friability (Type: TAP, NR: 16170 Germany) for 100 rotations.

\[ \text{Friability} \% = \left( \frac{W_0 - W}{W_0} \right) \times 100 \]  

(2)

Figure 1. Analysis of a tablet force–displacement curve.
Loose dust and particles were brushed off individual tablets with a soft brush and initial tablet weights recorded as $W_0$, final tablet weights after 100 rotations were recorded as $W_T$. Tablet disintegration testing was in accordance with the British Pharmacopoeia using a conventional bottom-meshed 6 unit per sample rack system without discs.

**Results and discussion**

A preliminary compaction study was performed at a range of precompression pressures to select the precompression pressure to be used in the main experiment. The effect of precompression at one-third, one-quarter or one-half of the main compaction pressure on tablet tensile fractures stress was measured at 165 MPa. The tablets with the one-third precompression load ratio appeared to show least variability, and so this ratio was selected for the main experiment.

Tablets were produced and evaluated with the GTP-1 at various compression loads using the four different modes of compaction – single, pre-compression, double and triple compression – and evaluated for tensile strength, friability and disintegration time using the test protocols outlined earlier. Typical force–displacement curves generated are shown in Figure 2 for precompression, and for precompression and main compression events superimposed. One striking feature of this plot is the substantial shortening of the main compaction event which is seen following precompression. This consequence of the use of precompression is largely unrecognized and unreported, and may in part account for the limited effectiveness of precompression as a production technique; precompression is well known for making some formulations compress worse rather than better, and the decrease in compaction time resulting from pre-compression may adversely affect the product.

The effect of precompression on the work of compaction of Avicel PH101 and Starch 1500 is shown in Figure 3, which compares the work of compaction of a single compaction with the sum of the precompression and main compaction areas for a tablet made using precompression. There is no indication from these data that dividing the compaction event into pre-compression and main compression results in more work being put into the tablet for these materials. The work of compaction measured for Avicel PH101 was much higher than that for Starch 1500, data which are consistent with the well-known compression characteristics of microcrystalline cellulose and pregelatinized starch.

The effect of precompression on the work of compaction of Avicel, Avicel/Calipharm and Calipharm is seen in Figure 4. The work of compaction of Calipharm is <50% of that of Avicel at all compaction pressures. The increase in work of compaction resulting from the addition of 50% Avicel to the Calipharm is substantially less than would have been expected if the mixture effect was simply additive, and implies that mixtures of poorly compressible materials with Avicel respond in a distinctly nonlinear fashion. This observation has important implications for the development of poorly compressible materials and will be further investigated.

The data for the repeat compactions at constant pressure are shown in Figure 5. To the best of our knowledge this is the first time that such data have been reported. In most cases, although
work is expended on the tablet during recompression, this results in a minimal change in tablet dimensions (and therefore minimal irrecoverable work done). The only material for which recompression resulted in a significant reduction of tablet thickness was dicalcium phosphate; the dimensional changes for Avicel and Avicel/DCP were very small (a few microns) and there was no change at all for Starch 1500. Repeated compaction did result in increases in tablet strength in the case of Starch 1500, which indicates that the second compaction does change material properties.

One of the purposes of in-die measurements during compaction, such as work of compaction and the evaluation and use of compaction equations, as opposed to out-of-die measurements such as hardness and friability, is that useful data can be generated on a sample whether or not the tablet formed can be ejected. For example, the low work of compaction of dicalcium phosphate powder measured in-die is a strong indicator that the material is very poorly compressible. This can be seen even if no coherent tablet is produced. Furthermore the extensive work done on Starch 1500 during repeat compaction measured in-die is a clear indicator that the original compaction process was incomplete and that further work can be done on the material. The work of Armstrong on the impact of compaction interval on the consolidation of compressible starch supports this hypothesis. It is also possible that excessive remaining compaction potential is linked to capping propensity.

The ability to characterize materials without necessarily being able to form a coherent compact would also be extremely useful in situations such as salt selection, and polymorph evaluation. It enables information on compaction properties to be obtained using a single compaction event which in extremis only requires 5–10 mg of material. Further applications could be for excipient evaluation; many excipients do not form tablets in the pure state but still have an effect on tablet compaction. Evaluation of excipient compaction properties and consistency from batch to batch could be useful if linked to tablet Critical Quality Attributes.

Figure 6 shows the effect of routine compaction on the tensile fracture stress of Avicel PH101® tablets; no significant change in tensile fracture stress was seen. The tensile fracture stress data generated on Avicel PH101 was consistent with the results of Vezin et al. The precompression force used by Vezin was very low compared with this study. Even at the higher levels of repeated compaction pressures used in this study, which slightly exceeded the original compaction pressures, no increase in tablet tensile fracture stress was seen on recompression although some increases in disintegration time, and reductions in friability.
were observed. Figure 7 shows the effect of repeated compaction on the tensile fracture stress of DCP/Avicel tablets. Pre-compression had no effect on tablet strength but a small increase in tablet fracture stress was seen with repeated compaction.

The effect of repeat compaction on the tensile fracture stress of DCP alone is seen in Figure 8. The tablets produced were of very poor quality, and a proportion capped on ejection. On the basis of the available data, repeated compaction reduced tablet fracture stress. Bearing in mind the poor compressibility of this material, this is not entirely surprising. Using a low precompression pressure, Vezin et al. found no improvement in tensile strength with use of low levels of precompression for DCP. In this study, small increases in tablet strength were seen with repeated compaction of 50:50 DCP/Avicel mixtures using much higher precompression (or repeated) pressures. This may indicate that the impact of precompression is force dependent, and that some benefit in compressibility may be seen by using high precompression forces.

The effects of repeated compaction on the tensile strength of Starch 1500 tablets are seen in Figure 9. Starch 1500 tablets made at low compaction pressures fell to pieces on ejection. Some improvement in tablet strength with repeated compaction was definitely observed as it produced tablets of adequate strength for handling. This could be as a result of work-hardening on repeated compaction; based on these data, formulations based on Starch 1500 may benefit from the use of precompression during tablet manufacture.

The effects of repeated compaction on the friability of Avicel and DCP/Avicel tablets are seen in Table 1. Both pre-compression and repeated compaction significantly reduced the friability of Avicel tablets, despite the lack of effect of repeat compaction on tablet tensile fracture stress. Based on this observation, repeated compaction may have effects on tablet properties which are not apparent from work of compaction and tensile fracture stress measurements.

Friability of DCP/Avicel tablets was also reduced by both pre-compression and repeated compaction. The friability reductions were quite substantial, and indicative of additional robustness as a consequence of repeated compaction. Tablet friability is an important tablet quality attribute during packaging and transport,
so it is possible that repeated compaction might produce an improvement in tablet quality. The data generated here are consistent with manufacturing expectations.

The impact of repeated compaction on tablet disintegration is seen in Table 2. Repeated compaction produced increases in the disintegration times of Avicel tablets, but the effect was relatively small. DCP/Avicel showed increased tablet disintegration time with repeated compaction, which could be sufficient to cause problems in manufacturing.

These data were generated, in part, during a student project on compaction. The GTP-1 was found by the student to be easy to use and suitable for rapid generation of data using small amounts of material. The training requirements were minimal and the machine performed reliably which enabled the data to be generated accurately on an instrumented press requiring minimal operator training.

**Conclusion**

The large reduction in duration of the main compaction event after a material has been pre-compressed has been noted as a possible cause of the unwanted material-dependent effects during tablet manufacture. Repeated compaction to constant compaction pressure resulted in no change to the dimensions of Starch 1500 tablets, very small changes to Avicel PH101 and Avicel PH101/ dicalcium phosphate tablets, and small changes in the dimensions of dicalcium phosphate tablets. The only compensations needed for work of compaction calculations are for the elastic recovery of the tablet during the compaction event, and the compliance of the compaction system. Laboratory based measurement of in-die compaction behaviour may offer a new technique for drug and excipient assessment on a batch to batch basis. Starch 1500 showed increases in tabletability with repeated compaction, which correlated with measurable increases in tablet work with second and third compactions. In contrast, dicalcium phosphate dihydrate powder showed reduced tensile fracture stress with repeated compaction, with no further work of compaction on repeated compaction.
compaction. A 50/50 mixture of dicalcium phosphate dihydrate powder with Avicel showed intermediate properties, but was much closer in behaviour to the pure dicalcium phosphate dihydrate, implying a non-linear relationship between Avicel content and tabletability. Precompression and repeated compaction had minimal effects on the properties of Avicel PH101 tablets. The instrumented laboratory tablet press was found to be simple to use, suitable for student or laboratory use, and capable of accurate measurement of force and displacement data during the compaction event.

Declaration of interest

Dr Gamlen is owner of Gamlen Tableting Ltd who manufactures the Gamlen Tablet Press GTP-1. No other relevant interests.

References


