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Unified compaction curve model for tensile strength of tablets made by roller compaction and direct compression

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Abstract

A model that describes the relationship between roller-compaction conditions and tablet strength is proposed. The model assumes that compaction is cumulative during roller compaction and subsequent granule compaction, and compact strength (ribbon and tablet) is generated irreversibly as if strength is controlled by plastic deformation of primary particles only. Roller-compaction is treated as a compaction step where the macroscopic ribbon strength is subsequently destroyed in milling. This loss in strength is irreversible and tablets compressed from the resulting granulation are weaker than those compressed by direct compression at the same compression force. Roller-compacted ribbons were produced at a range of roll forces for three formulations and subsequently milled and compacted into tablets. Once the total compaction history is taken in account, the compaction behavior of the uncompacted blends and the roller-compacted granules ultimately follow a single master compaction curve—a unified compaction curve (UCC). The model successfully described the compaction behavior of DC grade starch and formulations of lactose monohydrate with 50% or more microcrystalline cellulose, and may be more generally applicable to systems containing significant proportions of any plastically deforming material, including MCC and starch.
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1. Introduction

Roller-compaction, also known as dry granulation, creates a granulated blend by compressing a powder mixture between two rotating rolls to form a "ribbon", which is subsequently milled. Roller-compaction is used to agglomerate powders in a variety of industries, including mining, minerals processing, food, chemical, and specialty chemicals. Operating variables may include feeder speed, roll type, and dimensions, roll speed, roll gap, and roll "force" (i.e. force applied to rolls). The roll force is usually controlled via hydraulics and hydraulic pressure is often used as a substitute for the roll force (Kleinebudde, 2004).

In the pharmaceutical industry, roller-compaction is frequently used to improve the handling properties of powders, especially where the active ingredient is not stable in the presence of moisture, and therefore cannot be wet granulated. The formulation components are typically pre-blended before being added to the roller-compactor feed hopper. After roller-compaction, the ribbon is milled into granules, and undergoes additional blending and lubrication before being compressed into tablets. Generally, roller-compaction is considered to be a robust process provided that there are no issues with segregation or poor compactability of the granulation.

When the formulations are roller-compacted (RC) and milled, the resulting tablets often do not develop as much strength as tablets made by direct compression (DC) of the initial (ungranulated) blend. This is usually referred to as a "loss of compactability" or "reduction in crushing strength" and has been reported by several workers (Kochhar et al., 1995; Bultmann, 2002; Freitag and Kleinbudde, 2003).

The concept of a "rework potential" has been proposed in the literature as an empirical method to describe the magnitude of the reduction in compactability (Malkowska and Khan, 1983). The rework potential is the ratio of the areas under the

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roller-compacted compression curve compared to the original DC compression curve. Although the rework potential quantitatively describes the relative loss of strength, it does not predict the loss of compactability for RC blends. As a result, development of a roller-compacted product usually includes extensive investigation of the effects of roll force, speed, and roll gap on ribbon and granule properties, and how these properties subsequently affect the final tablet properties. Typical characterization includes ribbon density, ribbon tensile strength, ribbon porosity, granule size distribution, granule porosity, tablet strength and tablet porosity.

Currently, there are no physical or phenomenological models that can quantitatively predict the loss of compactability for RC blends. In this paper, we focus on developing a relationship between roller compaction and tablet compaction behavior and propose a tool that quantitatively describes this relationship for blends of lactose monohydrate and microcrystalline cellulose (MCC).

2. Unified compaction curve (UCC) model

2.1. Underlying considerations

On a micro-scale, primary particles experience deformation and "interlocking" which confer macroscopic strength to the compact (either tablet or ribbon). When the ribbon is milled, its macroscopic strength is destroyed, but the deformation of primary particles is largely unaffected in the resulting granules. Granules must "remember" the compaction step experienced during RC, because this is how the granules were created. When these granules are compressed into tablets, it is logical to assume that the primary particles continue to deform and interlock as compaction pressure increases. This additional deformation and interlocking confers macroscopic strength to the tablet. We propose that compaction of RC granules into tablets can be considered as a continuation on the micro-scale of the compaction experienced during RC. Thus the deformation behavior of the RC material during tablet compaction is directly connected to the previous deformation state of the particles.

The deformation state of the particles depends on the magnitude and path of the stress they experience. It should be independent of the consolidation method if the stress state path experienced by the material is similar. There are strong similarities between roller compaction and die compaction. They both compress powder in a confined space by mechanical force. Roller-compaction creates ribbons from the initial blend by compressing the particles between two rotating rolls—this is similar to unconfined uniaxial compression (see Fig. 1a). Die compaction is a confined uniaxial compression (see Fig. 1b). There are hydrostatic pressure (normal stress) and deviatoric (shear) stress involved in both processes. The major difference between the roller and die compaction is that the ratio of shear to normal stress is somewhat higher in roller compaction. However, because the hydrostatic pressure (normal stress) is largely responsible for the consolidation, i.e. densification or volume reduction, the impact of the difference in shear stress on the properties of the compact/ribbon between the two operations is negligible if the normal stress is similar. At lower consolidation pressures these two processes can be considered to have similar stress states path. As a result, material created either by DC (slugs) or RC (ribbons) at relatively low consolidation pressure should have similar properties. This was recently experimentally confirmed (Zinchuk et al., 2004), where the strength and density of ribbons produced by RC were very similar to slugs produced by die compaction.

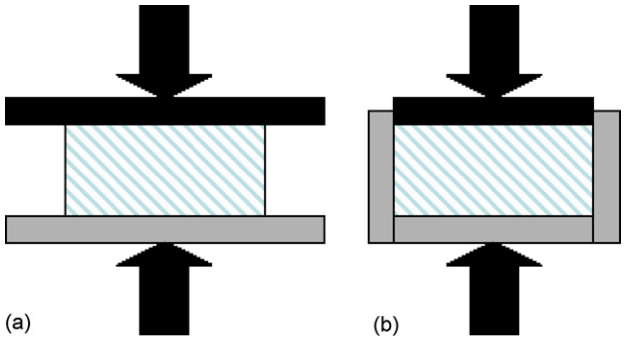

Fig. 1. (a) Unconfined uniaxial compression and (b) confined uniaxial compression.

Finally, when the RC granules are compacted into tablets, the resulting tablets do not develop as much strength as tablets made by direct compression of the initial (ungranulated) blend. Currently there are no models that can predict either the magnitude of tablet strength as a function of compaction force, i.e. the compaction curve of an RC blend, or the magnitude of the strength "deficiency" of compacted RC granules versus the initial blend. We propose that this strength "deficiency" is associated with the strength of the ribbon that is lost irreversibly during milling.

2.2. Unified compaction curve (UCC)

To develop a relationship between roller compaction and tablet properties, we propose the following phenomenological assumptions:

- Tensile strength behavior of tablets depends on the cumulative compaction of primary particles during roller compaction and tabletting.
- The process that generates tensile strength is irreversible.
- Milling of the ribbon does not affect the compaction state of primary particles in the resulting granules but destroys tensile strength generated during RC.

We propose that once the total cumulative compaction history is considered, the compaction behavior of the dry blends and the roller-compacted granules should follow a single master compaction curve—a "unified compaction curve" (UCC). This is shown schematically in Fig. 2. Compaction during roller-compaction follows the uncompacted blend curve in Fig. 2 to the point corresponding to the tensile strength of the ribbon, T_{RC}, which is attained by compressing the blend to the pressure

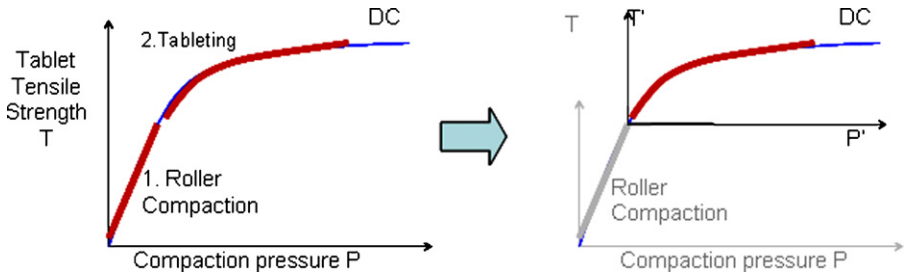

Fig. 2. Proposed relationship between DC and RC compaction curves.

between the rolls, P_{RC}.[2] After milling, a second compaction step occurs, this time of the roller-compacted granules to generate a tablet. This second compaction step commences at the endpoint of the roller-compaction step, and continues to follow the original compaction curve of the uncompacted blend. When plotting tablet tensile strength versus compaction pressure made from roller-compacted granules, only the second portion of this curve is plotted (see right side of Fig. 2). This is equivalent to moving the origin of the tablet compaction curve to P_{RC} and T_{RC} after the roller compaction. If the compaction curve curves toward the x-axis, the tablet tensile strength, T', is smaller than that of a DC tablet compressed at the same tabletting pressure, P'.

In effect, we are assuming that compaction of the roller-compacted granules to form tablets is identical to compaction of the primary particles, at least at compaction pressures in excess of the roller compaction pressure. This implies that the primary particles deform plastically and irreversibly, and the magnitude of deformation is controlled solely by the applied pressure. We ignore any other effects such as rearrangement or elastic recovery, and do not consider any dependence of tablet strength on granule morphology, packing, and structure. These factors are likely to be significant at lower compaction pressures, but we assume that they have minimal influence at typical pressures required to produce pharmaceutical tablets (approximately 200–300 MPa). Additionally, we recognize that the above approach will only be applicable to formulations containing significant amounts of a plastically deformable excipient, e.g. MCC or starch. This is discussed in more detail in Section 5.3.

2.3. Modeling the compaction curves

In order to quantify these concepts, we need a quantitative expression for the compaction curve of the uncompacted blend. We use an empirical relationship developed by Leuenberger (1982) to describe the tensile strength of tablets, T, formed at a compaction pressure, P:

$$T = T_{max}(1 - e^{-\gamma\rho P}) \quad (1)$$

where ρ is the relative density of the compact (ratio of compact density to theoretical density). T_{max} is the maximum tensile strength of a compact, extrapolated to $P = \infty$ (or $\rho = 1$). A high T_{max} value means that the powder can be easily compacted and will develop strength even at low compaction pressures. The pressure susceptibility, γ is a constant for each formulation and is a measure of the compactability or volume reduction behavior and is also related to Heckel analysis (Leuenberger, 1982).

The typical compaction pressures of interest in pharmaceutical tablet manufacture are 200–300 MPa. In this range of pressures, tablet density can often be considered to be approximately constant (we will experimentally verify this assumption later). Since γ is also constant for each formulation, Eq. (1) then can be simplified:

$$T = T_{max}(1 - e^{-bP}) \quad (2)$$

where $b = \gamma\rho$. Using Eq. (2), the value of T_{max} and b can be determined for each formulation from the DC compaction curve of the powder blend.

As discussed above, the compaction curve of granules produced by milling a ribbon produced at roll pressure P_{RC} is determined by translating the origin to the point (P_{RC} and T_{RC}). Thus, the granulation compaction curve is described by Eq. (2), with $T' = T - T_{RC}$ and $P' = P - P_{RC}$, where T' is the tensile strength of tablets produced from RC granules at tablet compaction pressure P':

$$T' + T_{RC} = T_{max}(1 - e^{-b(P' + P_{RC})}) \quad (3)$$

Noting that

$$T_{RC} = T_{max}(1 - e^{-bP_{RC}}) \quad (4)$$

Eq. (3) can be simplified to

$$T' = T_{max}(e^{-bP_{RC}} - e^{-b(P' + P_{RC})}) \quad (5)$$

This approach separates the material properties (T_{max} and b) from the process parameters (P_{RC} and P'). This allows the effects of formulation and processing parameters to be probed independently and the separate contributions of the roller compaction and tabletting behavior to be analyzed.

3. Experimental

Three formulations were studied, differing in the ratio of microcrystalline cellulose (FMC Avicel PH102) to lactose monohydrate (Foremost Farms, grade 312). A3:L1 represents the formulation with a MCC:lactose ratio of 3:1. Each formulation contained 3% croscarmellose sodium and 1% magnesium stearate.

[2] Note that this is actual compaction pressure (compressive stress) between the rolls and not the hydraulic pressure setpoint.

Table 1
Composition of formulations

Formulation	Avicel PH102 (%)	Lactose monohydrate (%)	Intergranular MgSt (%)	Extragranular MgSt (%)	CCNa (%)
A3:L1	72	24	0.5	0.5	3
A1:L1	48	48	0.5	0.5	3
A1:L3	24	72	0.5	0.5	3

Data from a factorially designed roller-compaction study that explored some fixed combinations of formulations and processing conditions was used to test the UCC model. Some of the combinations were repeated as a part of the study. MCC, lactose, croscarmellose, and 0.5% magnesium stearate were blended in a V-blender at 45 rpm for 5 min before being roller compacted on a Alexanderwerk WP120 (40 mm knurled rolls, single flight feed screw). Typical batch size was approximately 2 kg. Roll hydraulic pressure was set at either 40, 60 or 80 bar. To eliminate potential changes in tensile strength due to roll speed and roll gap, those parameters were fixed. The roll speed and the feed screw speed were fixed at 5 and 19 rpm, respectively.

Tensile strength of the roller-compacted ribbon was measured with a TA-XT2i Texture Analyzer (Stable Micro Systems) using three-point bend test (e.g. Rowe and Roberts, 1996; Bika et al., 2001). For the test, a whole piece of ribbon approximately 3 cm long along the rolling axis was cut into three equal bands along the rolling direction. The three-point bend test was conducted for each band, and the weighted average of the strength was calculated. The probe applying the force at the upper side of the ribbon travelled at 0.1 mm/s. The instrument was equipped with a 5 kg load cell and 0.1 g sensitivity. The load (measured under compression) versus displacement curve was recorded at an acquisition rate of 250 points/s. The approximate distance between fulcrums was 20 mm. All tests were performed inside a chamber controlled at ambient temperature and 30% relative humidity.

The ribbons were milled using the rotary fine granulator at 100 rpm with a 1.60 mm wire primary granulator screen and a 0.63 mm wire secondary granulator screen. Some ribbons were also milled using a co-mill at 980 rpm with a 40G screen. Particle size distribution of the milled material was measured via laser diffraction using Sympatec particle size analyzer equipped with a dry powder feed system. For dispersing the material, a pressure of 1 bar was used. An additional 0.5% extra granular magnesium stearate was added and blended in a Turbula mixer (100 rpm) for 3 min. The blending batch size of 50 g and the blending conditions were selected based on a preliminary development work. Tablets weighing 300 mg were compressed at several compaction pressures between 50 and 360 MPa using an MTS Alliance RT/50 and 13/32 in. plain round flat tools. Tensile strength was calculated from the tablet geometry and crush strength measurements (Key International Hardness Tester). To extend the range of compaction pressures, selected lubricated roller-compacted granules were also compressed on a compaction simulator (ESH, Testing Ltd., UK) using a set of 12/32 in. round flat-faced tool over ~50–600 MPa compaction pressure. Tablet density was calculated using tablet weight, thickness, and diameter measurements taken after the compaction using either the MTS or the compaction simulator.

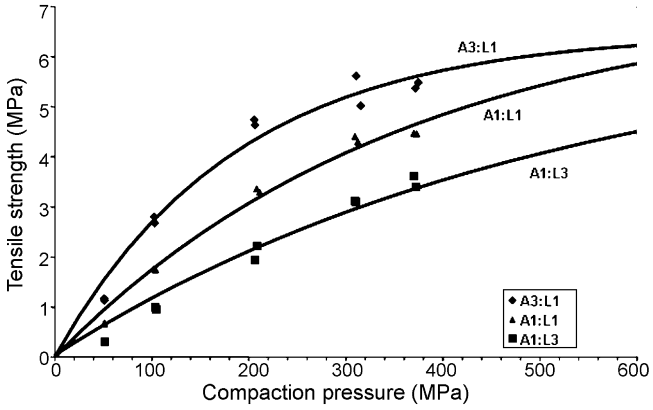

Fig. 3. DC Compaction curves of three MCC–lactose blends. (Solid lines) Fit of Eq. (2), fitted parameters (T_{max}, b) listed in Table 2.

4. Results

Eq. (2) and a commercial spreadsheet package was used to fit the dry blend compaction curves by minimizing the sum of the square of the errors. Results for the three formulations are shown in Table 1. The fitted curves are shown in Fig. 3 and the values of T_{max} and b are summarized in Table 2. Eq. (2) is a good fit for formulations containing at least 50% MCC. For the A1:L3 formulation, the uncertainty in the fitted parameters is large because the available data was essentially linear. More data at higher compaction pressures is required to obtain a good fit for this formulation to the Leuenberger's model (1982) and the proposed UCC model. Therefore this formulation is not considered further in this analysis.

To verify our assumption that the tablet density can be considered approximately constant in the typical industrial compaction pressures, Fig. 4 plots average tablet density as a function of compaction pressure for all three formulations. Tablet density increases rapidly with compaction pressure below 200 MPa. Above 200 MPa, however, the density becomes more or less

Table 2
Fitted T_{max} and b values

Formulation	Avicel PH102 (%)	Lactose (%)	T_{max} (MPa)	b (MPa^{-1})
A3:L1	72	24	6.48	0.0054
A1:L1	48	48	7.24	0.0028
A1:L3	24	72	31.3[a]	0.0003[a]

[a] Compaction data at higher pressures required for this formulation.

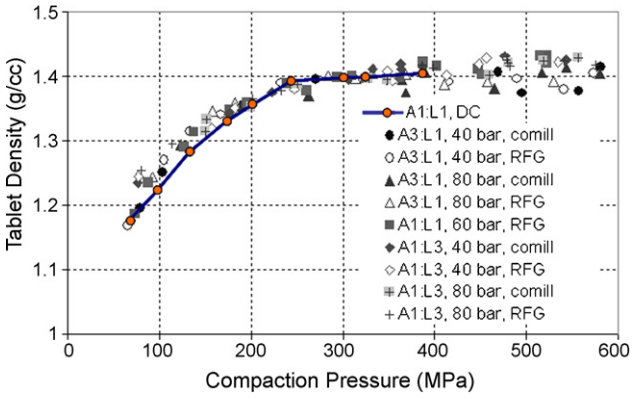

Fig. 4. Relationship between tablet density and compaction pressure for various MCC–lactose roller-compacted granulations.

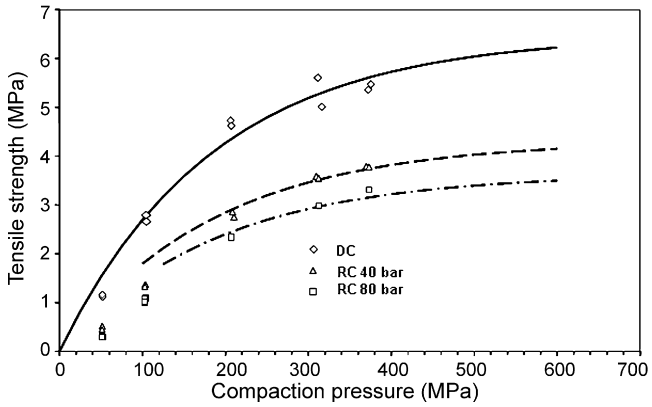

Fig. 5. Prediction of tablet strength for formulation A3:L1 as a function of roller-compaction force. (Solid line) Fit of Eq. (2); (Broken lines) Fit of Eq. (5). Corresponding model parameters are listed in Table 3.

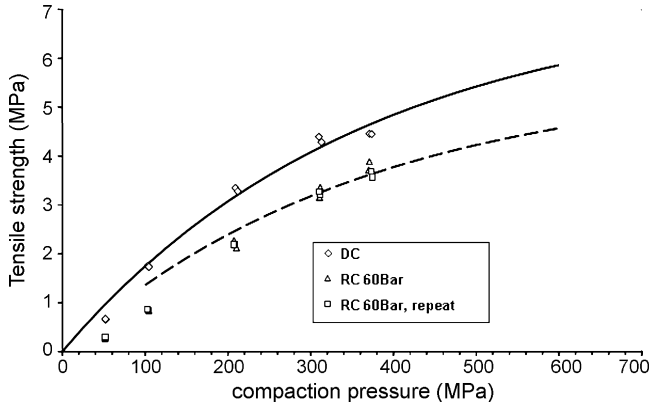

Fig. 6. Prediction of tablet strength for formulation A1:L1 as a function of roller-compaction force. (Solid line) Fit of Eq. (2); (dashed line) fit of Eq. (5). Corresponding model parameters are listed in Table 3 ("repeat" denotes the data for an additional batch run at the indicated conditions).

constant at ~90% of theoretical maximum density, regardless of the MCC–lactose ratio used. Tablet density is unaffected by differences in RC conditions. A representative density curve for a DC formulation is plotted in Fig. 4. It can be seen that it is similar to the density profile of RC blends. Fig. 4 also includes data for granules produced with the rotary fine granulation (RFG) screen and with a co-mill, which produce different particle size distributions. Overall, mean volume particle size ranged from 136 to 390 μm in the study. It can be seen that different particle size distributions do not affect tablet density, even in the increasing density region. Therefore we conclude that density is effectively constant above 200 MPa and application of Eq. (2) to our system is valid above this range.

To create the unified compaction curves, values of P_{RC} corresponding to the applied hydraulic pressure were determined by fitting Eq. (5) to the compaction curves of the RC granulations, using the values of T_{max} and b in Table 2. The fitting was performed by minimizing the sun of the square of the errors in a spreadsheet package using between 3 and 12 data points (depending on the experimental condition) and the constraint that the model must pass through the origin. Only data where tablet density is approximately constant (i.e. RC data above 200 MPa) was fitted. Once the fitted value of P_{RC} was known, the corresponding values of T_{RC} were then computed with Eq. (4). The fitted results for P_{RC} and T_{RC} for each formulation are shown in Figs. 5 and 6 and Table 3. There is good agreement between fitted curves and experimental data above 200 MPa. Below 200 MPa, the data diverges from Eq. (5), as the data does not pass through the origin, presumably because granule rearrangement is important in this region. This region is of little commercial interest as tablets manufactured at such low compaction pressures typically have inadequate strength.

To demonstrate that compaction of RC granules can be modelled as a continuation of the DC blend compaction, the RC data was re-plotted by adding (P_{RC} and T_{RC}) to each (P and T) raw data point, and superimposing them on the dry blend compaction curve. The resulting unified compaction curves are shown in Figs. 7 and 8. The re-plotted roller-compaction data points lie on the DC blend master curve, with the compaction pressure on the x-axis equal to the total cumulative compaction pressure experienced by the material.

Table 3
Pressure offset P_{RC} and strength offset T_{RC} for three roller-compacted blends

Formulation	Roll force (bar)	Normalized roll force (kN/cm)	P_{RC} (MPa)	T_{RC} (MPa)	Average Ribbon strength (kN/cm)
A3:L1	40	3.7	75.4	2.16	1.6
	80	7.4	107.1	2.84	3.1
A1:L1	60	5.5	90.5	1.60	1.9
	60	5.5	91.3	1.61	1.9

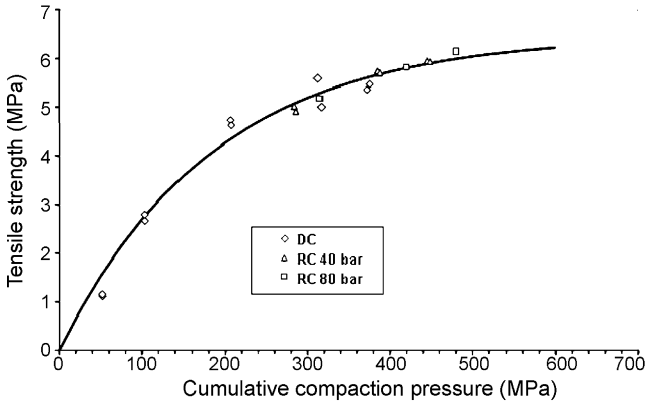

Fig. 7. Unified compaction curve for formulation A3:L1. (Solid line) Fit of Eq. (2) to DC compaction curve.

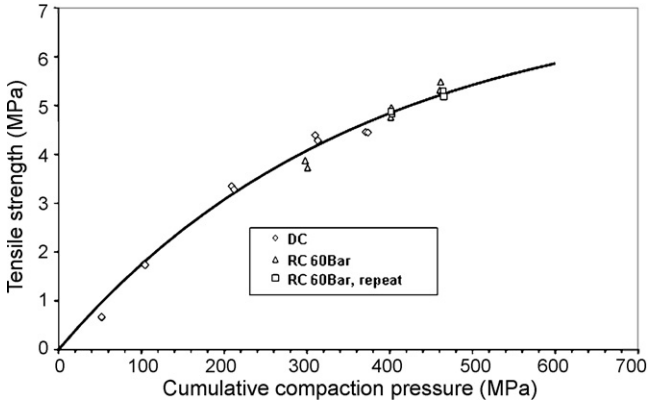

Fig. 8. Unified compaction curve for formulation A1:L1. (Solid line) Fit of Eq. (2) to DC compaction curve ("repeat" denotes the data for an additional batch run at the indicated conditions).

5. Discussion

5.1. Physical meanings of P_{RC} and T_{RC}

P_{RC} represents the stress experienced by a blend during roller compaction, i.e. the actual stress applied by the rollers. Thus, P_{RC} reflects a physical operating parameter and should be independent of the formulation. The P_{RC} values shown in Table 3 agree well with the reported pressures of 50–150 MPa directly measured at the surface of the rolls (Simon and Guigon, 2003).

P_{RC} is closely related to the roll force, a key scale up parameter. Fig. 9 shows P_{RC} plotted against the normalized roll force (hydraulic pressure divided by roll length) for both formulations. Although the compaction profiles of these formulations are different, there is a common linear relationship between P_{RC} and the roll force for both formulations. This supports our hypothesis that P_{RC} represents the stress imposed by the rolls and is independent of formulation, although more data is required to prove this.

T_{RC} represents the strength generated during roller compaction and should be equal to the average ribbon strength. It is important to note that ribbon density varies across the width of the ribbon (Simon and Guigon, 2003) and it is important to use the average ribbon strength when comparing the data with

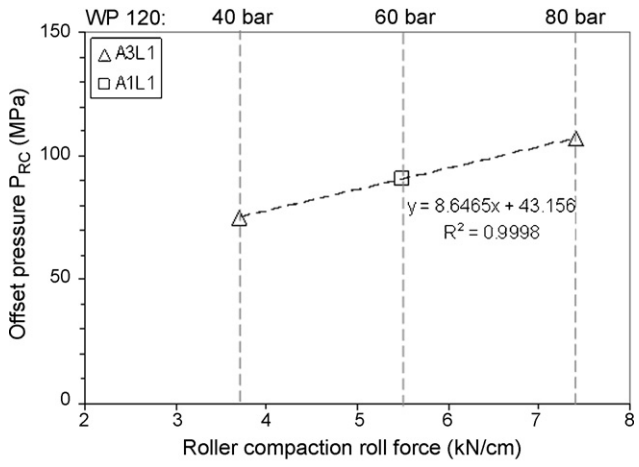

Fig. 9. Relationship between roll force and P_{RC} for two formulations.

the T_{RC} value. Table 3 shows that there is reasonable agreement between T_{RC} and the average ribbon tensile strengths for medium and high roller-compaction pressures, i.e. where the proposed model is applicable.

5.2. Calculating the strength of a tablet made from roller-compacted granules

The utility of the UCC model is that it minimizes the number of process experiments required to determine the loss of tablet compactability due to roller compaction. The model relates RC tablet strength to the corresponding DC compaction curve, the true roll pressure, and the tablet compaction force. The DC compaction–tensile strength curve must be determined experimentally, for example with a compaction simulator. Predictive approaches have been proposed, but they are not yet realized (Dec et al., 2003).

Fitting Eq. (2) to the compaction curve allows one to determine parameters T_{max} and b. Without instrumented rolls, the true roll pressure must be determined empirically using the relationship between ribbon tensile strength and the compaction curve to "calibrate" the roll pressure and the roll force as discussed above. Based on the observed linearity of this relationship, calibration may require only two roller-compaction experiments. We hope that over time a general correlation will be developed or that P_{RC} will be predicted in advance from knowledge of the roller-compactor geometry. In this case, only the DC compaction curve would need to be measured, and this could be done early in development when drug quantities are limited. Once the compaction curve and P_{RC} are known, Eq. (5) can be used to predict the strength of tablets after roller compaction. Prediction of tablet strength from RC granules is only valid above ~200 MPa, where the tablet density is unaffected by compaction pressure.

5.3. UCC applicability to other material systems

Current work has demonstrated that the UCC approach generally works well for 3:1 and 1:1 MCC:lactose mixtures, but does not predict 1:3 mixtures due to the linear compaction curve. The

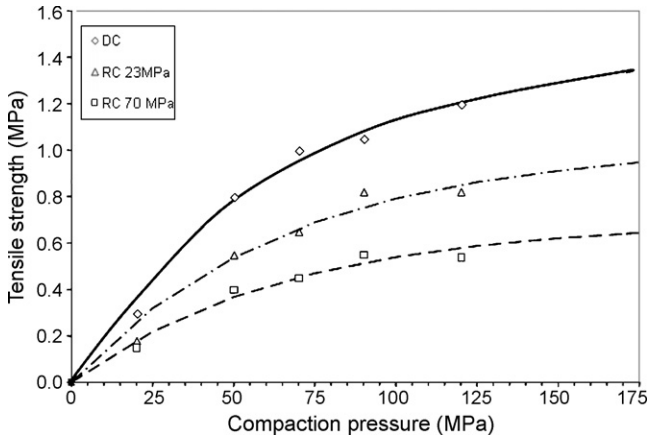

Fig. 10. UCC applied to a starch formulation (data from Malkowska and Khan, 1983). P_{RC} = 23.6 and 48.8 MPa for 23 and 70 MPa roll pressure, respectively. (Solid line) Fit of Eq. (2); (broken lines) fit of Eq. (5).

mechanisms underlying UCC are most likely associated with the ductile compaction properties of MCC (Rowe and Roberts, 1996). For example, unlike most other powders, MCC compaction curves are unaffected by particle size (McKenna and McCafferty, 1982). Since the mechanism(s) controlling the consolidation and cohesion of stronger, brittle lactose monohydrate crystals (Rowe and Roberts, 1996) are probably very different, the UCC approach may not work for mixtures in which not enough MCC is present. This is the most likely reason that the UCC approach did not describe the A1:L3 formulation, which contains only 25% MCC. Alternatively, it is possible that a broader data range is required for the UCC approach to describe the A1:L3 mixture.

The UCC theory can also be applied to DC grade starch. Like MCC, DC grade starch is believed to deform due to plastic deformation (Malkowska and Khan, 1983; Roberts and Rowe, 1996). Literature data for a formulation of 100% DC starch (100–160 μm) compressed directly and after slugging (Malkowska and Khan, 1983) was re-analyzed using the UCC approach. In the original study, 200 mg slugged samples were prepared in a instrumented single punch tablet machine at compaction pressures of 23 and 70 MPa with a short 0.1 s dwell time and an extended dwell time of 15 s. The slugged samples were milled through a 0.04 in. screen and sieved to the original particle size of 100–160 μm. No lubricant was used during slugging or retabletting. Tablet and slug strength was measured using diametrical compression. Full details are provided in Malkowska and Khan (1983).

Fig. 10 shows that starch dry blend (0.1 s short dwell time) can be fitted to Eq. (2) using the same procedure described above with T_{max} = 1.45 and b = 0.0151. The re-compressed data (short dwell time only) can also be modelled using the UCC theory (P_{RC} = 23.6 and 48.8 MPa, respectively).

However, the UCC approach did not describe Malkowska and Kahn's data for samples slugged and recompressed with long dwell time (15 s). It was noted that the shape of the DC blend compaction curve for an extended dwell time differs significantly from the corresponding curve for a short dwell time: it contained a point of inflection and was not consistent with Leuenberger's model (Eq. (1)). Malkowska and Kahn's long dwell time data has no practical relevance since dwell times in commercial production are only a fraction of a second.

The UCC approach was also tried by the authors on three MCC–dicalcium phosphate-based formulations. Dicalcium phosphate is an irregular star-shaped particle and fragments easily under load. The UCC approach was unsuccessful with these formulations, as the actual tablet tensile strengths were higher than the UCC prediction. It is suspected that this is due to preferential breakage of dicalcium phosphate particles during milling of the RC ribbons. This should result in creation of significant amount of new dicalcium phosphate surfaces which will modify the binding properties of the original blend.

Thus, UCC may be applicable to the direct compression materials that deform by plastic deformation, such as DC starch, microcrystalline cellulose (Rowe and Roberts, 1996). UCC may also be applicable to mixtures based on those materials, if the proportion of these materials is sufficiently high to ensure that plastic deformation is the dominant mechanism of deformation and compaction. However, more work is required to understand the underlying physical processes, including plastic deformation and breakage mechanisms, and how these are affected by the formulation composition.

5.4. Implications of UCC for pharmaceutical development

Formulations based on MCC, starch and lactose mixtures are widely used in pharmaceutical industry. Further work is required to determine how applicable the UCC approach is to these combinations, and identify the formulation composition limits that the UCC model can be applied.

For formulations where the UCC model is found to be valid, formulation selection can be simplified. By generating a set of DC master curves for each potential formulation, together with knowledge of the PRC values for the roller-compactor to be used, UCC can be used to predict which formulation(s) will meet tablet strength specification and what maximum RC force(s) should be used. To maximize tablet strength for a roller-compacted product, the UCC model implies that the minimum possible roll force during RC should be used (low P_{RC}) whilst still maintaining adequate granule properties.

More work is required to prove the link between P_{RC} and the actual pressure exerted by the rolls. Fig. 9 shows that P_{RC} and roll force are strongly correlated, and suggests that the relationship is independent of formulation (provided the formulation follows Leuenberger's model). If Fig. 9 is shown to be generally true and formulation independent, then the UCC approach could be used as a scale-up and technology transfer method. First, differences between roller-compactor equipment could potentially be quantified using P_{RC} values at similar roll pressures. Secondly, knowledge of the relationship between the roll pressure and compression stress, tablet strengths manufactured on roller-compaction equipment with different designs and different scales could be predicted in advance. This would be a significant advantage when transferring pharmaceutical products in an international organization.

There will be still a need to perform roller-compaction experiments to characterize granule and ribbon properties (such as flow and strength), assess segregation, evaluate content uniformity, etc. However, once the formulation limitations are known, the UCC approach can be used to determine the effect of RC conditions on final tablet tensile strengths and reduce the number of RC experiments performed during development of roller-compacted pharmaceutical products.

6. Conclusions

The unified compaction curve is a new approach to describe the relationship between roller-compaction conditions and tablet strength. Based on Leuenberger's compaction model (1982), roller-compaction is treated as the first stage of compaction, but the strength is irreversibly destroyed during milling. Tablets compressed from the resulting granulation are weaker than those compressed by direct compression at the same compression force. By considering the total cumulative compaction history, the compaction behavior of 1:1 and 3:1 Avicel to lactose dry blends and the roller-compacted granules ultimately followed a single master compaction curve—a unified compaction curve (UCC). The model successfully described the compaction behavior of 100% DC grade starch and formulations of lactose monohydrate with 50% or more microcrystalline cellulose, and may be more generally applicable to systems containing significant proportions of any plastically deforming material, including MCC and starch. Further work is required to determine how applicable the UCC approach is to these combinations, and identify the formulation composition limits that the UCC model can be applied. Additional experiments using different scales and designs of roller-compactors are required to verify whether P_{RC} is a formulation independent parameter, indicative of the compaction pressure applied during the roller-compaction process.

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