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Predicting Tablet Strength from the Wet Granulation Conditions via the Unified Compaction Curve

Thanh H. Nguyen[a], David A.V. Morton[b] and Karen P. Hapgood[a]*

[a]*Monash Advanced Particle Engineering Laboratory, Department of Chemical Engineering, Monash University, Melbourne, 3800, Australia*
[b]*Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences,Monash University, Melbourne, 3052, Australia*

Abstract

Tablets make up approximately one third of all drug dosage forms which makes tablet manufacture a common process in the pharmaceutical industry. The unified compaction curve [1] is a model developed initially to look at the impact of the roller compaction conditions on the tablet strength. The tensile strength of the tablets made from formulations containing at least 50% microcrystalline cellulose produced at roller compaction pressures were measured and the profiles were collapsed into a single master "unified compaction curve" (UCC). This allowed for the tablet strength to be predicted from the roller compaction condition and formulations and target the required tablet strength criterion set by standards or specifications [1].

The unified compaction curve was applied to investigate the effects of the wet granulation conditions in a 5L Key granulator on the tablet tensile strength. The study was based on a placebo formulation comprising of 50wt% microcrystalline cellulose, 50wt% lactose and a 5w/v% PVP (K90) binder solution. The effects of the liquid level (20-50wt%), wet massing time (0-10 minutes), binder flow rate (130g/min and 280g/min) and impeller speed (150, 285 and 600 rpm) on the tablet strength were explored. Scale-down experiments to a 1L mixer bowl were also conducted. Tablets were produced on a single station carver press with controlled force.

A series of compaction profiles were created to represent the relationship between the tablet tensile strength, compaction pressure and the granulation condition. By fitting the unified compaction curve model to the data using a shifting intercept approach, the profiles exploring each granulation condition collapsed onto a single master curve which predicts the tablet strength as a function of the liquid level, wet massing time or the binder flow rate. Increasing the liquid level and/or wet massing time caused a reduction in the tablet hardness when compressed at the same compaction force, and the reduction is postulated to be

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* Corresponding author. Tel.: +61-3-9905-3445; fax: +61-3-9905-5686.
E-mail address: Karen.hapgood@monash.edu

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proportional to the effective compaction forces experienced during granulation, P_{WGC}. The P_{WGC} data further collapses onto a single master curve which is solely a function of the total number of impeller revolutions. Further characterization of the granules produced at these conditions showed that the UCC intercept parameter, P_{WGC} was inversely proportional to the granule porosity, linking the granule microstructure directly and quantitatively to the tablet strength during compaction. This is a significant finding that will allow formulators to optimize tablet hardness via a simple adjustment to the granulation conditions.

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Keywords: high shear wet granulation; mixer granulation; Liquid level; Wet massing time; Binder flow rate; compaction

1. Introduction

Tablets are a popular form of solid dosage-form for drug delivery, which is not surprising, given that tablets are a more stable dosage-form for the pharmaceutical industry, as well as, the ease of handling and identification by the consumer. As simple as tablets appear to be, a complex relationship exists between the two main steps in tablet manufacture: (1) wet granulation; and (2) tableting, which is not well understood. Currently, case studies on wet granulation and tabletting are carried out with a range of processing conditions to try to define the breadth of tablet strengths produced at each compression force, before selecting a desired set of operating conditions. These case studies are seen in both dry granulation processes using roller compactors, and wet granulation processes using either fluid bed granulators or high-shear mixers. This work will concentrate on the relationship between wet granulation and the final tablet strength to enhance the understanding the effects of the up-stream processes on the final tablet strength and allow for tablet manufacture to be designed more efficiently reducing costs and resources.

In tablet manufacture using dry roller compaction, the effect of the roller compaction pressure on the final tablet strength was investigated by Farber *et al.* [1]. The roller compactors produced a ribbon from various powder formulations containing at least 50wt.% microcrystalline cellulose, prior to milling the ribbon into granules and tableting. The study showed that the tablet strength as a function of the compaction pressure has the same overall profile as the compaction profile produced from direct compaction, in which the raw powder is directly compacted. However the compaction profiles revealed that the maximum tablet strength decreased as the roller compaction force increased (Fig. 1). This trend led Farber *et al.* [1] to propose that the final tablet strength was controlled by the cumulative compaction history of the powder (roller compaction and tableting), which could be predicted from a "Unified Compaction Curve" (UCC).

Nomenclature

b	Product of the formulation dependent pressure susceptibility constant and the ratio of the tablet density to the theoretical density ($b = \gamma\rho$)
L2M	Lactose Monohydrate, 200mesh
MCC	Microcrystalline Cellulose
N_{rev}	Number of impeller revolutions
P	Compaction pressure
P_R	Roller compaction pressure
P_{WGC}	Equivalent wet granulation compaction pressure
T	Final tablet tensile strength
T_{max}	Maximum tensile strength of the tablet for a given formulation
T_R	Equivalent roller-compacted ribbon tensile strength
T_{WGC}	Equivalent wet granulation granule tensile strength
UCC	Unified Compaction Curve (model)
χ	Effective granulation compaction pressure per revolution

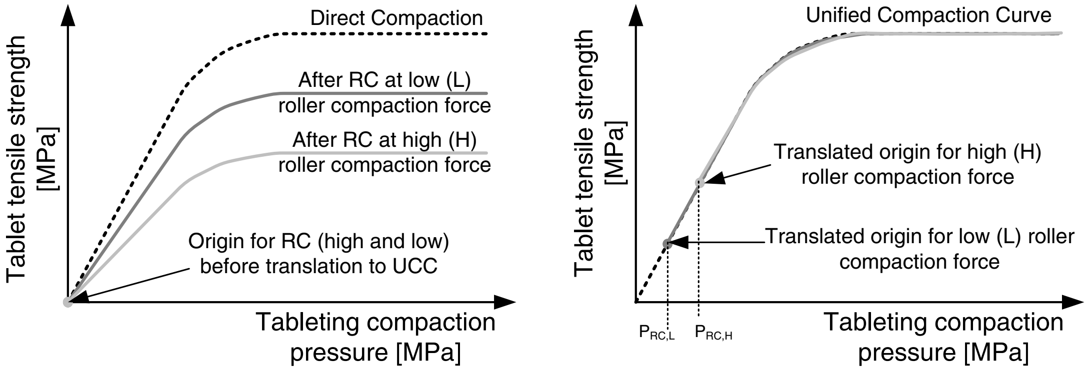


Fig. 1: (left) Schematic diagram of the loss of tablet compactability after Roller Compaction (RC) at low (L) and high (H) roller compaction forces; and (right) the same data combined onto a Unified Compaction Curve (UCC). The translation in origin points for the UCC allows for the roller compaction pressure (PRC) to be extrapolated from the data (adapted from Farber *et al.* [1]).

The roller compaction step was considered to be equivalent to a direct compaction step but milling destroyed the bonds in the ribbon. Therefore the maximum final tablet strength was reduced by an amount equal to the strength generated during the roller compaction step. The unified compaction curve represents this mathematically through the translation of the roller-compacted data along the formulation's direct compaction curve forming a new origin.

The unified compaction curve considers the roller compaction process to be equivalent to pre-compressing the powder in the tablet press at a compaction pressure equivalent to P_{RC} to generate a tensile strength equivalent to T_{RC}, prior to tabletting. However during the milling of the ribbon, the tensile strength is destroyed, reducing the final tablet strength to T_{max} - T_{RC} (the difference between the maximum tablet strength by direct compaction and the ribbon tensile strength from the roller compaction process).The starting point, P_{RC}, was found to be proportional to the roller compaction force. The unified compaction curve model allows the tablet strength, as a function of the compaction pressure, to be predicted in advance once P_{RC} is known for a particular roller compactor design. This has beneficial applications in optimizing the tablet production via the roller-compaction process and trouble-shooting [1].

The "loss of compactability" phenomenon observed in roller compaction has also been noted in various studies [2-4] and can be observed in wet granulation studies [5,6]. The decline in the overall compaction behaviour from the effects of the liquid level and the wet massing time suggests that the unified compaction curve model can potentially be applicable to the wet granulation process where the granulator impeller exerts compaction pressure on the granules, which inherently decreases the final tablet strength. This paper proposes a new idea of applying the unified compaction curve to wet granulation and investigates the potential of applying this model to link the wet granulation conditions, such as liquid level and wet massing time, with the tablet strength.

2. Materials and Experimental Procedure

A binary powder mixture of 50wt.% microcrystalline cellulose (denoted as MCC, Avicel PH-101, FMC Biopolymer) and 50wt.% lactose monohydrate (denoted as L2M, Pharmatose 200M, DMV-Fonterra) with various proportions of 5w/v% polyvinyl pyrrolidone (denoted as PVP, K90 Sigma-Aldrich) was chosen as the standard wet granulation powder formulation. The formulation was chosen due to its prevalent use in the pharmaceutical industry and to compare the results attained in the study of Farber *et al.* [1]. The powders were used 'as received' for the experiments.

Wet granulation experiments were carried out using a high-shear wet granulator (KG5, Key International) comprising of a main impeller only. The effect of the granulator liquid level (20-50wt% on a dry basis), the liquid binder flow rate (130g/min and 280g/min), the impeller speed (150rpm, 285rpm and 600rpm), wet massing time (0-10mins) and scale (1L and 5L) were investigated. The granulator bowl and impeller design for the 1L and 5L granulator have different geometries as seen in Fig. 2. The blade diameter to height ratio was 3:1 for the 1L bowl impeller compared to 4.5:1 for the 5L bowl impeller. The small granulator bowl has a side chute was covered by a Teflon chute cover to prevent the powder being thrown out the bowl. For the small granulator bowl, 200g of powder with the liquid binder delivered in a drop-wise fashion using a peristaltic pump. The peristaltic pump speed was set to 23mL/min which gave a PVP liquid binder flow rate of approximately 26g/min and a total liquid binder delivery time of 2 minutes 30 seconds. For the large granulator bowl, 1kg of powder was used with the liquid binder delivered as atomized droplets using a spray nozzle (Spraying systems: SS650017 to give 130g/min; and SS650050 to give 280g/min). The wet granulation experiments are in contrast to roller compaction which incorporates a liquid into the formulation, rather than having a dry "pure" compaction of the powder taking place.

The granules produced from the experiments were dried overnight in a fan-forced oven at 60°C. The dried granules were compressed into flat-faced placebo tablets using a single station tablet press (Carver Inc.). The granules underwent compaction forces between 68-550MPa to produce 5 tablets for each compaction force per granulation batch. The tablet thickness was determined using a digital calliper while the tablet hardness was measured using a diametrical compression tester (Schleuniger Pharmatron 6D). The data obtained was used to calculate the tablet tensile strength according to Fell and Newton [7].

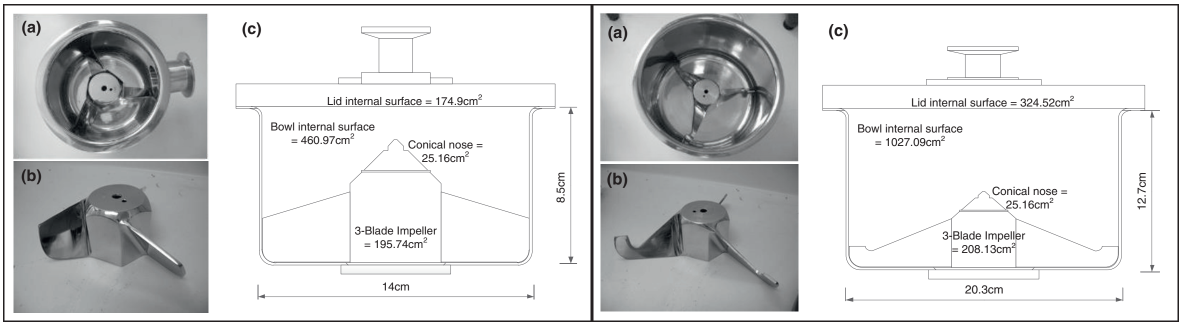


Fig. 2: Images of the (a) bowl; (b) impeller and (c) dimensional drawings of the: (left) small 1L; and (right) large 5L laboratory granulator (KG5 high-shear granulator) bowl.

The unified compaction curve was applied to the wet granulation compaction data by applying a powder compaction model [8] to the compaction data to determine T_{max} and b (see Eqn.1).

$$T = T_{\max}\left(1 - e^{-bP}\right) \tag{1}$$

Each of the compaction curves were translated onto the master reference curve by using the wet granulation Unified Compaction Curve (Eqn.2) and iterating the P_{WGC} value and minimising the sum of the square of the errors in a conventional Microsoft Excel spread-sheet.

$$T = T_{WGC} + T_{\max}\left(e^{-bP_{WGC}} - e^{-b\left(P' + P_{WGC}\right)}\right) \tag{2}$$

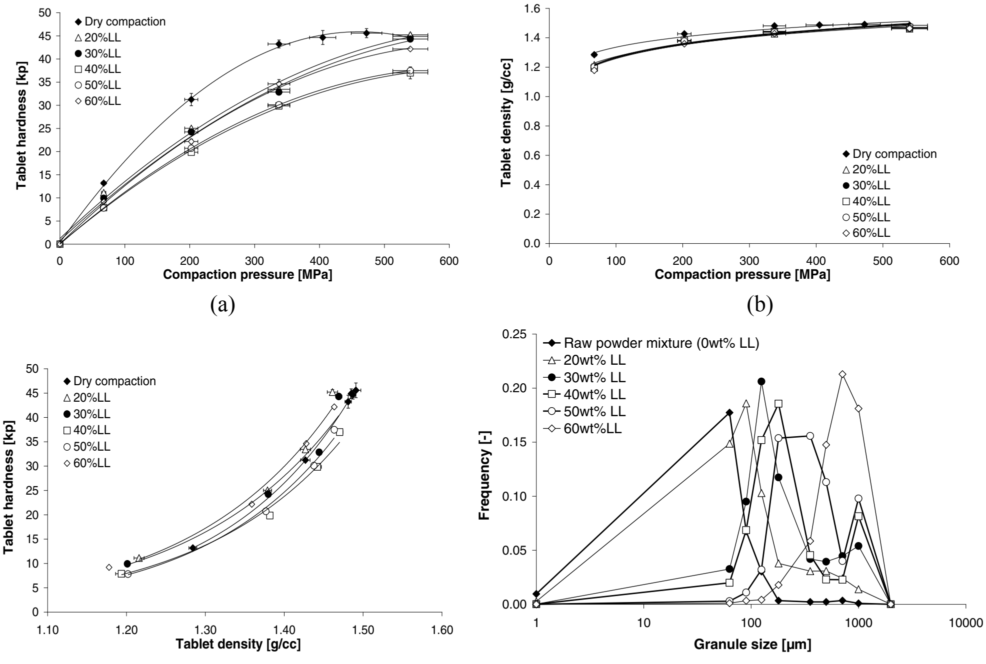
where T is the final tablet strength, P' is the compaction pressure in the tablet press, T_{max} is the maximum tablet tensile strength that can be obtained by direct compaction, and b is the material-dependent exponent parameter that is a function of the relative density of the tablet and the compactability of the formulation [1].

3. Results and Discussions

The wet granulation process directly affects the tablet properties. The effect of the granulator liquid level and the wet massing time on the tablet hardness and the tablet density are seen in Figure 3 and Figure 4. In each figure, the wet granulation data represent 5 tablets measured, while for the direct compaction data points represent 3 replicates. The data presented has an estimated error of ±5% of the compaction pressure and the standard error of the mean is used to represent the error in the tablet properties.

3.1 Effect of liquid level

The liquid level can have an impact on the tablet properties, particularly the tablet strength, as evident from Figure 3. For each liquid level, the tabletability behaviour forms its own distinct profile, which is the suggestive of the "loss of compactibility" observed in other studies (Figure 3(a)). However for 50 and 60wt% liquid levels, the profiles are very similar to each other, which may indicate that the granules produced have similar compaction behaviour. The granulator impeller exerts compaction forces on the granules during the wet granulation process which irreversibly deforms the granules and reduces the compactability. This is evident in the tablet hardness decreasing as the liquid level increases (See Figure 3(a)). The results suggest that the introduction of liquid into the granulator means that the granules are exposed to more compaction forces from the impeller than for low liquid levels (shorter mixing time). Subsequently, as the tabletting compaction force increases, the granules experience more deformation and fragmentation which creates more contact bonds and friction within the tablet to increase the tablet hardness. The reduction in compactability supports previous studies [1-4]. The liquid level does not significantly affect the tablet density as shown in the compressibility (Figure 3(b)) and the compactibility (Figure 3(c)) curves. This could indicate that the tablet volume is unaffected by the liquid level for a given compaction pressure and that the extent of fragmentation and deformation within the tablet volume is the dominant factor for the final tablet strength. The granule size appears to have little effect on the tablet properties which contradicts previous work [9, 10]. As seen in Figure 3(d), as the liquid level increases the granule size distribution curve shifts progressively to the right indicating that more liquid bridges are being formed in between the particles to produce coarse granules. However despite the increase in the average granule size for higher liquid levels, the particle size appears to significantly affect only the tablet hardness (Figure 3(a)).



(a) (b)

(c) (d)

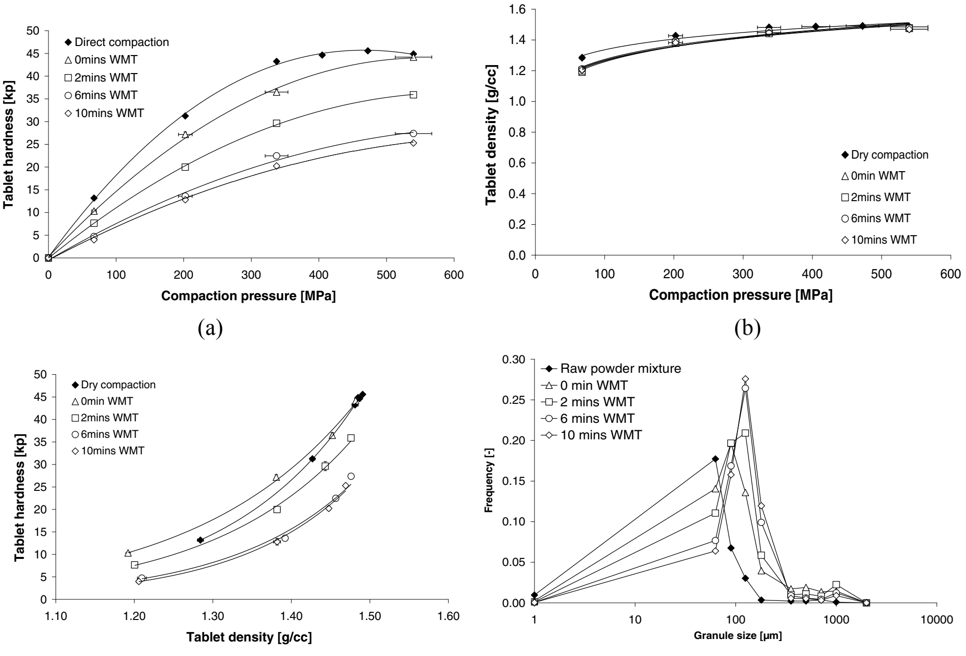
Fig. 3: The effect of granulator liquid level on (a) tabletability; (b) compressibility; and (c) compactibility behaviour for tablets produced using high-shear wet granulation (powder formulation is 1:1 microcrystalline cellulose and lactose granulated with 5w/v% polyvinyl pyrrolidone).

3.2 Effect of wet massing time

Wet massing, during wet granulation, induces significant amounts of compaction forces on the granules which would have a significant impact on the compaction behaviour of the granules during tabletting. The strong effect of wet massing time on the tablet strength can be seen in the tabletability behaviour (Figure 4(a)) in which the tablet hardness reduces significantly from 45kp to 25kp as the wet massing increases towards 10 minutes. The longer the wet massing period, the more compaction forces the granules experience and hence granule consolidation takes place. Therefore the granules undergo irreversible deformation which limits the amount of compaction that can take place during tableting, thereby decreasing the tablet strength.

The irreversible deformation of the granules would alter the granule properties and hence the granule properties would play a major role in influencing the tablet strength. Work on the examination of the granule morphology, size distribution and porosity has been carried out and will be presented in the future.

The tablet density is not strongly influenced by the wet massing time, as seen in both the compressibility (Figure 4(b)) and the compactibility (Figure 4(c)) behavior. For the compressibility behaviour, for a given tablet density, a range of tablet strength magnitudes can be seen across all wet massing times, suggesting that the tablet density is the not a dominant factor in influencing the tablet strength. Similar to the trend found in the liquid level results, the granule size does not appear to be a major influence on the tablet strength. The wet massing time gradually increases the granule size as noted in Figure 4(d), although a large proportion of granules have a granule size of around 125μm. Therefore the irreversible deformation of the granules contributes to the final tablet strength.



(a) (b)

(c) (d)

Fig. 4: The effect of wet massing time on (a) tabletability; (b) compressibility; and (c) compactibility behaviour for tablets produced using high-shear wet granulation (powder formulation is 1:1 microcrystalline cellulose and lactose granulated with 5w/v% polyvinyl pyrrolidone).

3.3 Application of the unified compaction curve model to wet granulation

From the liquid level and wet massing time effects on the tablet properties, it can be seen that the wet granulation process controls the quality of the tablets produced which can be attributed to the exertion of compaction forces inducing irreversible deformation on the granules during wet granulation. The "loss of compactability" during wet granulation suggests that the Unified Compaction Curve model can serve as an analogy for the roller compaction pressure in roller compaction, with the granulator impeller compaction pressure in wet granulation to predict the tablet strength. The unified compaction curve model is adopted for the first time in this study to see if the model can be applicable to the wet granulation as it is for roller compaction [1].

From the application of the Unified Compaction Curve model on the effects of liquid level and the wet massing time on the tablet strength, it can be seen that the model gives a good prediction of the tablet strength for a given compaction pressure (See Figure 5). As the liquid level or the wet massing time increases, the compaction curve is shifted upwards and to the right on the master curve. This was seen for all binder flow rates and impeller speeds. The Unified Compaction Curve model is able to take the compaction curve for each of the granulation conditions and translate onto the dry direct compaction reference curve to a new origin point (T_{WGC}, P_{WGC}). The new origin point (T_{WGC}, P_{WGC}) represents the equivalent average granule strength T_{WGC}, and the equivalent wet granulation compaction pressure P_{WGC}. For the formulation used in this study (1:1 microcrystalline cellulose/lactose 200mesh, granulated with 5w/v% PVP liquid binder), the maximum tablet tensile strength that can be attained is approximately 3.6MPa. The tablet strength for a given granulation condition would be determined to be 3.6MPa – T_{WGC}. Compaction and consolidation during wet granulation creates strength in the granules which reduces the maximum possible compaction pressure that can be applied to the granule during tabletting. Therefore there is a reduction in the tablet tensile strength. It is speculated that this will be reflected in the granule structure and porosity, although the gradual reduction in the number of fine particles (see Figure 3(d) and Figure 4(d)) may also play a role.

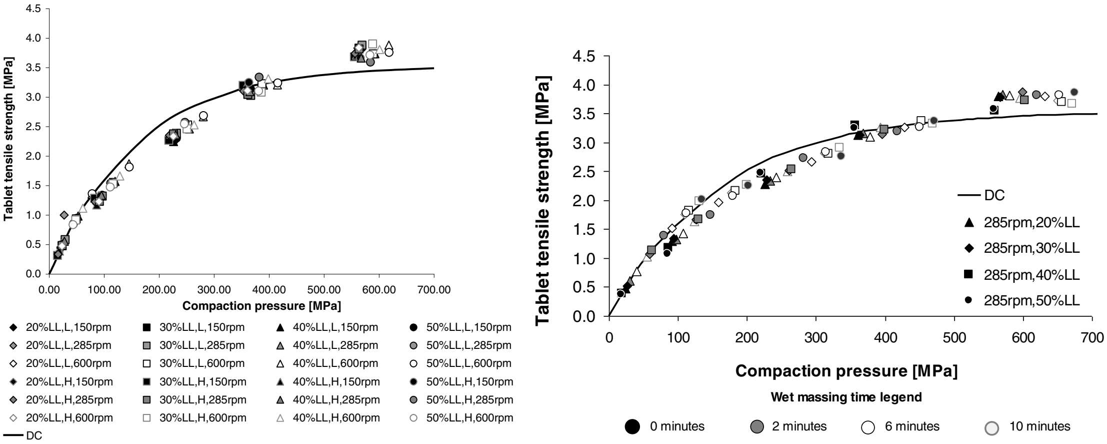


Fig. 5: Unified compaction curve for granules produced under varying granulator liquid levels (with 10 seconds wet massing time) and wet massing times (at 40% liquid level). Powder formulation is 1:1 microcrystalline cellulose and lactose granulated with 5w/v% polyvinyl pyrrolidone.

Therefore the unified compaction curve model is able to give a quantitative measure of the compaction force from the granulator impeller is able to be quantitatively incorporated into the unified compaction curve model. This will have significant implications for tablet manufacture in which the number of case studies to determine the tablet strength from granules produced from varying production formulations will be reduced, saving resources and time taken. What makes the unified compaction curve an exciting model to work with wet granulation studies is the ability to predict the compaction pressure the granules experience in the wet granulation process. There has been interest in determining the amount of impact, shear and compaction a granule experiences in the granulator, since this is responsible for the success of granule collision and coalescence and the resulting granule porosity, size and morphology [11, 12]. However the compaction force the granules experience during wet granulation is difficult to quantify without using sophisticated equipment. The unified compaction curve can potentially bypass the sophisticated experimental process and predict the granulation compaction pressure through the wet granulation compaction pressure P_{WGC}.

The wet granulation compaction pressure (P_{WGC}) can be analysed further by looking at the relationship between the wet granulation compaction pressure and the cumulative number of impeller revolutions as seen in Figure 6. The relationship between the P_{WGC} and the wet granulation conditions reveal that the liquid level and wet massing time data all collapse onto a single curve, with the exception of the 20wt.% liquid level granulation batches. After 10 minutes wet massing time (equivalent to approximately 12.3 minutes of granulation time), the number of impeller revolutions reaches approximately 8000 revolutions, leading to a maximum wet granulation compaction pressure of PWGC = 140MPa. Because P_{WGC} is related to the wet granulation tensile strength and the tablet tensile strength), the wet granulation compaction pressure indirectly suggests that the final tablet strength is governed by the number of impeller revolutions as evident by the amalgamation of the all the wet granulation data onto a single curve.

The divergence of the 20wt.% granulation data from the main trend suggests that a minimum amount of liquid binder is required for the unified compaction curve model to be valid. For this formulation, the liquid level needs to be above 30wt.% to ensure that the impeller force is effectively transmitted to the powder for agglomeration to occur. When the liquid level increases above 30wt.%, the microcrystalline cellulose particles and granules become saturated with liquid binder which alters the way the particles and granules deform and compact during wet granulation. Therefore the granules need to have a sufficient amount of saturation for the compaction pressure from the granulator impeller to cause a physio-chemical change in the microcrystalline cellulose or other alterations to the granule structure, which increases the granule strength (through the increase in the T_{WGC} parameter) and ultimately reduce the final tablet strength.

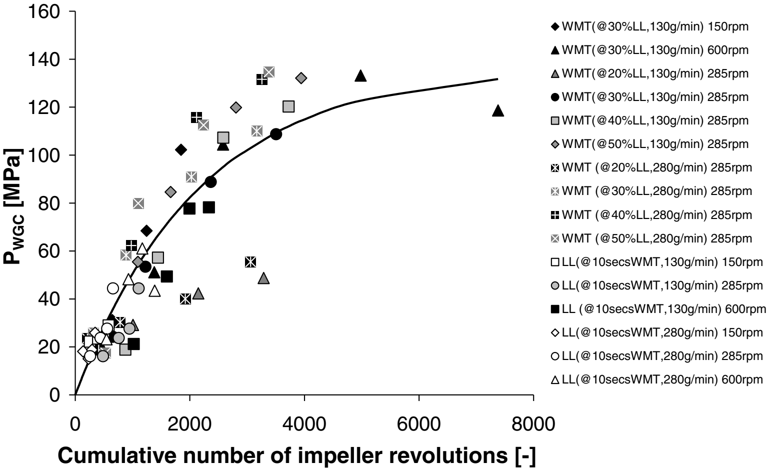


Fig. 6: Relationship between the wet granulation compaction pressure PWGC and the granulator liquid level (left); and the wet massing time (right) (Powder formulation is 1:1 microcrystalline cellulose and lactose granulated with 5w/v% polyvinyl pyrrolidone).

The wet granulation compaction pressure (P_{WGC}) can be used as the basis for the scale-up of the granulation process. Because the final tablet strength is strongly affected by P_{WGC} and the cumulative number of impeller revolutions, the scale-up of wet granulation processes can be based upon the principle of maintaining 'constant compaction pressure' during wet granulation. The application of the Unified Compaction Curve to wet granulation compaction curves for the one litre scale is presented in left image of Figure 7 and the combination of the large (5L) and small scale in the right image of Figure 7. Similar to the 5L scale, a first-order exponential curve was fitted to the relationship between the tensile strength and the number of impellor revolutions for the small 1L scale results ($P_{WGC,max}$ = 129.3MPa; b = 0.0006). For the large scale result in Figure 6, the curve fitting parameters was found to be $P_{WGC,max}$ = 134.8MPa; b = 0.0005. From the comparison of the fitting parameters between the small and large scale, it can be seen that there is a significant difference in the amount of compaction pressure exerted on the granules during granulation with the 5L scale exerting greater compaction forces compared to the smaller 1L scale.

From Figure 7, it can be seen that the first-order exponential relationship can be viewed two parts: (1) initial linear slope up to 2000 impeller revolutions; and (2) linear horizontal slope at approximately 130MPa denoting a formulation and/or equipment limitation to attain the maximum tablet strength. The initial linear slope can be defined as the average effective wet granulation compaction pressure per revolution, χ. It was found that the small-scale granulator induced a larger compaction pressure (χ = 50kPa per revolution) compared to the large-scale granulator (χ = 39kPa per revolution). The linear slope appears to give an insight into the mixing intensity of the powder and granules for a given granulation operating condition and granulator-scale.

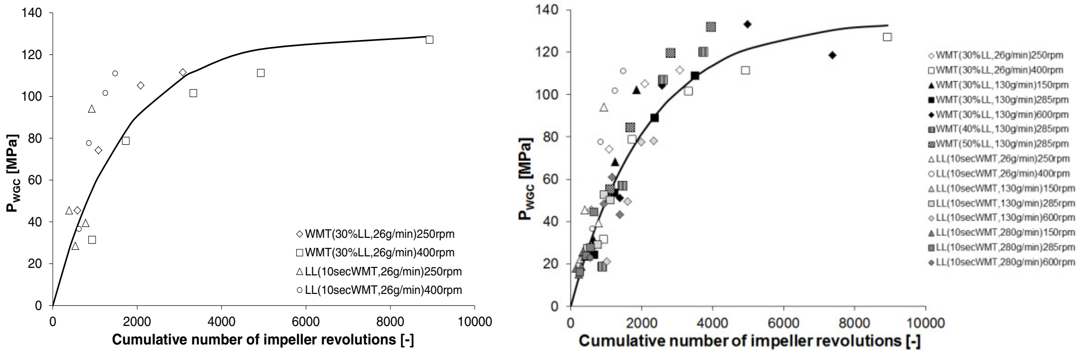


Fig. 7: The wet granulation compaction pressure P_{WGC} as a function of the number of impeller revolutions from the application of the Unified Compaction Curve for: (left) small (1L); and (right) combination of small (denoted by hollow symbols) and large (5L, denoted by filled symbols) granulator bowls.

The scale-up guideline is proposed to be based on maintaining "constant compaction" pressure between small and large scales. The tablet strength was found to be dependent on the number of the impeller revolutions (N_{rev}) and the effective granulation compaction pressure per revolution, χ (Equation 3).

$$\chi = \frac{P_{WGC}}{N_{rev}} \tag{3}$$

The size of the granulator would be expected to exhibit different compaction pressures based on the granulator bowl and impeller geometry. This would mean that to maintain the equivalent amount of compaction pressure, P_{WGC}, induced on the granules between the scales, the number of impeller revolutions would be dependent on χ, as described in Equation 4 and Equation 5.

$$P_{WGC} = \chi \times N_{rev} \tag{4}$$

$$\chi_1 \times N_{rev,1} = \chi_2 \times N_{rev,2} \tag{5}$$

Therefore for a given χ_1 and χ_2 for the small and large scale respectively, for a given number of impeller revolutions for the small scale granulator, N_1, the number of impeller revolutions (N_2) required to achieve the same P_{WGC} for the small scale for the large scale is given by Equation 7.4.

$$N_{rev,2} = \frac{\chi_1}{\chi_2} \times N_{rev,1} \tag{6}$$

Therefore the effect of granulator scale can give an insight into the compaction behaviour of microcrystalline cellulose during wet granulation and its sensitivity to the granulation operating conditions, particularly the impact with the impeller and the liquid saturation of the microcrystalline cellulose particles. The Unified Compaction Curve is able to unify the compaction data for varying granulation conditions at different scales, which enable manufacturers to design the wet granulation process with the primary basis being the number of impeller revolutions to achieve the desired tablet strength. Since the compaction pressure from the impeller is the variable of interest in the Unified Compaction Curve, the model is able to provide an alternative scale-up guideline to help design the wet granulation process.

4. Conclusions

From the investigation between the effects of the liquid level and wet massing time on the tablet strength, it was seen that the wet massing time has a stronger influence on the tablet strength compared to the liquid level. This is due to the compaction and densification of the granules during wet massing which reduces the compactability of the granules during tabletting. The application of the unified compaction curve model from a previous study to wet granulation has shown promising results with the model providing a good prediction of the tablet strength for varying granulator liquid levels, wet massing times, binder flow-rates and impeller speeds. Therefore the Unified Compaction Curve serves as an elegant link between the wet granulation and tabletting processes.

The unified compaction curve model is able to quantitatively measure the effective compaction pressure (P_{WGC}) exerted on the granules by the impeller during granulation, which links granulation conditions and stresses in the granulator for the first time. Further analysis on wet granulation compaction pressure revealed that P_{WGC} can be coupled with the cumulative number of impeller revolutions to give a predictive guideline to the final tablet strength for all wet granulation conditions. However for the formulation used in this study, a liquid level of at least 30wt.% is required for the unified compaction curve model to effectively capture the compaction pressure the granules experience during wet granulation.

From the wet granulation compaction pressure parameter, a new wet granulation scale-up rule was proposed which is based on the principle of maintaining constant compaction pressure during the scaling up processes. The unified compaction curve was able to distinguish the difference in the average effective wet granulation compaction pressure per revolution, χ, for the 1L small scale (χ = 50kPa per revolution) and 5L large scale (χ = 39kPa per revolution) granulators. It is anticipated that the constant wet granulation compaction pressure scale-up rule will provide an alternative scale-up guideline during wet granulation designing process.

Therefore application of the unified compaction curve model to the wet granulation process was found to be beneficial in giving a quantitative measure of the compaction pressure experienced by the granules during wet granulation and providing a potential wet granulation scale-up guideline. This ultimately facilitates in predicting the final tablet strength and/or target the tablet strength by designing the wet granulation process based on the magnitude of compaction pressure exerted on the granules and the number of impeller revolutions.

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