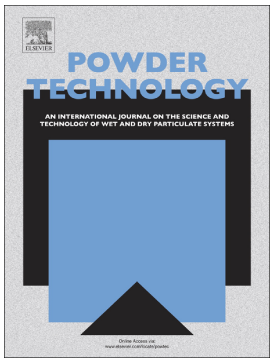

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A novel approach to minimize loss of compactibility in a dry granulation process using superdisintegrants

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Abstract

Dry granulation via roller compaction is increasingly being used as granulation method for the production of oral solid dosage forms. Advantages of roller compaction include a simplified process compared to wet granulation and the inherently continuous nature of the process. A common problem of dry granulation, however, is the loss of compactibility of the granules compared to the ungranulated powders. Here we show a novel approach to minimize the loss of compactibility during dry granulation. The intra-granular addition of superdisintegrant reduces the loss of compactibility of anhydrous lactose-based granules produced via roller compaction. This effect is explained by a reduced hardness of the granules, which promotes granule fragmentation upon tablet compression. This higher degree of fragmentation increases the lactose surface available for bonding, thereby improving tablet strength. The results presented here show how intra-granular superdisintegrants can be used to minimize the loss of compactibility of a dry granulation formulation.

Keywords: Roller compaction; Dry granulation; Excipients; Superdisintegrants; Compactibility; Tablets

1. Introduction

Granulation of powders is often used in the production process of pharmaceutical solid dosage forms. In a pharmaceutical granulation step, larger granules are produced from fine active pharmaceutical ingredient (API) and excipient particles. This improves powder flowability and handling and reduces the propensity to segregate upon further processing. Dry granulation via roller compaction (RC) is increasingly being used over wet granulation because of the simplified process without the need of a drying step [1,2]. Furthermore, dry granulation is of particular interest for moisture-sensitive compounds because of the absence of water or

other solvents [3]. Granulation via RC, being an inherently continuous process, is especially suitable for incorporation in pharmaceutical continuous manufacturing lines.

A major drawback of implementing a dry granulation step in the production process of pharmaceutical tablets, however, is the loss of compactibility of the resulting granules compared to the starting materials [4–6]. Here, compactibility is defined as the ability of a powder to be compressed into a tablet of specified strength [7]. The loss of compactibility results in a reduced tablet strength for tablets produced via a dry granulation process compared to a direct compression (DC) process. Several different mechanisms have been proposed to explain the loss of compactibility of granules prepared via dry granulation [8]. The two main mechanisms are granule size enlargement [9] and granule hardening [10]. Granule size enlargement results in lower tablet strength due to less available bonding area between the granules during tableting. Granule hardening is explained by densification of the granules upon increasing the specific compaction force during RC. This results in harder granules with a lower porosity, which show increased resistance towards deformation and fragmentation upon tableting and thereby show reduced compactibility [10].

The dominant mechanism for the loss of compactibility of a dry granulation formulation largely depends on the deformation behavior of the primary particles that form the granules [11–14]. Plastically deforming materials such as microcrystalline cellulose (MCC), generally show a larger loss of compactibility than brittle materials such as lactose [12,15]. This is because plastically deforming materials show loss of compactibility due to both size enlargement and granule hardening mechanisms [8,9,16]. For brittle materials on the other hand, granule size enlargement is considered not to result in loss of compactibility because of extensive fragmentation of the granules during tableting [8,11]. Granule hardening, however, results in decreased compactability of granules composed of brittle materials [12,13,17]. Granule hardening leads to a reduction of the porosity of the granules, which makes them, in turn, more resistant to fragmentation during tableting. This lower propensity to fragmentation results in less available bonding area, which reduces tablet strength for the granulated materials compared to the ungranulated starting materials.

A recent study by Skelbæk-Pedersen et al. showed that the degree of fragmentation of granules produced via RC largely determines the compactibility of granules composed of lactose or MCC [13]. It was shown that increasing the specific compaction force during granulation resulted in harder granules for both excipients. This hardening effect makes the granules less susceptible to fragmentation upon tablet compression. Therefore, increasing the specific compaction force causes a decrease in tablet tensile strength (TTS) for

tablets compressed from lactose granules, especially after lubrication. The decreased fragmentation tendency of lactose granules prepared at higher specific compaction forces reduces the formation of lubricant-free lactose surface, thereby decreasing compactibility [13]. This study demonstrates that for both brittle and plastically deforming materials, granule hardening occurs upon increasing the specific compaction force. The resulting loss of compactibility of the granules depends on the deformation behavior of the materials, the specific compaction force applied during granulation and the addition of lubricant.

A comparative study of the compactibility of several grades of lactose and MCC after dry granulation was performed by Hein et al. [18]. This study showed that anhydrous β-lactose is a very suitable excipient for dry granulation applications, because of the relatively small loss of compactibility. Other grades of lactose and MCC were considered less suitable due to relatively poor (re-)compactibility of these excipients after dry granulation, resulting in a decreased tablet strength. The superior performance of anhydrous β-lactose in terms of compactibility after dry granulation can be explained by the brittle deformation behavior of the primary particles. Anhydrous lactose particles consist of smaller microcrystals and are therefore highly susceptible to fragmentation [19,20]. The brittleness and high susceptibility to fragmentation of anhydrous lactose particles makes this excipient very suitable to use in a dry granulation process, as size enlargement will not affect its compactibility.

Even though several different studies have focused on mechanistically understanding the loss of compactibility of different materials after dry granulation [8,12,21], very little has been published on how to minimize this undesired effect. The general recommendations to obtain satisfactory compactibility are to apply a low specific compaction force in the granulation process and to use starting materials with high compactability (e.g. using powders with a very small particle size). The aim of the current study is to present a new approach to minimize the granule hardening effect and resulting loss of compactibility in a dry granulation process. Through the intra-granular addition of small amounts of superdisintegrant, the loss of compactability of anhydrous lactose granules prepared by RC is strongly reduced. The observed effects of the addition of superdisintegrant are explained by considering granule hardening as the main mechanism for the loss of compactability of brittle anhydrous lactose. The intra-granular addition of superdisintegrant reduces granule hardness and promotes fragmentation of the granules during tablet compression. This results in a reduced loss of compactibility of the granules compared to the ungranulated powders. The results of this study present a

new approach to minimize the loss of compactibility of pharmaceutical formulations containing brittle excipients in a dry granulation process.

2. Materials and methods

2.1 Materials

Anhydrous lactose (SuperTab® 21AN), croscarmellose sodium (Primellose®) and sodium starch glycolate (Primojel®) were obtained from DFE Pharma (Goch, Germany). The anhydrous lactose used in this study predominantly consists of ß-lactose (84% w/w) with a smaller fraction of α-lactose (16% w/w), as measured by gas chromatography according to the European Pharmacopoeia. Magnesium stearate (technical grade) was purchased from Sigma-Aldrich (St. Louis, USA) and was used as received.

2.2 Roller compaction

The anhydrous lactose and the superdisintegrant were dry blended for 15 minutes at 6 rpm using a PM 600 bin blender (L.B. Bohle, Ennigerloh, Germany) prior to granulation. Dry granulation was performed using a BRC 25 roller compactor (L.B. Bohle, Ennigerloh, Germany) with a constant roller speed of 2 rpm and a gap width of 1.5 mm. Powders were compressed at four different specific compaction forces of 3, 7, 11 and 16 kN/cm. At compaction forces below 3 kN/cm the material was not sufficiently granulated, whereas 16 kN/cm was chosen as the maximum as higher values would approach the limit of the equipment used. The resulting ribbons were milled using an integrated conical sieve (BTS 100) at 400 rpm equipped with a 1.5 mm rasp sieve. At each specific compaction force, the process was run for approximately one minute before collection of the product was started. About 2 – 2.5 kg of granules were collected before adjusting the specific compaction force to the next setting.

2.3 Granule size characterization

Particle size distributions of the granules and the ungranulated starting materials were characterized (n = 3) by dry laser diffraction measurements (Helos/KR, Sympatec, Clausthal-Zellerfeld, Germany). A dry dispersion unit (RODOS, Sympatec, Clausthal-Zellerfeld, Germany) with a feed rate of 75% and an air pressure of 1.5 bar was used to disperse the powders. Particle size distributions are reported as the volume equivalent sphere diameter.

2.4 Tableting

Prior to tableting, both the granulated products and the ungranulated powders used for direct compression were lubricated by adding 0.5% w/w of magnesium stearate (MgSt) and blending for 2 minutes at 90 rpm in a Turbula blender (Turbula T2F, Willy A. Bachofen, Basel, Switzerland). Tablets were compressed using a rotary tablet press (RoTab T, Luxner, Berlin, Germany) at compression forces of 5 kN, 10 kN and 15 kN. Tablets with a weight of 250 mg were compressed using flat beveled punches (iHolland, United Kingdom) with a diameter of 9 mm. The rotating frequency was kept constant at 25 rpm, resulting in a dwell time of 60 ms. The tableting procedure used for direct compression of the ungranulated powders was the same as for the granulated materials.

2.5 Tablet characterization

Tablet weight, diameter, height and crushing strength (n = 20) were analyzed using an automated tablet tester (AT50, Sotax, Basel, Switzerland). The force required to break a tablet was measured at a constant speed of 2 mm/s. The tablet tensile strength (TTS) was calculated from the tablet crushing strength (TCS), tablet diameter (D) and tablet height (H) using equation 1 [22]:

$$TTS = \frac{2 \cdot TCS}{\pi \cdot D \cdot H} \tag{1}$$

The loss of compactibility after roller compaction was quantified as the slope of a linear fit of the TTS as a function of the specific compaction force. The relative loss of compactibility was calculated as the ratio of the absolute loss of compactibility and the TTS of tablets produced via a direct compression process.

The solid fraction (SF) of the tablets was calculated based on the true density ρ_{true} and the apparent density of the tablets $\rho_{apparent}$, according to equation 2:

$$SF = \frac{\rho_{apparent}}{\rho_{true}} \times 100\% = \frac{\frac{m}{\pi \cdot r^2 \cdot h}}{\rho_{true}} \times 100\% \tag{2}$$

where *m* is the tablet mass, *r* is the tablet radius and *h* is the tablet height. For the true density, values of ρ_{true} = 1.58 g cm^{-3} for anhydrous lactose, ρ_{true} = 1.53 g cm^{-3} for croscarmellose sodium and ρ_{true} = 1.52 g cm^{-3} for sodium starch glycolate were used, as determined by helium pycnometry (AccuPyc II 1340, Micromeritics, Norcross, USA) [23]. For the mixtures of anhydrous lactose and superdisintegrant, a weighted average of the ρ_{true} values of the individual components was used to calculate SF.

Tablet disintegration time was measured in demineralized water at a temperature of 37 °C using a tablet disintegration tester (Erweka ZT122, Germany). The disintegration time was reported in seconds for each tablet individually. A tablet was considered disintegrated when all lactose was fully dissolved and no powder was visible anymore. The reported disintegration time is the average of six individual measurements.

3. Results

3.1 The effect of croscarmellose sodium on granule compactibility

Croscarmellose sodium (CCS) is a superdisintegrant that is commonly used in formulations of pharmaceutical tablets. Particles of CCS show a fibrous structure and are hydrophilic in nature. Within a tablet, CCS forms a network-like structure throughout the tablet matrix which promotes the penetration of water [24]. Blends of anhydrous lactose with varying amounts of CCS (2%, 4% and 8% w/w) were granulated by RC, in order to study the effect of CCS on compactibility in a dry granulation process. As a reference, pure anhydrous lactose without any superdisintegrant was included. Powders were granulated using varying specific compaction forces, resulting in a median granule size (x50) of approximately 500 µm. The addition of CCS showed little effect on the size distribution of the granules produced (Figure S1).

To quantify the loss of compactibility of the granules, tablets were compressed from granules prepared at different specific compaction forces. Direct compression of the ungranulated starting materials was performed as a reference. Figure 1 shows how the tablet tensile strength decreased upon increasing the specific compaction force for anhydrous lactose with varying amounts of CCS. For all formulations, increasing the specific compaction force in the granulation process resulted in a lower TTS. Increasing the amount of CCS in the formulation reduced TTS for tablets produced via a direct compression process (data at 0 kN/cm in Figure 1). For tablets produced from roller compacted granules, however, the effect of CCS on tablet strength was dependent on the specific compaction force used in the granulation process. At specific compaction forces in the range of 7 - 16 kN/cm, the addition of small amounts of CCS (2% – 4% w/w) prior to granulation resulted in

an increase in tablet strength compared to pure anhydrous lactose. At these higher specific compaction forces, the highest TTS values are obtained for the formulation with 4% w/w CCS. Further increasing the amount of CCS to 8% w/w decreased TTS over the whole range of specific compaction forces tested, indicating that an optimum level of CCS exists.

The loss of compactibility due to dry granulation could be described with a linear fit of the decrease in TTS upon increasing specific compaction force (Figure 1). The slope of the linear fits was used to quantify the loss of compactibility, with the values shown in Table 1. Anhydrous lactose without any CCS (black lines in Figure 1) showed the strongest decrease in TTS after granulation. Increasing the amount of CCS in the formulation reduced the loss of compactibility. The loss of compactibility also depends on tablet compression force, where tablets produced at the highest compression force of 15 kN showed the strongest decrease in TTS. The relative loss of compactibility values (Table 1), however showed little dependence on tablet compression force. The relative loss of compactibility was clearly dependent on the amount of CCS added. For pure anhydrous lactose, a 3 to 4% decrease in tablet strength for each kN/cm of force applied in the granulation process was found. Upon addition of 2% w/w of CCS prior to granulation, the relative decrease in TTS was reduced to values of 2 to 2.5% per kN/cm. Further increasing the amount of CCS reduced the loss in TTS to only 1 to 2% per kN/cm of specific compaction force applied.

Table 1. Loss of compactibility and relative loss of compactibility values for tablets of anhydrous lactose with varying amounts of CCS, prepared at three different tablet compression forces.

CCS (% w/w)	**Tablet compression force (kN)**	**Loss of compactibility (MPa cm/kN)**	**Relative loss of compactibility (% cm/kN)**	
0	5	-0.034	-3.0	-3.4
	10	-0.070	-2.9	
	15	-0.176	-4.4	
2	5	-0.024	-2.2	-2.4
	10	-0.055	-2.3	
	15	-0.097	-2.6	

	5	-0.015	-1.6	
4	10	-0.040	-1.8	-1.7
	15	-0.060	-1.8	
	5	-0.001	-0.2	
8	10	-0.023	-1.6	-1.1
	15	-0.034	-1.5	

Since the relative loss of compactibility showed little dependence on tablet compression force, one general value for the relative loss of compactibility could be obtained for each formulation. This general value is based on a linear fit of the decrease in relative tablet strength upon increasing specific compaction force for the TTS data obtained at the three compression forces taken together (Figure S2). The resulting slope of these linear fits is shown in the last column of Table 1 as the relative loss of compactibility for each formulation. These values confirmed that the addition of CCS prior to granulation reduces the loss of compactibility after RC. While anhydrous lactose without any CCS showed a 3.4% decrease in TTS for each kN/cm increase in specific compaction force, this value was reduced to only 1.7% for the formulation with 4% w/w of CCS. This effect also resulted in higher absolute TTS values for the formulations with 2% and 4% w/w CCS compared to pure anhydrous lactose, if a specific compaction force of 7 kN/cm or higher was used in the granulation process (Figure 1).

The solid fraction (SF) of the tablets with varying amounts of CCS were obtained using equation 2. Figure 2 shows how the SF changes upon increasing the specific compaction force for tablets produced at three different compressison forces. The SF showed a strong dependence on tablet compression force with tablets compressed at 5 kN showing the lowest SF (Figure 2a) and tablets compressed at 15 kN showing highest SF values (Figure 2c). The specific compaction force applied during RC also had an effect on tablet SF. In general, increasing the specific compaction force resulted in more densification of the material during granulation, which increased SF of the final tablets. For the formulations with 0% and 2% w/w of CCS, however, the 10 kN tablets showed no increase in SF upon increasing the specific compaction force (Figure 2b). The 15 kN tablets even showed a decrease in SF (Figure 2c). For the formulations with higher amounts of CCS, increasing the specific compaction force resulted in an increase in SF for all three tablet compression forces investigated.

3.2 The effect of sodium starch glycolate on granule compactibility

To test whether other superdisintegrants showed a similar effect on loss of compactibility of the granules, roller compaction and subsequent tableting was also performed for anhydrous lactose in combination with sodium starch glycolate (SSG). A formulation with 4% w/w of SSG was used, as this amount resulted in optimal TTS values after dry granulation with CCS. In contrast to CCS, SSG particles have a spherical morphology and the particles swell upon contact with water [25,26] Figure 3 shows the TTS for tablets with 4% w/w of both superdisintegrants, produced after RC with increasing specific compaction forces. Tablets with SSG showed a significantly lower tablet strength compared to CCS, both for DC and after dry granulation. The negative effect of SSG on compactibility is in line with the elastic deformation behavior of this excipient [27]. The loss of compactibility upon increasing specific compaction force was similar for both superdisintegrants (Table 2). Furthermore, the increase in tablet SF after roller compaction was also very similar for tablets with either CCS or SSG (Figure S3). Compared to anhydrous lactose without any superdisintegrant (black squares in Figure 3), the addition of SSG resulted in a reduced loss of compactibility, as indicated by the slope of the linear fits. The absolute TTS values, however, were not increased upon the addition of SSG. This indicates that this superdisintegrant reduces the loss of compactibility of the granules but does not improve the absolute compactibility of the formulation.

The relative loss of compactibility is again independent of tablet compression force for the formulation with SSG (Table 2). Therefore a single linear fit was used to describe the relative loss of compactability, using the TTS data obtained at the three different tablet compression forces (Figure S4). The obtained slope of 2.0% per kN/cm for the formulation with SSG was slightly higher than for the formulation with 4% w/w CCS. This indicated that CCS is slightly more effective in reducing the loss of compactibility in a dry granulation process. The value obtained, however, was significantly lower than the 3.4% per kN/cm obtained for the formulation without any disintegrant (Table 1). So SSG reduced the relative loss of compactibility after RC, as indicated by the linear fits in Figure 3. However, the absolute TTS values of the tablets with SSG were significantly lower than those of tablets made with CCS, making CCS a more suitable superdisintegrant for the optimization of tablet strength in a dry granulation process.

Table 2. Loss of compactibility and relative loss of compactibility values for tablets of anhydrous lactose with 4% w/w of CCS or SSG, prepared at three different tablet compression forces.

Superdisintegrant	Tablet compression force (kN)	Loss of compactibility (MPa cm/kN)	Relative loss of compactibility (% cm/kN)	
4% CCS	5	-0.015	-1.6	-1.7
	10	-0.040	-1.8	
	15	-0.060	-1.8	
4% SSG	5	-0.015	-2.0	-2.0
	10	-0.039	-2.2	
	15	-0.051	-1.8	

To test whether the compaction forces applied during RC affected the disintegration properties of the superdisintegrants used, disintegration time of the tablets was measured. Previous research on the effects of dry granulation on superdisintegrant function has shown that RC has little effect on the performance of CCS [28]. Data on the disintegration time of tablets with varying amounts of CCS or SSG is given in the supplementary information (Figure S5). The specific compaction force used in the granulation process had limited effect on the disintegration time of tablets with superdisintegrant. The addition of CCS or SSG prior to granulation did promote tablet disintegration, as the disintegration time was shorter compared to that of tablets without any superdisintegrant. Increasing the amount of CCS in the formulation resulted in shorter disintegration times for tablets produced both via DC and after RC. A minor decrease in disintegration time was observed upon increasing specific compaction force, which was in line with the lower TTS of the tablets prepared at increased specific compaction forces. Therefore, the disintegration mechanisms of CCS and SSG were not significantly affected by the forces applied during the dry granulation process.

4. Discussion

In order to explain how the addition of superdisintegrant prior to granulation reduces the loss of compactibility of anhydrous lactose, the proposed mechanisms for the loss of compactibility need to be considered. Granule size enlargement has been previously shown not to affect the compactibility of brittle materials such as lactose [11,29]. Also for the current study, size enlargement cannot explain the observed loss in compactibility since the size of the granules does not increase upon increasing the specific compaction force from 7 to 16 kN/cm (Figure S1). The granules prepared at higher specific compaction force, however showed

reduced compactibility. Granule hardening has been shown to affect the compactibility of granules prepared from brittle materials such as lactose monohydrate [13]. Increasing the specific compaction force in the granulation process results in harder granules that are less susceptible to fragmentation upon tableting. It is therefore likely that a similar granule hardening mechanism accounts for the loss of compactibility of the anhydrous lactose used in this study.

The observation that the addition of superdisintegrant reduces the loss of compactibility of the granules can be explained by a reduced granule hardening effect. The poor compactibility of the superdisintegrant particles reduces the hardness of the granules, making them more prone to fragmentation during tableting. The higher degree of fragmentation of granules with intra-granular superdisintegrant results in more available bonding area during tableting and thereby reduces the loss of compactibility of the granules compared to the ungranulated powders. It is only at high specific compaction forces, where the loss of compactibility is relatively large, that the addition of superdisintegrant also has a positive effect on the absolute compactibility of the granules. The higher degree of fragmentation of granules with superdisntegrant is further supported by the solid fraction of the tablets produced from granules prepared at varying specific compaction forces (Figure 2). For tablets with 4% or 8% w/w of CCS, increasing the specific compaction force results in an increase in SF. This higher SF is the result of densification of the powders during dry granulation. For anhydrous lactose without any superdisintegrant, the increase in SF is reduced. At a tablet compression force of 15 kN, a decrease in SF upon increasing the specific compaction force is observed (Figure 2c). Granule hardening could be a reason for this decrease in SF, as the integrity of the harder granules structure survives the tablet compression step [10,12]. Granulation at high specific compaction force results in granules that are less prone to fragmentation during tablet compression. A similar mechanism was recently proposed for dry granulation of lactose monohydrate, where the decreased fragmentation tendency of granules compacted at higher specific compaction force resulted in decreased tabletability [13]. This resistance to fragmentation or deformation results in more resistance of the granules towards densification upon tablet compression, thereby causing the observed decrease in SF of the tablets. The intra-granular addition of superdisintegrant promotes granule fragmentation and therefore an increase in SF upon increasing specific compaction force is observed.

Previous studies on the reduced compactibility of granules produced via RC have indicated that lubrication of the granules prior to tableting strongly affects compactibility [8,12,13]. It has been shown that increasing the specific force has negligible effect on the compactibility of lactose monohydrate granules without the addition

of lubricant [13]. For lactose granules lubricated with MgSt on the other hand, a higher specific compaction force results in a decreased TTS. This can be explained by the decreased fragmentation tendency of granules prepared at higher specific compaction force, which results in greater MgSt coverage of the granule surfaces upon tableting [13]. In the current study, 0.5% w/w MgSt was added to all granules prior to tableting, since in a pharmaceutical manufacturing process the addition of a lubricant is generally required to reduce friction during tableting. The combination of the decreased fragmentation tendency of harder granules and the coverage of the granule surface with MgSt therefore results in the observed decrease in TTS with increasing specific compaction force. Intra-granular superdisintegrant promotes granule fragmentation, thereby creating clean lactose surface that is free form lubricant during the tableting process, which reduces the loss of compactibility of the granules. A schematic overview of the proposed mechanism is shown in Figure 4.

A positive effect of CCS on the absolute TTS values is only observed when a high specific compaction force is used in the granulation process. At low specific compaction forces, the poor compactibility of the superdisintegrant outweighs the positive effect of the superdisintegrant on granule fragmentation. Only at higher specific compaction forces, where fragmentation of the granules is strongly decreased due to granule hardening, the superdisintegrant positively contributes to the absolute tablet strength. The crossover point from a negative effect to a positive effect of superdisintegrant on TTS shows a dependence on the compression force used in the tableting process. At the lowest compression force of 5 kN (Figure 1a), the addition of CCS only shows a positive effect on TTS at the highest specific compaction force of 16 kN/cm. At this low tablet compression force, the degree of granule fragmentation is relatively low and therefore the effect of CCS is limited. At a compression force of 15 kN (Figure 1c), the addition of CCS already shows a positive effect on absolute TTS at a specific compaction force of 7 kN/cm. At this higher tablet compression force, granules show a higher degree of fragmentation and therefore the effect of the superdisintegrant is more pronounced. Therefore, the cross-over point from a negative effect to a positive effect of superdisintegrant on TTS depends on the tableting process. For tablets with SSG, the TTS values obtained are much lower compared to CCS and a positive effect of SSG on tablet strength is only observed at both a high specific compaction force during granulation and a high tablet compression force (Figure 3c). For all other process settings, the formulation without superdisintegrant shows higher tablet strength compared to the formulation with SSG.

The results of the current study show that the mechanism proposed in Figure 4 can be applied for the dry granulation of anhydrous lactose, an excipient that shows very brittle deformation behavior with a high propensity to fragment. It is likely that this positive effect of superdisintegrants on granule compactibility is only valid for granules composed of brittle materials. Excipients with plastic deformation behavior such as MCC do not show extensive fragmentation upon tablet compression. Therefore, the mechanism proposed in Figure 4 cannot be applied for materials that deform plastically. Such materials generally show a much larger loss of compactability after dry granulation due to both granule hardening and size enlargement [12]. Minimizing the loss of compactibility of MCC using the approach presented here would therefore be challenging. It would be of interest, however, to further investigate the effect of superdisintegrants on granule compactibility using other excipients with varying deformation mechanisms. Furthermore, it is likely that the positive effect of CCS on granule compactibility could also be achieved through the intra-granular addition of other components. For example, the addition of a small amount of an elastically deforming polymer prior to dry granulation may also reduce granule hardness and improve granule compactibility. Further investigation of varying excipients in combination with different minor components is required to explore the applicability of the described mechanism in a pharmaceutical manufacturing process.

5. Conclusions

The results presented in this study show that intra-granular addition of superdisintegrant in a dry granulation formulation can significantly reduce the loss of compactibility of the granules produced. The observed effects are explained with granule hardening as the main mechanism behind the loss of compactibility. Increasing the specific compaction force applied during roller compaction results in harder granules that are less prone to fragmentation during tablet compression. This reduced degree of fragmentation decreases the formation of unlubricated lactose surfaces available for bonding, which reduces tablet strength. Incorporating small amounts of superdisintegrant within the granules counteracts the hardening effect, thereby increasing the propensity of the granules to fragment during tablet compression and reducing loss of compactibility. The reduced loss of compactibility is observed for the intra-granular addition of both CCS and SSG. To optimize tablet strength, however, the addition of CCS is preferred as this results in significantly improved tablet strength compared to SSG. The intra-granular addition of superdisintegrant presents a new approach to minimize the decrease in tablet strength for a dry granulation process, compared to a direct compression

process. It should be noted that only small amounts of superdisintegrant will have a positive effect on compactability, as larger amounts will reduce the overall compactibility of the formulation and thereby reduce tablet strength. The applicability of the mechanism described here remains to be tested for powders with varying deformation behaviors in future work.

Credit author statement

Maarten Jaspers: Writing – Original Draft, Methodology, Investigation, Formal analysis, Visualization **Timo P. Roelofs:** Investigation, Formal analysis **Pauline H.M. Janssen:** Formal analysis, Writing – Review & Editing **Robin Meier:** Methodology, Investigation, Writing – Review & Editing **Bastiaan H.J. Dickhoff:** Writing – Review & Editing, Supervision

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Supplementary data

Supplementary material

References

[1] M. Leane, K. Pitt, G. Reynolds, A proposal for a drug product Manufacturing Classification System (MCS) for oral solid dosage forms, Pharmaceutical Development and Technology. 20 (2015) 12–21. https://doi.org/10.3109/10837450.2014.954728.

[2] M. Leane, K. Pitt, G.K. Reynolds, N. Dawson, I. Ziegler, A. Szepes, A.M. Crean, R. Dall Agnol, T.M.C.S. (MCS) W. Group, Manufacturing classification system in the real world: factors influencing manufacturing process choices for filed commercial oral solid dosage formulations, case studies from industry and considerations for continuous processing, Pharmaceutical Development and Technology. 23 (2018) 964–977. https://doi.org/10.1080/10837450.2018.1534863.

[3] P. Kleinebudde, Roll compaction/dry granulation: Pharmaceutical applications, European Journal of Pharmaceutics and Biopharmaceutics. 58 (2004) 317–326. https://doi.org/10.1016/j.ejpb.2004.04.014.

[4] S. Malkowska, K.A. Khan, Effect of re-compression on the properties of tablets prepared by dry granulation, Drug Development and Industrial Pharmacy. 9 (1983) 331–347. https://doi.org/10.3109/03639048309044678.

[5] M.G. Herting, P. Kleinebudde, Studies on the reduction of tensile strength of tablets after roll compaction/dry granulation, European Journal of Pharmaceutics and Biopharmaceutics. 70 (2008) 372–379. https://doi.org/10.1016/j.ejpb.2008.04.003.

[6] J.M. Bultmann, Multiple compaction of microcrystalline cellulose in a roller compactor, European Journal of Pharmaceutics and Biopharmaceutics. 54 (2002) 59–65. https://doi.org/https://doi.org/10.1016/S0939-6411(02)00047-4.

[7] H. Leuenberger, The compressibility and compactibility of powder systems, International Journal of Pharmaceutics. 12 (1982) 41–55. https://doi.org/10.1016/0378-5173(82)90132-6.

[8] C.C. Sun, P. Kleinebudde, Mini review: Mechanistic to the loss of tabletability by dry granulation, European Journal of Pharmaceutics and Biopharmaceutics. 106 (2016) 9–14. https://doi.org/10.1016/j.ejpb.2016.04.003.

[9] C. Sun, M.W. Himmelspach, Reduced tabletability of roller compacted granules as a result of granule size enlargement, Journal of Pharmaceutical Sciences. 95 (2006) 200–206. https://doi.org/10.1002/jps.20531.

[10] S. Patel, S. Dahiya, C. Calvin Sun, A.K. Bansal, Understanding size enlargement and hardening of granules on tabletability of unlubricated granules prepared by dry granulation, Journal of Pharmaceutical Sciences. 100 (2011) 758–766. https://doi.org/10.1002/jps.22315.

[11] S.J. Wu, C. Sun, Insensitivity of compaction properties of brittle granules to size enlargement by roller compaction, Journal of Pharmaceutical Sciences. 96 (2007) 1445–1450. https://doi.org/10.1002/jps.20929.

[12] J. Mosig, P. Kleinebudde, Critical evaluation of root causes of the reduced compactability after roll compaction/dry granulation, Journal of Pharmaceutical Sciences. 104 (2015) 1108–1118. https://doi.org/10.1002/jps.24321.

[13] A.L. Skelbæk-Pedersen, T.K. Vilhelmsen, J. Rantanen, P. Kleinebudde, The relevance of granule fragmentation on reduced tabletability of granules from ductile or brittle materials produced by roll compaction/dry granulation, International Journal of Pharmaceutics. 592 (2021). https://doi.org/10.1016/j.ijpharm.2020.120035.

[14] M. Tofiq, J. Nordström, A.-S. Persson, G. Alderborn, Effect of excipient properties and blend ratio on the compression properties of dry granulated particles prepared from microcrystalline cellulose and lactose, Powder Technology. 399 (2022) 117207. https://doi.org/10.1016/j.powtec.2022.117207.

[15] K.A. Riepma, H. Vromans, K. Zuurman, C.F. Lerk, The effect of dry granulation on the consolidation and compaction of crystalline lactose, International Journal of Pharmaceutics. 97 (1993) 29–38. https://doi.org/https://doi.org/10.1016/0378-5173(93)90123-w.

[16] J. Nordström, G. Alderborn, The granule porosity controls the loss of compactibility for both dry- and wet-processed cellulose granules but at different rate, Journal of Pharmaceutical Sciences. 104 (2015) 2029–2039. https://doi.org/10.1002/jps.24439.

[17] F. Freitag, K. Reincke, J. Runge, W. Grellmann, P. Kleinebudde, How do roll compaction/dry granulation affect the tableting behaviour of inorganic materials? Microhardness of ribbons and mercury porosimetry measurements of tablets, European Journal of Pharmaceutical Sciences. 22 (2004) 325–333. https://doi.org/10.1016/j.ejps.2004.04.001.

[18] S. Hein, K.M. Picker-Freyer, J. Langridge, Simulation of roller compaction with subsequent tableting and characterization of lactose and microcrystalline cellulose, Pharmaceutical Development and Technology. 13 (2008) 523–532. https://doi.org/10.1080/10837450802288972.

[19] H. Vromans, G.K. Bolhuis, C.F. Lerk, H. van de Biggelaar, H. Bosch, Studies on tableting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products, 1987.

[20] J.F. Gamble, W.S. Chiu, V. Gray, H. Toale, M. Tobyn, Y. Wu, Investigation into the degree of variability in the solid-state properties of common pharmaceutical excipients-anhydrous lactose, AAPS PharmSciTech. 11 (2010) 1552–1557. https://doi.org/10.1208/s12249-010-9527-4.

[21] L. Farber, K.P. Hapgood, J.N. Michaels, X.Y. Fu, R. Meyer, M.A. Johnson, F. Li, Unified compaction curve model for tensile strength of tablets made by roller compaction and direct compression, International Journal of Pharmaceutics. 346 (2008) 17–24. https://doi.org/10.1016/j.ijpharm.2007.06.022.

[22] K.G. Pitt, M.G. Heasley, Determination of the tensile strength of elongated tablets, Powder Technology. 238 (2013) 169–175. https://doi.org/10.1016/j.powtec.2011.12.060.

[23] P.H.M. Janssen, S. Depaifve, A. Neveu, F. Francqui, B.H.J. Dickhoff, Impact of powder properties on the rheological behavior of excipients, Pharmaceutics. 13 (2021). https://doi.org/10.3390/pharmaceutics13081198.

[24] A. Berardi, L. Bisharat, J. Quodbach, S. Abdel Rahim, D.R. Perinelli, M. Cespi, Advancing the understanding of the tablet disintegration phenomenon – An update on recent studies, International Journal of Pharmaceutics. 598 (2021) 120390. https://doi.org/10.1016/j.ijpharm.2021.120390.

[25] J. Quodbach, A. Moussavi, R. Tammer, J. Frahm, P. Kleinebudde, Tablet disintegration studied by high-resolution real-time magnetic resonance imaging, Journal of Pharmaceutical Sciences. 103 (2014) 249–255. https://doi.org/10.1002/jps.23789.

[26] A. Berardi, L. Bisharat, A. Blaibleh, L. Pavoni, M. Cespi, A simple and inexpensive image analysis technique to study the effect of disintegrants concentration and diluents type on disintegration, Journal of Pharmaceutical Sciences. 107 (2018) 2643–2652. https://doi.org/10.1016/j.xphs.2018.06.008.

[27] Z.A.M. Al-Ibraheemi, M.S. Anuar, F.S. Taip, M.C.I. Amin, S.M. Tahir, A.B. Mahdi, Deformation and mechanical characteristics of compacted binary mixtures of plastic (microcrystalline cellulose), elastic (sodium starch glycolate), and brittle (lactose monohydrate) pharmaceutical excipients, Particulate Science and Technology. 31 (2013) 561–567. https://doi.org/10.1080/02726351.2013.785451.

[28] S. Berkenkemper, J. Lee Keizer, M. Lindenberg, A. Szepes, P. Kleinebudde, Functionality of disintegrants with different mechanisms after roll compaction, International Journal of Pharmaceutics. 584 (2020) 119434. https://doi.org/10.1016/j.ijpharm.2020.119434.

[29] P.H.M. Janssen, M. Jaspers, R. Meier, T.P. Roelofs, B.H.J. Dickhoff, The effect of excipient particle size on the reduction of compactibility after roller compaction, International Journal of Pharmaceutics: X. 4 (2022) 100117. https://doi.org/10.1016/j.ijpx.2022.100117.

Figure 1. Tablet tensile strength plotted as a function of specific compaction force for tablets with varying amounts (% w/w) of CCS, compressed at (a) 5 kN, (b) 10 kN and (c) 15 kN. Error bars represent standard

deviations calculated over 20 tablets for each data point. Solid lines represent linear fits to quantify the loss of compactibility upon increasing specific compaction force.

Figure 2. Solid fraction of tablets produced at compression forces of (a) 5 kN, (b) 10 kN and (c) 15 kN. Error bars represent standard deviations calculated over 20 tablets. The amount of CCS in the formulation affects the impact of the specific compaction force on tablet solid fraction.

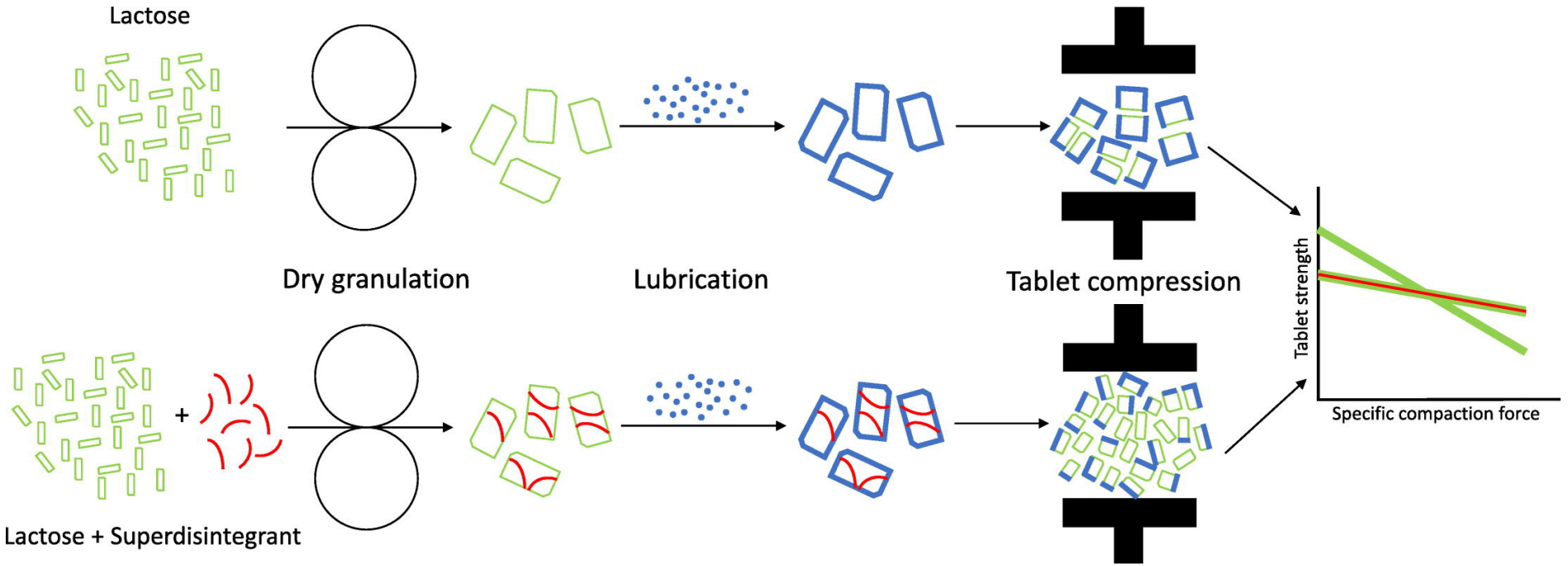
Figure 3. Tablet tensile strength plotted as a function of specific compaction force for tablets with 4% w/w of CCS or SSG and without superdisintegrant, compressed at (a) 5 kN, (b) 10 kN and (c) 15 kN. Error bars represent standard deviations calculated over 20 tablets for each data point. Solid lines represent linear fits to quantify the loss of compactibility upon increasing specific compaction force.

Figure 4. Schematic representation of the proposed mechanism for the loss of compactibility after dry granulation of anhydrous lactose with and without superdisintegrant. The intra-granular addition of superdisintegrant promotes the fragmentation of granules during tablet compression, resulting in more unlubricated lactose surface available for bonding. The resulting effect on tablet strength depends on the amount of superdisintegrant added, the specific compaction force during granulation and the tablet compression force used.

Graphical Abstract

Highlights

- Superdisintegrants can reduce loss of compactibility in dry granulation
- Intra-granular superdisintegrant promotes granule fragmentation during tableting
- Granule hardening reduces the compactibility of anhydrous lactose
- Superdisintegrants can be used to reduce the granule hardening effect
- Superdisintegrant performance is not affected by dry granulation



Graphics Abstract

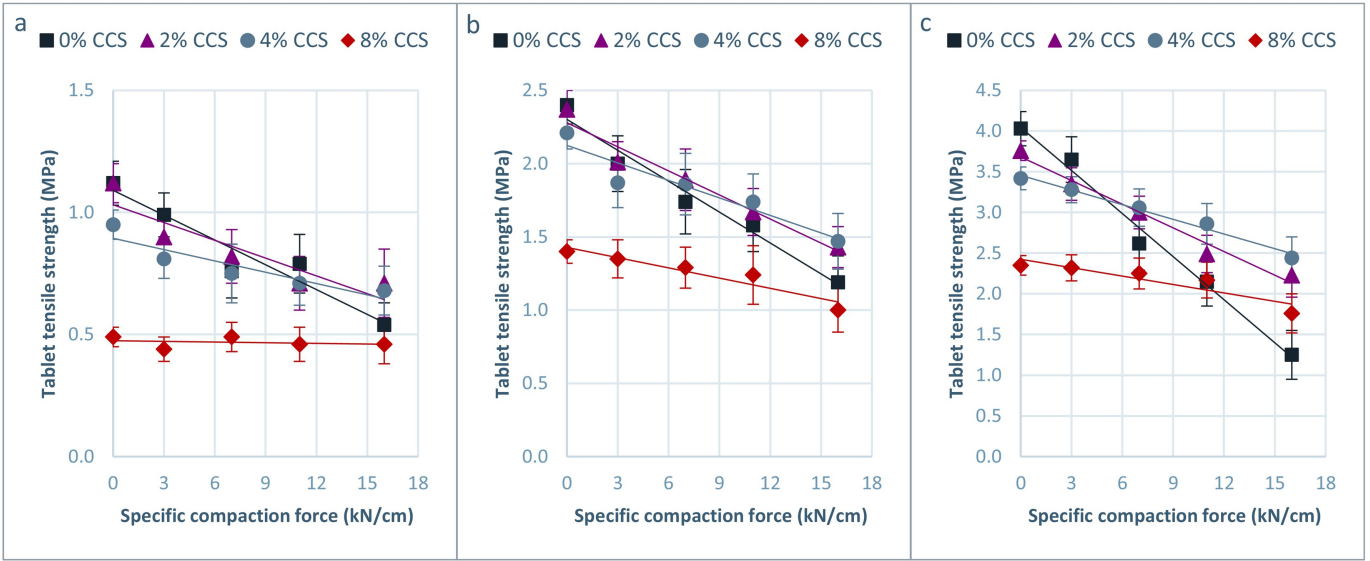

a
0% CCS
2% CCS
4% CCS
8% CCS
Tablet tensile strength (MPa)
Specific compaction force (kN/cm)
b
0% CCS
2% CCS
4% CCS
8% CCS
Tablet tensile strength (MPa)
Specific compaction force (kN/cm)
c
0% CCS
2% CCS
4% CCS
8% CCS
Tablet tensile strength (MPa)
Specific compaction force (kN/cm)

Figure 1

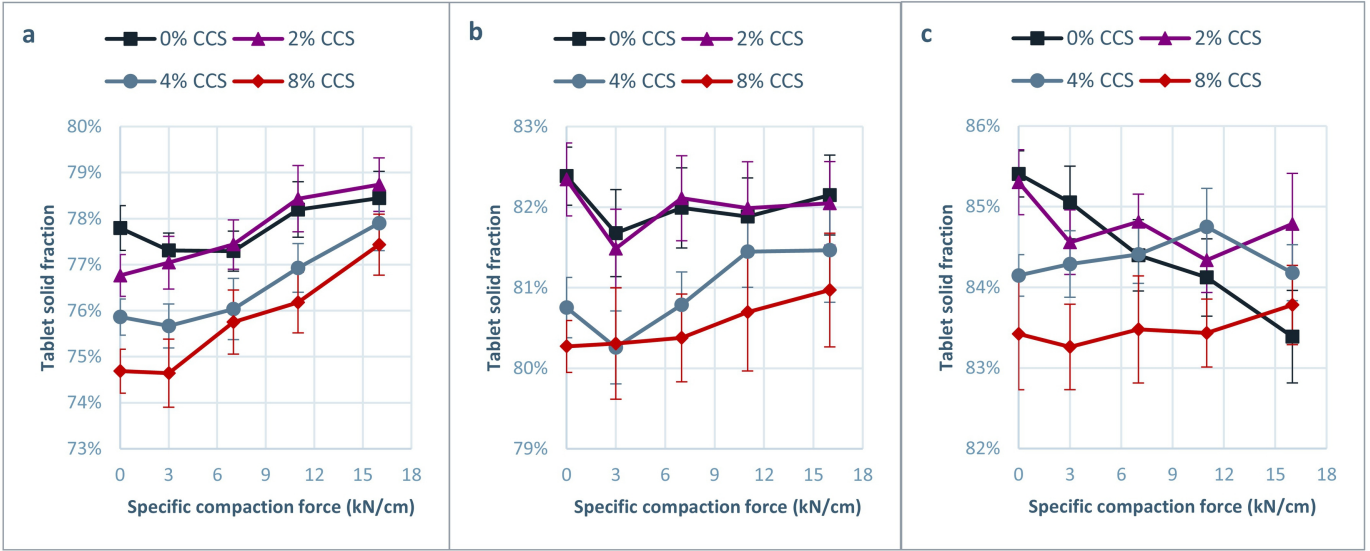

a
0% CCS
2% CCS
4% CCS
8% CCS
80%
79%
78%
77%
76%
75%
74%
73%
Tablet solid fraction
0 3 6 9 12 15 18
Specific compaction force (kN/cm)
b
0% CCS
2% CCS
4% CCS
8% CCS
83%
82%
81%
80%
79%
Tablet solid fraction
0 3 6 9 12 15 18
Specific compaction force (kN/cm)
c
0% CCS
2% CCS
4% CCS
8% CCS
86%
85%
84%
83%
82%
Tablet solid fraction
0 3 6 9 12 15 18
Specific compaction force (kN/cm)

Figure 2

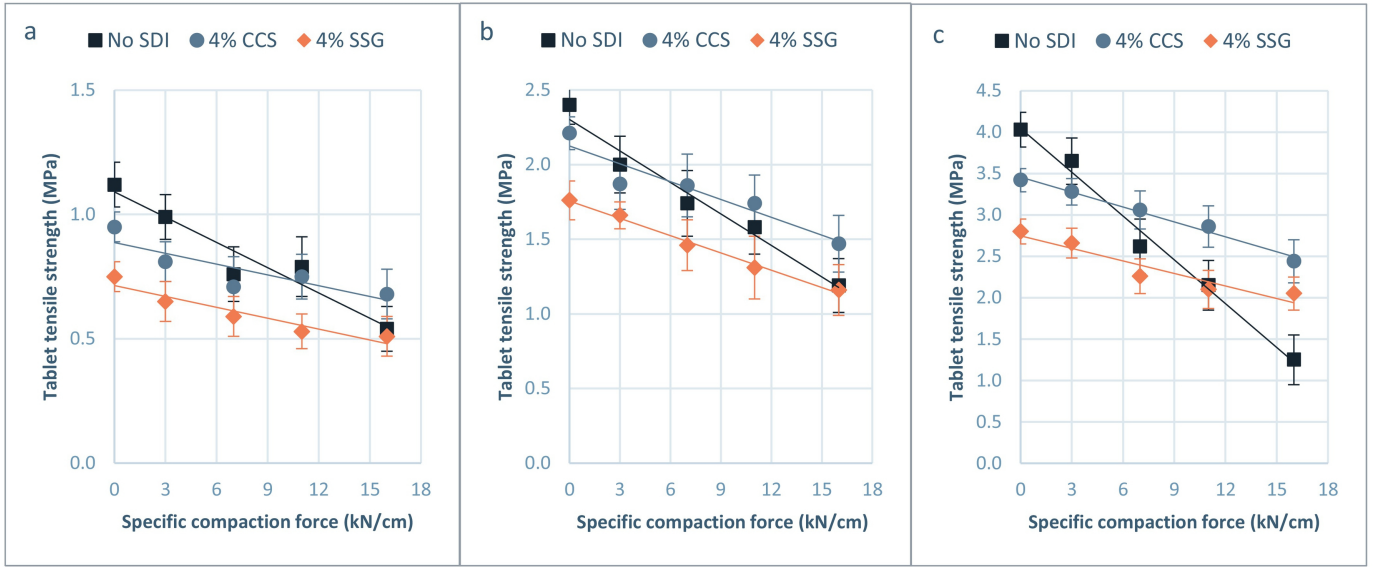

a
No SDI
4% CCS
4% SSG
Tablet tensile strength (MPa)
1.5
1.0
0.5
0.0
0
3
6
9
12
15
18
Specific compaction force (kN/cm)
b
No SDI
4% CCS
4% SSG
Tablet tensile strength (MPa)
2.5
2.0
1.5
1.0
0.5
0.0
0
3
6
9
12
15
18
Specific compaction force (kN/cm)
c
No SDI
4% CCS
4% SSG
Tablet tensile strength (MPa)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
3
6
9
12
15
18
Specific compaction force (kN/cm)

Figure 3

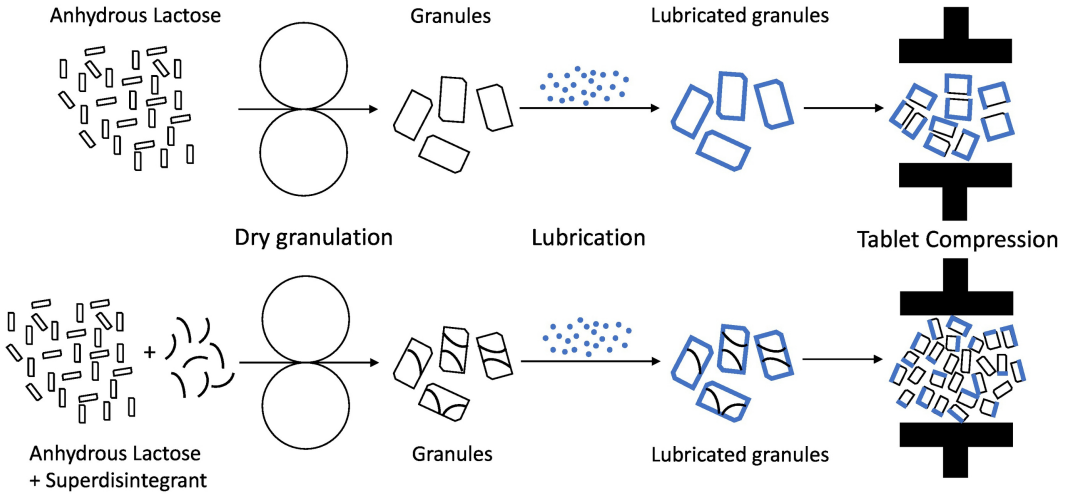

Anhydrous Lactose
Granules
Lubricated granules
Dry granulation
Lubrication
Tablet Compression
Anhydrous Lactose
+ Superdisintegrant
Granules
Lubricated granules

Figure 4