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Effect of force feeder on tablet strength during compression

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ABSTRACT

Mechanical strength of tablets is an important quality attribute, which depends on both formulation and process. In this study, the effect of process variables during compression on tablet tensile strength and tabletability (the ratio of tensile strength to compression pressure) was investigated using a model formulation. Increase in turret and force feeder speeds reduced tablet tensile strength and tabletability. Turret speed affected tabletability through changes in dwell time under the compression cam and the kinetics of consolidation of granules in the die cavity. The effect of force feeder was attributed to the shearing of the granulation, leading to its over-lubrication. A dimensionless equation was derived to estimate total shear imparted by the force feeder on the granulation in terms of a shear number. Scale-independence of the relationship of tabletability with the shear number was explored on a 6-station Korsch press, a 16-station Betapress, and a 35-station Korsch XL-400 press. The use of this relationship, the exact nature of which may be formulation dependent, during tablet development is expected to provide guidance to the scale-up and interchangeability of tablet presses.

1. Introduction

Mechanical strength of tablets is an important quality attribute that affects tablet integrity and attrition during the downstream unit operations such as coating and packaging. Maintaining acceptable and consistent tablet strength during the scale-up of a formulation is critical to successful new tablet formulation development. Tablet tensile strength is affected by both formulation and manufacturing process. Reduction in tablet tensile strength and tabletability (the ratio of tensile strength of tablets to compression pressure) are often observed during the scale-up of the tableting unit operation. This effect is mainly attributed to the press speed (Heinz et al., 2000).

Tablet strength is a function of the consolidation mechanism of formulation components (Van Der Voort Maarschalk and Bolhuis, 1999). For example, the main consolidation mechanism of α-lactose monohydrate (LM) is brittle fracture, leading to particle fragmentation; while microcrystalline cellulose (MCC) undergoes plastic deformation (Edge et al., 2009; Guy, 2009). MCC is a powder containing agglomerated primary particles, which are more porous than LM. Particle shape, size, and density of MCC affect flow, lubricity, and compactibility (Ishino et al., 1990; Iida et al., 1997; Pesonen and Paronen, 1990). MCC is often combined with LM in immediate release tablet formulations (Arida and Al-Tabakha, 2008; Horisawa et al., 2000). While powdered grade of lactose may be used for wet granulation formulations, a coarse and relatively uniform particle size grade of LM is used for directly compressible formulations. Tablet strength of formulations that use MCC and LM generally increases with increasing proportion of MCC. Also, tablet strength generally decreases with increasing lubricant (magnesium stearate) concentration.

In addition, speed of the die table, or turret, affects both the speed of upper punch penetration in the die during tablet compression and the duration of time the powder bed stays in its most consolidated state under the compression cam (dwell time). The plastic deformation of the granulation in the die during compression is a stress- and time-dependent rheological phenomenon. Hence, compression pressure and turret speed significantly affect tablet strength (Akande et al., 1998).

During tablet formulation development, the effects of compression force and turret speed are assessed at the laboratory scale before scale-up. Instruments, such as the Presster linear rotary tablet press simulator (Metropolitan Computing Corporation, East Hanover, NJ), are used to compress tablets at various compression forces and punch speeds, thus simulating different press types and turret speeds (Cantor et al., 2009). However, for a given formulation, the reduction in tablet tensile strength at constant compression force during product scale-up is frequently greater

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than what would be expected based on the effects of turret speed alone.

In rotary tablet presses, a force feeder is used for efficient filling of the die with the granulation before compression. During tablet manufacture, both turret speed and force feeder speed are adjustable parameters. The turret speed is adjusted based on the competing needs to maximize production capacity, while keeping the dwell time within a range that produces tablets with acceptable tensile strength. Selection of force feeder speed, however, is empirical. It is adjusted to achieve desired tablet weight and acceptable tablet-to-tablet weight variation. Several investigators have studied the effect of force feeder on die filling (Ridgway et al., 1972; Yaginuma et al., 2007; Sinka et al., 2009). However, the effect of force feeder on tablet tensile strength has not been reported quantitatively.

In this study, the effect of force feeder speed on tablet strength during compression was investigated using a model formulation. A 1:1 (w/w) mixture of MCC:LM was used in this study since these excipients are commonly used in combination in immediate release oral solid dosage forms. Therefore, the results obtained using this formulation are expected to be relevant to a majority of commercial tablet formulations.

Tablet strength correlated inversely with force feeder speed. Shearing of the granulation containing magnesium stearate along its axis of movement in the force feeder was hypothesized to result in over-lubrication of the granules. A dimensionless equation was derived for the shear number (S_N) to estimate the shear imparted by the force feeder on the granulation. This analysis accounted for the design elements of the force feeder, tablet weight, turret speed, number of punches, mass of granulation in the force feeder during compression, and the force feeder speed. Scale-independence of the relationship of tabletability with the shear number was explored across a 6-station Korsch press, 16-station Betapress, and 35-station Korsch XL-400 press using a placebo tablet formulation. The dimensionless shear number accounted for the observed effects of force feeder speed on tabletability on these presses.

2. Materials and methods

A directly compressible placebo blend was prepared with microcrystalline cellulose (MCC; Avicel PH-102®, FMC BioPolymer, Philadelphia, PA), lactose monohydrate (LM; directly compressible grade, Kerry Bio-Science, Norwich, NY), 5% (w/w) croscarmellose sodium (CCS; Ac-Di-Sol®; FMC BioPolymer, Philadelphia, PA), and magnesium stearate (MgSt; Mallinckrodt, Inc., St. Louis, MO) using equal MCC/LM w/w ratios and 0.5% or 2.0% (w/w) MgSt. LM, MCC, and CCS were mixed in a bin blender (A&M Process Equipment Ltd., Toronto, ON, CA) at 25 rpm for 10 min. Then, MgSt was sifted through #30 mesh and added to the blender. Lubrication in the blender was carried out at 25 rpm for 10 min.

In addition, a model low drug load wet granulation formulation was prepared by wet granulation using 2.5% (w/w) BMS Compound A as the active ingredient, 33% (w/w) MCC and 50.5% (w/w) LM as fillers, 5% (w/w) crospovidone as the disintegrant, 5% (w/w) povidone as the binder, 3% (w/w) colloidal silicon dioxide as the glidant, and 1% (w/w) MgSt as the lubricant. Disintegrant, glidant, and MCC were split between the intra-granular and extra-granular portions in approximately equal quantities. After granulation in a high shear granulator, the granules were sized using comil (Quadro Engineering Corp., Waterloo, ON, Canada) and blended with extra-granular excipients in a bin blender at 25 rpm for 10 min. Lubrication with MgSt was carried out similar to that described above for the directly compressible placebo formulation.

The blends were compressed into tablets on instrumented presses – Korsch press (PH106, 6-stations; Korsch Maschinenfabrik, Berlin, Germany), Manesty Betapress (16-stations; Manesty Machines Ltd, Liverpool, England), or Korsch XL-400 press (35-stations). Tablets of 200 or 900 mg press weight were compressed using 5/16″ or 1/2″ diameter standard concave, unembossed punches (Elizabeth Carbide Die Co., Inc., McKeesport, PA). Compression forces during tableting were monitored using Advanced Instrumentation Monitor (Metropolitan Computing Corporation, East Hanover, NJ) for the 6-station Korsch and the 16-station Beta press, and using the vendor supplied press software for the Korsch XL-400 press.

The presses were operated at 3–4 force feeder (FF)/turret (TR) speed ratios depending on the permissible range of FF and TR speeds. At each speed ratio, tablets were collected at 8–10 different compression forces after equilibration of compression run for 5–15 min at each compression force. Weight, thickness, and hardness (using Dr. Schleuniger 6D Tablet Tester, Dr Schleuniger Pharmatron, Inc., Manchester, NH) of 10 tablets were recorded at each compression force. In one set of experiments, residence time of the blend in the force feeder was varied by changing the number and size of punches. The effect of tablet dwell time (during compression) on tablet strength was simulated using Presster tablet press simulator.

Weight, thickness, and hardness of tablets were measured and converted into tensile strength (σ_t, in Pascals) (Pitt et al., 1989; Pitt and Newton, 1988) and compaction pressure (CP, in Pascals) using the following formulae.

$$\sigma_t = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1}$$

where 'P' is the fracture load, or the force required to break the tablet in Newton and is calculated from crushing strength or hardness (1 Strong Cobb Unit (SCU) = 7 N); 'D' is the diameter of the tablet in meter; 't' is the thickness of the tablet in meter; and 'W' is the central cylinder thickness for biconvex tablets.

$$\text{CP} = \frac{\text{CF}}{A}$$

where 'CF' is the compaction force under the main compression cam during tableting in Newton; and 'A' is the calculated tablet crown surface area in m^2.

Tabletability was estimated as the ratio of tensile strength of tablets to the applied compaction pressure through the initial, linear (coefficient of determination (R^2) ≥ 0.98) part of the compaction profile.

3. Results

The effect of tablet press or turret speed on the mechanical strength of tablets was estimated using the Presster simulator. A directly compressible placebo formulation was used to compress tablets of constant (target ± 1%) weight using different linear speeds of the punches at various compression forces. Tensile strength of tablets was calculated using their diametrical crushing strength, or hardness, and thickness. Compression pressure on the granulation was calculated using the force used for compression and the face area of the punches. As shown in Fig. 1, decreasing dwell time, reflective of increasing punch speed, led to lower achievable tensile strength as well as lower initial slope of the compression pressure-tensile strength curves. The achievable mechanical strength correlated with the initial slope of the curve, which represents tabletability.

A plot of log(tabletability) against dwell time used for compression (Fig. 2) showed that at relatively high dwell times (30–120 ms), commonly encountered in small scale rotary tablet presses, log(tabletability) is significantly affected by the dwell time. Thus, at small scales, increasing the press or turret speed would

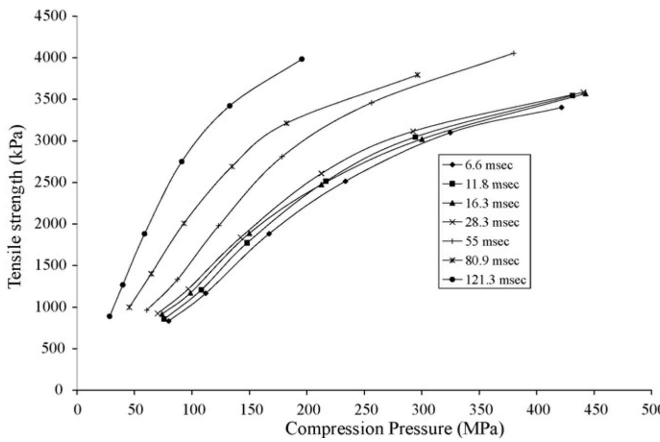

Fig. 1. Effect of turret speed, inversely reflected in the dwell time of the granulation under the compression cam, on the compression profile of a directly compressible placebo formulation. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 0.5% (w/w) magnesium stearate as a lubricant. Tablets of 200 mg press weight were compressed using 5/16″ standard concave, round punches on a Presster tablet press simulator at different compression forces for each dwell time. Each data point represents an average of $n = 3$ tablets.

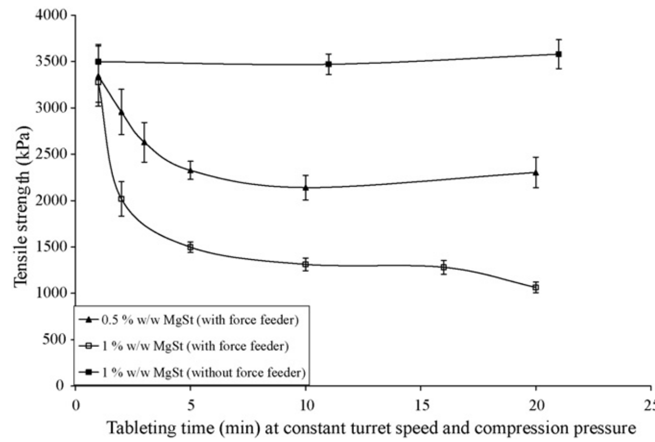

Fig. 3. Effect of force feeder on the tensile strength of tablets as a function of time during tableting. Tablets of 100 mg press weight were compressed on a 6-station Korsch press using a low (2.5%, w/w) drug load wet granulation formulation containing either 0.5% (w/w) or 1.0% (w/w) magnesium stearate (MgSt). The 1.0% (w/w) MgSt containing formulation was also compressed by gravity feed, i.e., without the use of a force feeder. Each data point represents the average and standard deviation of $n = 10$ tablets.

significantly reduce dwell time and log(tabletability). At low dwell times (<30 ms), typically representative of high speed production presses, the change in tabletability with dwell time was marginal (Fig. 2).

Reduction in tensile strength of tablets is sometimes observed under conditions of constant compression pressure and press speed. As shown in Fig. 3, a model low drug load wet granulation formulation, when compressed on a 6-station Korsch press, showed time-dependent decrease in the tensile strength of tablets at a constant compression force of ∼10 kN. The rate of decline in the tensile strength as well as its achievable limit after a certain period of time were dependent on the amount of lubricant and the use of force feeder. Thus, a formulation with 1.0% (w/w) magnesium stearate (MgSt) showed greater absolute decline as well as the rate of decrease of tablet strength at a constant compression force than a similar formulation with 0.5% (w/w) MgSt. This indicated that the loss in tablet strength during compression was related to the over-lubrication of the blend. Further, the absence of this loss in tablet strength over the same period of time with the use of gravity feed (no force feeder) indicated that the over-lubrication of the blend could be attributed to the force feeder. The initial rapid decline followed by reaching an apparent state of constant tablet tensile strength reflected the process of reaching an equilibrium in the flow of the granulation through the force feeder during tablet compression. Therefore, tablet strength measurement for all subsequent studies was carried out after 10–20 min of compression to reflect the equilibrium state of compression.

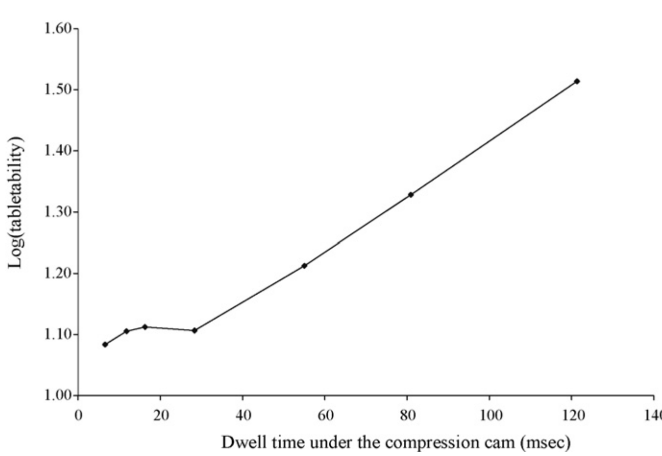

Fig. 2. Effect of turret speed, inversely reflected in the dwell time of the granulation under the compression cam, on the tabletability of a directly compressible placebo formulation. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 0.5% (w/w) magnesium stearate as a lubricant. Tablets of 200 mg press weight were compressed using 5/16″ standard concave, round punches on a Presster tablet press simulator at different compression forces for each dwell time. Tensile strength of an average of $n = 3$ tablets for each compression force was used for tabletability calculation. Tabletability was estimated as the ratio of tensile strength of tablets to the applied compression pressure through the initial, linear (coefficient of determination (R^2) ≥ 0.98) part of the compression profile.

The compression profiles at equilibrium were investigated further with a directly compressible MCC/LM-based placebo formulation on a 6-station Korsch press, a 16-station Betapress, and a 35-station Korsch XL-400 press (Fig. 4). Increasing the force feeder (FF) speed at a constant turret (TR) speed during compression resulted in significant decrease in tablet strength as a function of compression pressure. It is notable that the use of lower turret speed (20 rpm instead of 30 rpm, corresponding to a dwell time of 121.3 ms instead of 80.9 ms) did not compensate for the reduction in tablet tensile strength when the force feeder speed was increased from 90 to 180 rpm for the 6-station Korsch press.

Scale-up of the placebo formulation from a 6-station Korsch press to a 16-station Manesty Betapress resulted in improved tablet strength and tabletability (Fig. 4A). However, the tensile strength achievable on the high speed 35-station Korsch XL-400 press (Fig. 4B) was intermediate between that obtained on the 6-station Korsch press and the 16-station Betapress (Fig. 4A).

As expected, the tensile strength of tablets increased with compression pressure. The rate of increase of and the maximum achievable tablet strength reduced with increasing force feeder speed. In other words, greater compression pressures were needed to achieve a target tensile strength at higher force feeder speeds and, in some cases, a target tensile strength could not be achieved. These results clearly implicated the role of force feeder in the achievable mechanical strength of tablets in rotary tablet presses.

Increasing the speed of the force feeder increases the shearing of the granulation, which increases the over-lubrication of the granules resulting in lower mechanical strength of tablets. The total shear on the granulation by the force feeder could be changed

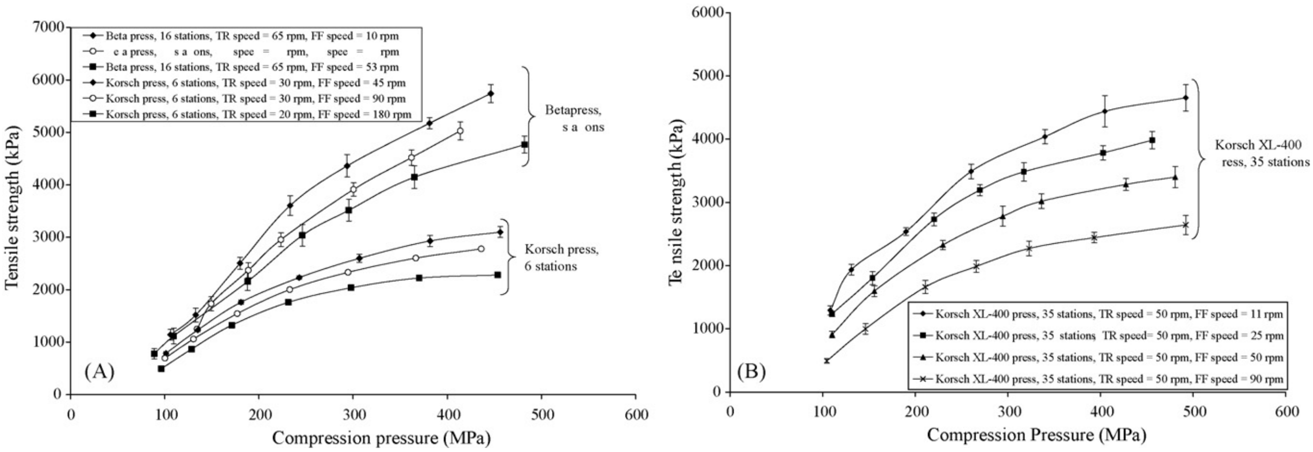

Fig. 4. Effect of force feeder (FF) on the compression profile of a directly compressible placebo formulation. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 0.5% (w/w) magnesium stearate as a lubricant. Tablets of 200 mg press weight were compressed using 5/16″ standard concave, round punches on a 6-station Korsch press (A), 16-station Betapress (A), and 35-station Korsch XL-400 press (B). Different FF speeds were used at a constant turret (TR) speed; except in the case of Korsch press operated at 180 rpm FF speed, where 20 rpm TR speed was used. Each data point represents the average and standard deviation of $n = 10$ tablets.

by changing the shear intensity (i.e., force feeder speed) or the total duration of shear. Therefore, to verify that shearing action of the force feeder is indeed responsible for the over-lubrication of granulation and loss of mechanical strength of tablets, the effect of duration of shearing of the granulation in the force feeder was studied. It was hypothesized that changing the rate of flow of the granulation through the force feeder without changing the force feeder speed should affect the shearing and lubricating effect of the force feeder.

To test this hypothesis, a 6-station Korsch press was operated with 2, 4, or 6 punches resulting in the granulation residence times in the force feeder of 7.5, 5.0, or 2.5 min, respectively (calculated using Eq. (3), described later). To obtain a significant range of residence times in the force feeder, higher tablet press weight (900 mg) was used in this study. Correspondingly, higher lubricant concentration (2% (w/w) MgSt) and force feeder speed were used. The results of this study (Fig. 5) indicated that tablet strength and

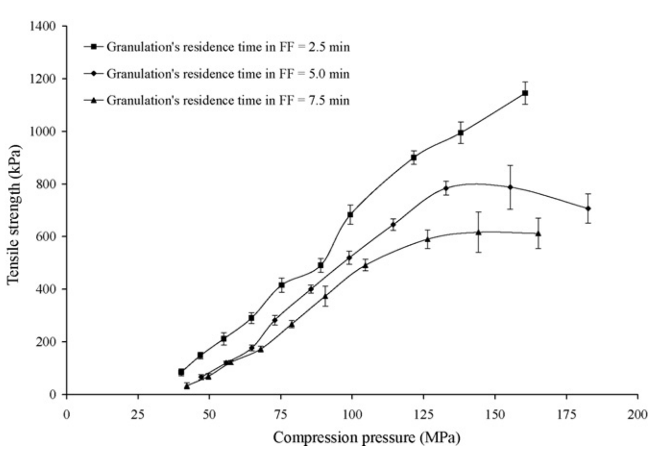

Fig. 5. Effect of residence time (RT) of the blend in the force feeder (FF) on the compression profile of a directly compressible placebo blend. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 2% (w/w) magnesium stearate as a lubricant. Tablets of 900 mg press weight were compressed using 1/2″ standard concave, round punches on a 6-station Korsch press. The FF/turret (TR) ratio was kept constant at 9:1. Residence time in the FF was varied by changing the number of punches installed on the press and was calculated using the equation mentioned in the text. Each data point in the compression profile represents the average and standard deviation of $n = 10$ tablets.

tabletability reduce with an increase in the residence time of the powder blend in the force feeder.

The combined effect of turret and force feeder speeds on the compression profile of a directly compressible placebo blend was studied on a 35-station Korsch XL-400 press (Fig. 6). Increasing the turret speed from 50 to 75 rpm reduced tablet strength and compression profile at all force feeder speeds. The effect of turret speed reflected a combined effect of the change in the dwell time of the granulation under the compression cam (11.8 ms at 50 rpm to 6.6 ms at 75 rpm) and the residence time of the granulation in the force feeder.

The effect of turret speed indicates the role of kinetics of powder consolidation during compaction, while the effect of force feeder speed indicates the impact of shearing action of the force feeder. It is notable that the effect of force feeder speed on the tensile strength of tablets (reflected in the changing y-axis scale between different sub-graphs in Fig. 6) was much greater than the effect of turret speed at any given force feeder speed.

These results indicated a need to estimate the total shear on the granulation by the force feeder which would take into account both the shear intensity (force feeder speed) and the total time of shear (residence time in the force feeder). An empirical equation was derived for the shear number (S_N), discussed later, as a quantitative estimate of total shear in the force feeder. A plot of log(shear number) against log(tabletability) for the directly compressible placebo formulation compressed on a 6-station Korsch press, a 16-station Betapress, and a 35-station Korsch XL-400 press resulted in an approximately linear decline in tabletability with total shear (Fig. 7). The maximum achievable tabletability was close to that obtained without the use of a force feeder (using gravity feed, T_G). Therefore, a critical level of shear (Sc) was defined, above which the tabletability of the granulation was significantly affected by the shearing action of the force feeder.

4. Discussion

Mechanical strength of tablets is an important quality attribute, which depends on both formulation and process. The mechanical strength of a tablet is expressed in terms of its tensile strength, which is calculated indirectly using the diametrical crushing strength, or hardness, for round tablets. Fell and Newton derived the following equation for calculating the tensile strength (σ_t, in

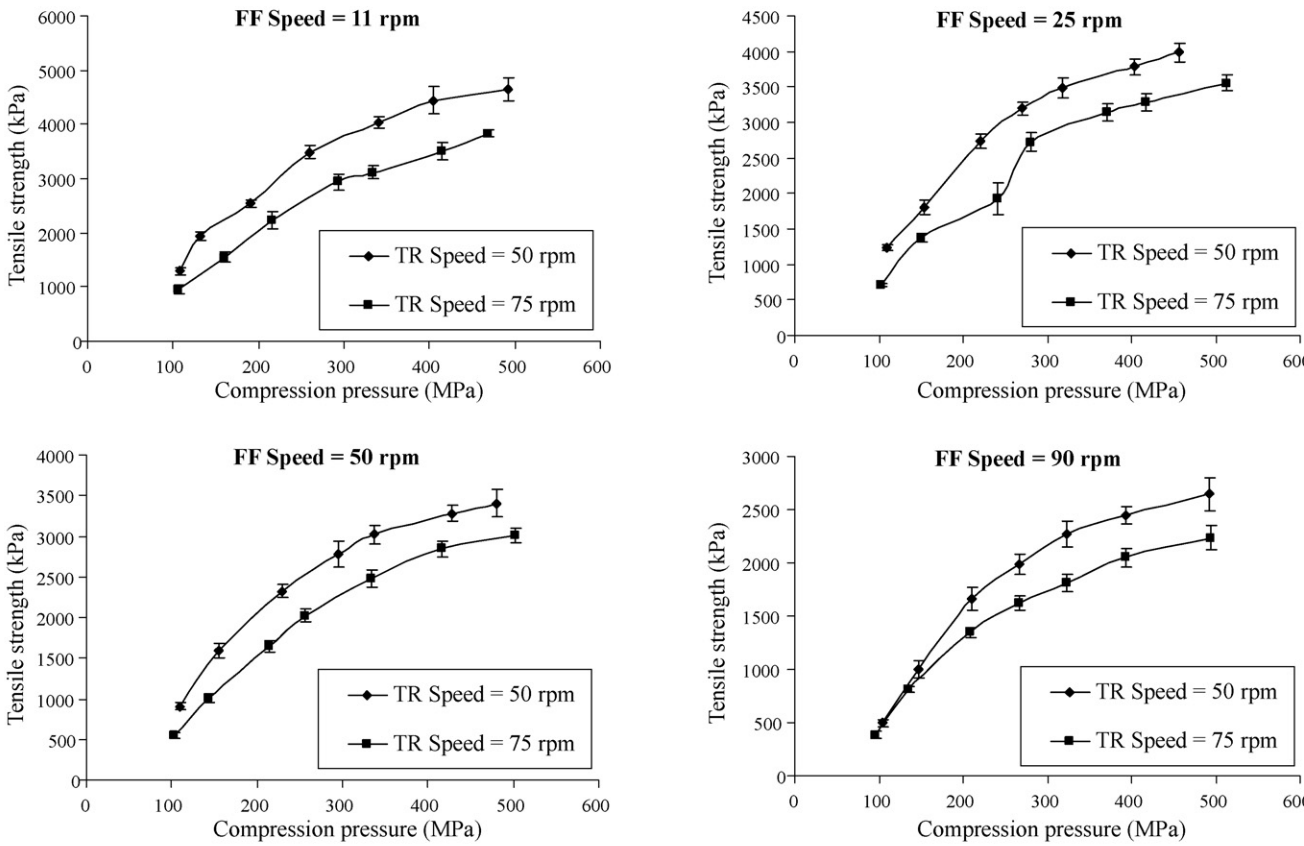

Fig. 6. Combined effect of turret (TR) and force feeder (FF) speeds on the compression profile of a directly compressible placebo blend. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 0.5% (w/w) magnesium stearate as a lubricant. Tablets of 200 mg press weight were compressed using 5/16″ standard concave, round punches on a 35-station Korsch XL-400 press. TR speeds of 50 or 75 rpm were used at FF speeds of 11, 25, 50, and 90 rpm. Each data point represents the average and standard deviation of $n = 10$ tablets.

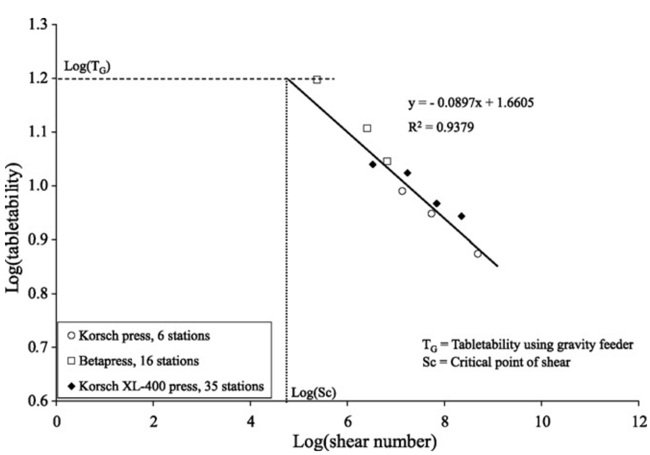

Fig. 7. Quantifying the effect of force feeder (FF) in terms of a dimensionless shear number (S_N). An approximately linear correlation of log(tabletability) with log(shear number) within and across different presses represents the effect of FF on the tabletability of a directly compressible placebo formulation. A 1:1 (w/w) mixture of microcrystalline cellulose and lactose monohydrate was mixed with 5% (w/w) croscarmellose sodium as a disintegrant and 0.5% (w/w) magnesium stearate as a lubricant. Tablets of 200 mg press weight were compressed using 5/16″ standard concave, round punches on a 6-station Korsch press, 16-station Betapress, and 35-station Korsch XL-400 press at different compression forces using different FF speeds. Tensile strength of an average of $n = 10$ tablets for each compression force was used for tabletability calculation. Tabletability was estimated as the ratio of tensile strength of tablets to the applied compression pressure through the initial, linear (coefficient of determination (R^2) ≥ 0.98) portion of the compression profile. The figure shows an approximately linear fit to the tabletability obtained across different presses. The tabletability obtained without the use of a force feeder (T_G) is indicated on the y-axis. A critical point of shear (Sc) is defined in terms of the S_N, above which the effect of FF on tablet strength becomes significant.

Pascals) of fragile flat faced cylindrical discs (Fell and Newton, 1970).

$$\sigma_t = \frac{2P}{\pi D t}$$

where 'P' is the fracture load, or the force required to break the tablet, in Newton; 'D' is the diameter of the tablet, in meter; and 't' is the thickness of the tablet, in meter.

Routine tableting operations in high speed rotary tablet presses, however, use biconvex tablets with beveling at the edges. The applicability of this equation to the biconvex tablets is limited due to the differences in the distribution pattern of forces. Pitt et al. modified this equation to the following expression for estimation of tensile strength of biconvex tablets (Pitt and Newton, 1988; Pitt et al., 1989), which was used for the calculation of tensile strength of tablets in this study.

$$\sigma_t = \frac{10P}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1}$$

where 'W' is the central cylinder thickness for biconvex tablets.

The compaction pressure (in Pascals) on the tablet was estimated by dividing the compression force by the punch face area.

$$\mathrm{CP} = \frac{\mathrm{CF}}{A}$$

where 'CF' is the compaction force under the main compression cam during tableting, in Newton; and 'A' is the calculated tablet crown surface area, in m^2.

Convexity of the tablet face and beveling at the edges leads to inaccuracy in the calculations of the tensile strength and the compaction pressure. Nevertheless, since the same tool sets were used for most of the reported studies, the results of these calculations could be compared with each other to derive trends and meaningful conclusions.

The speed of the tablet press, or the turret speed, is the main factor affecting the mechanical strength of tablets during compression. This effect is primarily attributed to the changes in dwell time of the granulation under the main compression cam and to the differences in the speed of punch penetration in the die cavity, leading to different consolidation kinetics of the granulation (Tye et al., 2005). The effect of changes in the linear speed of the punches, reflecting the turret speed during compression, is usually studied on the small scale using Presster simulator (Cantor et al., 2009).

As expected, compression of the directly compressible placebo granulation on a Presster simulator with increasing linear punch speeds, reflecting lower dwell times and higher turret speeds, resulted in lower tensile strength of the tablets and reduction in the initial slope of the compression pressure-tensile strength profile, or tabletability (Fig. 1).

Tabletability represents capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure (Sun and Grant, 2001). It is typically represented by a plot of tensile strength versus compaction pressure (Sun and Himmelspach, 2006). Tablet strength at a given compression pressure and tabletability are closely related and usually covary. To obtain a quantitative number for tabletability, the initial, linear portion of the compression profile was used to calculate the ratio of tensile strength of the tablets to the compression pressure.

The changes in tabletability with dwell times used in the Presster study are illustrated in Fig. 2. The effect of dwell time on tabletability is much more significant at higher dwell times (>30 ms), that are commonly associated with the small scale rotary tablet presses, than lower dwell times (<30 ms) associated with high speed tablet presses. This phenomenon can result in significant reduction of tablet strength on scaling up the formulation.

However, the dwell time effect does not explain changes in tablet strength and tabletability when tableting is carried out at the same scale using different force feeder speeds. For example, at constant compression pressure and turret speed, a rapid decline in the tablet tensile strength was observed at the initiation of tableting unit operation (Fig. 3). When a force feeder was not used, the tablet strength did not decline over time. This indicated that reduction in tablet strength at the initiation of compression was attributable to the action of force feeder on the granulation. The role of force feeder in shearing the granulation during tableting is well known. Some investigators have used a cylindrical cell model to simulate the shearing action of the force feeder on the granulation (Mehrotra et al., 2007). In this study, however, the actual force feeder and tablet presses were used to enable direct application of the results obtained to pharmaceutical manufacturing.

The decline in tablet tensile strength with the use of a force feeder was greater when 1.0% (w/w) magnesium stearate (MgSt) containing formulation was compressed, compared to the 0.5% (w/w) MgSt containing formulation (Fig. 3). This indicated that the effect of force feeder was related to the over-lubrication of the granulation. Also, tabletability data closely correlated with the compactibility of the blends (data not shown), indicating that the changes in tensile strength were not due to changes in the solid fraction, and could be attributed to the extent of lubrication.

Magnesium stearate is a commonly used lubricant in pharmaceutical manufacturing (Chowhan, 1993). The hydrophobic nature of magnesium stearate (Llusa et al., 2010) and its tendency to coat the surface of the granules can lead to undesirable effects on product performance attributes such as disintegration time, dissolution rate, and compaction properties of the blend (Rao et al., 2005; He et al., 2007; Patel et al., 2007). Tablet formulations whose one or more product attributes significantly change with the concentration and/or mixing with the lubricant are called lubrication sensitive formulations. These formulations frequently show changes in product quality attributes upon change of scale of manufacture during new tablet formulation development and change of tablet presses during routine production. Lubrication sensitivity of solid formulations is often investigated during new product development by studying the concentration and mixing time of lubricant in a low shear mixer/granulator (Eddington et al., 1998; Shah and Mlodozeniec, 1977).

Process conditions, such as prolonged mixing (Ragnarsson et al., 1979) or high shear during mixing (Van Der Watt and De Villiers, 1997) can lead to over-lubrication of the blend. The effects of over-lubrication on the compaction properties of the blend can affect the manufacturability of a formulation. These effects include limitation on the maximum hardness that can be achieved, need for higher compression forces to achieve the target hardness, and/or low slope of the compression force versus tablet hardness curve. These effects frequently vary in tandem and are interrelated. Therefore, in this study, the ratio of tensile strength of the tablets to the compression pressure (tabletability) was used as a quantitative expression of the lubrication effects on tablet strength.

The effect of force feeder was reflected both in the initial decline and the final achievable tablet tensile strength (Fig. 3). Since the initial decline is difficult to study due to the rapidity of the process and it is less relevant to prolonged compression operations, this study focused on the equilibrium tablet strength and tabletability.

Changing the force feeder speed resulted in reduction of tablet strength and compression profile at constant turret speed on three different types and scales of presses, viz. 6-station Korsch press, 16-station Betapress, and 35-station Korsch XL-400 press (Fig. 4A and B). The effect of force feeder speed on tabletability can be attributed to the total shear applied by the spokes of the wheels of the force feeder to the granulation (Mehrotra et al., 2007). To estimate total shear applied by the force feeder on the granulation, shear intensity was calculated in terms of shear rate and shear frequency.

A granulation in the force feeder is sheared between the moving wheels of the force feeder and the stationary base/roof and walls of the cavity. Assuming that the most of the granulation in the force feeder moves at the same rate as the wheels of the force feeder, the shear rate (SR) in the force feeder can be estimated by:

$$\mathrm{SR} = \frac{\pi d n}{c} \quad (1)$$

where 'd' is the diameter of the spokes of force feeder, in cm; 'n' is the speed of force feeder, in rpm; and 'c' is the clearance between spokes and base, in cm.

The frequency of shearing of granulation can be assumed to be similar to the rotational speed of the force feeder wheels. Thus, shear frequency (SF) in the force feeder can be estimated by:

$$\mathrm{SF} = kn \quad (2)$$

where 'k' are the number of spokes.

In addition to the shearing intensity attributable to the speed of the force feeder, the duration of time that the powder blend is exposed to the shearing action of the force feeder affects the total shear on the granulation. The force feeder has a continuous flow of granulation from the hopper and into the die cavities. Therefore, the total shear by the force feeder on the granulation would depend on the time it takes for a given mass of granulation to pass through the force feeder, herein defined as the residence time (RT) of the granulation in the force feeder. The residence time (RT) was estimated as a function of flow rate of the granulation through the force feeder and the granulation holding capacity of the force feeder by:

$$\mathrm{RT} = \frac{m}{wsn'} \quad (3)$$

Table 1
Process parameters used for lubrication sensitivity determination in tablet press force feeders.

Press type and number of stations	Turret (TR) speed (rpm)	Force feeder (FF) speed (rpm)	FF/TR ratio
Korsch press, 6-stations	30	45	1.5
	30	90	3.0
	20	180	9.0
Manesty Betapress, 16-stations	65	10	0.15
	65	33	0.5
	65	53	0.8
Korsch XL-400 press, 35-stations	50	11	0.22
	50	25	0.50
	50	50	1.00
	50	90	1.80
	75	11	0.15
	75	25	0.33
	75	50	0.67
	75	90	1.20

where 'm' is the mass of powder in the force feeder at equilibrium operation, in gram; 'w' is the tablet weight, in gram; 's' is the speed of turret, in rpm; and 'n'' are the number of punches.

To investigate the effect of residence time, while keeping all formulation and process parameters constant, the placebo blend was compressed on a 6-station Korsch press using 2, 4, or 6 punches. This corresponded to the granulation residence times of 7.5, 5.0, or 2.5 min in the force feeder, respectively (Fig. 5). The decline in tablet strength and tabletability with increasing residence time of the granulation in the force feeder indicated that residence time formed a significant component of the shearing action of the force feeder.

The total shear experienced by the granulation in the force feeder was estimated in terms of a dimensionless shear number (S_N), which was defined as a function of shear rate (SR), shear frequency (SF), and residence time (RT).

$$S_N = f\{\mathrm{SR} \times \mathrm{SF} \times \mathrm{RT}\} \tag{4}$$

An empirical equation was derived to correlate total shear in the force feeder with the tabletability of the blend. A linear correlation between the shear number and the tabletability of the blend was obtained when the effects of residence time were squared.

$$S_N = \mathrm{SR} \times \mathrm{SF} \times (\mathrm{RT})^2 \tag{5}$$

Using the equations for SR, SF, and RT, a dimensionless equation was obtained for S_N.

$$S_N = \left(\frac{\pi dn}{c}\right)(kn)\left(\frac{m}{wsn'}\right)^2 \tag{6}$$

This equation can also be converted to a combination of three dimensionless terms:

$$S_N = \left(\frac{\pi dk}{c}\right)\left(\frac{m}{wn'}\right)^2\left(\frac{n}{s}\right)^2 \tag{7}$$

The applicability of this dimensionless equation on the scale-up of a lubrication sensitive formulation was investigated by systematically scaling up the model placebo formulation from a 6-station Korsch press to a 16-station Manesty Betapress and a commercial scale, high speed 35-station Korsch XL-400 press. The operating parameters of force feeder and turret speed were varied within the permissible press ranges to study their effect (Table 1).

Scale-up of the formulation from a 6-station Korsch press to a 16-station Betapress resulted in improved tabletability (Fig. 4A). However, further scale-up of the process to the 35-station Korsch XL-400 press did not result in any further improvement in tabletability. The compaction profiles obtained on the Korsch XL-400 press were intermediate between those of the 6-station Korsch press and the 16-station Betapress (Fig. 4B). The combined effect of turret and force feeder speeds on the Korsch XL-400 press (Fig. 6) indicated that both force feeder and turret speed were important parameters in determining the mechanical strength of tablets.

Increasing the turret speed from 50 to 75 rpm, with corresponding dwell time reduction from 11.8 to 6.6 ms, significantly reduced tablet strength and compression profile at all force feeder speeds (Fig. 6). However, given the marginal contribution of dwell time effect in this range of 6–12 ms (Fig. 2), it is evident that at least a part of the effect of turret speed on tablet strength is attributable to the turret speed induced changes in the residence time of the granulation in the force feeder (see Eq. (3)). Thus, the effect of turret speed on high speed tablet presses reflects a combined effect of the change in the dwell time of the granulation under the compression cam, the speed of punch penetration into the die cavity, and the residence time of the granulation in the force feeder.

The tabletability plots of different presses indicated a near linear correlation of tabletability with total shear imparted by the force feeder on the granulation (Fig. 7). The maximum achievable tabletability without the use of a force feeder was defined as T_G. It incorporates the effect of turret speed on the dwell time of the granulation under the compression cam and the speed of punch penetration into the die cavity. A critical level of shear (Sc) was defined at the intersection of the log(S_N)–log(tabletability) curve with the log(T_G) value on the y-axis. Above Sc, the tabletability of the granulation was significantly affected by the shearing action of the force feeder. Below Sc, the shearing effect of the force feeder did not significantly affect tablet strength. The absolute values of log(T_G), Sc, and the slope of the log(S_N)–log(tabletability) curve are expected to be a function of the type of formulation.

The non-linearity of tabletability as a function of total shear among different presses in Fig. 7 could be attributed to the differences in force feeder geometry, which can affect powder mixing pattern and dynamics. The design of the force feeder is expected to play a significant role in the amount of shear applied to the granulation during tableting.

The shear number equation takes into account the geometry and operation of the force feeder. A typical force feeder consists of at least two rotating wheels housed in separate cavities that are interconnected to each other through a chord length gap in the outer wall of their cavities (Fig. 8). There is a small clearance between the base/roof of the cavity and the wheels. These two cavities typically are placed on the top of the turret (the die table). In the case of smaller scale presses, viz. 6-station Korsch press and 16-station Betapress, the hopper empties into one of these cavities. Interconnection between the two cavities allows both cavities to be filled by the aid of opposite directions of movement of the wheels. The wheels may (e.g., in the 6-station Korsch press,) or may not (e.g., in the 16-station Betapress) overlap depending on the interconnect-

Table 2
Force feeder design features considered for the calculation of shear.

Design element	Korsch press, 6-stations	Manesty Betapress, 16-stations	Korsch XL-400 press, 35-stations
Number of wheels	2	2	3
Number of spokes per wheel	6	8	12
Geometry of spokes	Straight	Straight	Straight on 2 of 3 wheels, angled (105.5°) at 3.0 cm from barrel on the 3rd wheel
Dimensions of spokes (length × width × height, cm)	2.8 × 0.3 × 0.5 (both wheels)	5.0 × 0.7 × 0.5 (both wheels)	Wheel 1: 7.5 × 0.6 × 1.0 Wheel 2: 6.8 × 0.6 × 1.0 Wheel 3: 6.25 × 0.6 × 1.0
Dimensions of central shaft (diameter × height, cm)	3.8 × 0.5 (both wheels)	5.0 × 0.5 (both wheels)	Wheel 1: 5.9 × 1.0 Wheel 2: 10.0 × 1.0 Wheel 3: 10.0 × 1.0
Cavity, in which the wheels are placed (diameter × height from roof to base, cm)	9.8 × 1.4 (both wheels)	Wheel 1: 15.5 × 0.8 Wheel 2: 15.5 × 1.6	Wheel 1: 21.0 × 1.4 Wheel 2: 23.0 × 1.4 Wheel 3: 23.0 × 1.4
Chord length for interconnection between cavities, which enables powder flow from one cavity to another (cm)	7.8	10.5	3.5 (between cavities 2 and 3, cavity 1 empties from an opening in its base into cavity 2 through an opening in its roof)

ing chord length. Further, the wheels may (e.g., in the 6-station Korsch press and the 35-station Korsch XL-400 press) or may not (e.g., in the 16-station Betapress) be coplanar. In the case of the larger scale Korsch XL-400 press, the hopper empties into another cavity bearing a third rotating wheel, which lies above and empties through an opening in its base into one of the two coplanar cavities close to the die table. These elements of force feeder design (summarized in Table 2) were considered for the calculation of the shear number.

This calculation of total shear may not be exact and Eq. (7) may be specific to lubrication effects on the tabletability performance of the placebo formulation used in this study. In addition, some of the assumptions and limitations underlying the use of shear number to estimate total shear include the inability to account for the effects of curvature of the spokes (and its effects on the forces on the powder and on the movement of the powder blend), interlocking of wheels in the coplanar cavities, gravitational pressure on the blend due to hopper fill, and the clearance between the wheel and the base/roof of the cavity. Nevertheless, this model reflects the key

Fig. 8. Image of a force feeder (FF) used with the 16-station Betapress. The FF is shown in its position on the turret (TR). The FF shown is a closed chamber with two rotating wheels and an opening each for (a) the granulation inflow from the hopper through the receptacle shown on the right and (b) granulation outflow to the die cavities through openings on the bottom, that are aligned with the position of the dies on the turret. As the granulation passes through the FF, it gets filled into the die cavities in the turret, which rotates in a clockwise direction. The transparent top of the FF allows visualization of the spokes of the wheels of FF that rotate during its operation.

design elements that are expected to impact most of the shear and lubrication in the force feeder.

The shear number equation can be used to estimate the critical point of shear (Sc), above which the effects of force feeder on the tabletability of the granulation become significant. A study of the effects of the force feeder on a laboratory scale press can be used to derive Sc and T_G (tabletability using gravity feeder). Although the absolute values of these parameters are expected to depend on the formulation, they can be reasonably assumed to be similar across tablet presses of similar force feeder designs. Therefore, Sc and T_G can be used as guiding tools for the scale-up and press interchangeability for lubrication sensitive formulations, and to assess the risk of over-lubrication of a formulation on the tablet press.

5. Conclusions

The effect of process parameters on the tablet strength and compression profile of a model placebo formulation was studied on three different types and scales of tablet presses, and Presster simulator. The effects of turret and force feeder speed were quantified separately. The total shear imparted on the granulation by the force feeder was quantified using a dimensionless equation for the shear number (S_N). The scale-independence of the relationship of tabletability with S_N was explored. This equation, along with the effect of turret speed, accounted for the observed compaction behavior of the formulation on three different types and scales of tablet presses operated over a range of process parameters. The use of S_N to account for the effect of force feeder along with the effects of turret speed on dwell time under the compression cam and the speed of punch penetration into the die cavity can provide a tool to the scale-up of compression unit operation.

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