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Research Article

To Study Capping or Lamination Tendency of Tablets Through Evaluation of Powder Rheological Properties and Tablet Mechanical Properties of Directly Compressible Blends

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ABSTRACT. Air entrapment efficiency of the powders is one of the main factors leading to occurrence of capping or lamination tendency of tablets manufactured from the directly compressible powder blends. The purpose of the current research was to study this underlying cause leading to occurrence of capping or lamination of tablets through evaluation of powder rheological properties. Powder blends were prepared by addition of 0% *w/w* to 100% *w/w* of individual active pharmaceutical ingredient (API) [two model API: acetaminophen (APAP) and ibuprofen (IBU)] with microcrystalline cellulose without and with 0.5% *w/w* Magnesium Stearate as lubricant. Powder rheological properties were analyzed using FT4 Powder Rheometer for dynamic, bulk, and shear properties. Tablet mechanical properties of the respective blends were studied by determining the ability of the material to form tablet of specific strength under applied compaction pressure through tabletability profile. The results showed that powder rheometer distinguished the powder blends based on their ability to relieve entrapped air along with the distinctive flow characteristics. Powder blend prepared with increasing addition of APAP displayed low powder permeability as compared to IBU blends with better powder permeability, compressibility and flow characteristics. Also, lubrication of the APAP blends did not ease their ability to relieve air. Tabletability profiles revealed the potential occurrence of capping or lamination in tablets prepared from the powder blends with high APAP content. This study can help scientist to understand tableting performance at the early-developmental stages and can avoid occurrence capping and lamination of tablets.

KEY WORDS: capping; cohesive; lamination; permeability; shear cell; tensile strength.

INTRODUCTION

The tablet is the most commonly used oral dosage form and is composed of powders or granules. The product development of tablet formulation, along with its scientific use, also takes into account cost-effective manufacturing, convenient administration, dispensing and storage, and the versatility of delivering the drug with excellent stability (1). For this purpose, direct compression is the preferred method for the preparation of tablets (2). The direct compression process involves tableting of a blend of pharmaceutical powders, i.e., drug substances, and one or more excipients without a preliminary granulation or aggregation process. Powders are heterogeneous in nature and are composed of individual particles of different sizes and shapes, randomly interspersed with air spaces (3). Understanding the fundamental physical properties of such complex systems is of great importance from the solid dosage formulation development perspective because to their contribution to the final product performance. The study of flow and deformation of matter is defined as 'Rheology' (4).

The process of formation of the tablet compact is a critical unit operation influenced by the properties of the pharmaceutical powders, thereby impacting the physical and mechanical properties of the final compact. As a result, this unit operation is governed by two major factors: compaction/compactibility (5), i.e., the ability of a formulation to form a tablet of specified hardness and friability, and compression/compressibility (6,7), i.e., the ability of powders to densify under applied pressure. Along with compactibility and compressibility, flowability of the powder blends are equally important (8,9). After transferring the powder blend to the die cavity, the particles undergo sliding, rearrangement, or fragmentation, thus forming a closer packing structure in the consolidation stage. In the compression stage, pressure is

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applied to the rearranged powder bed and the powder blend undergoes a reduction in volume. The powder particles rearrange, but at times depending on their inherent nature, air may become entrapped in the powder bed, resulting in tablet defects like capping or lamination of tablets on dimensional relaxation (10,11). Cohesive powders have high shear strength and are less permeable (12,13).

Failure to acquire a complete knowledge about powder behavior may cause product manufacturing problems and may require formulation redesign. Tablet defects like capping and lamination can also be exhibited by the tablets during physical testing of the tablet's breaking strength and friability or while processing, handling, packaging, shipping or storage. Although there has been research in this area and a new emphasis on quality by design (QbD) with specific guidelines provided by the FDA, the risk in developing and manufacturing tablets is unacceptably high and requires more input of time and cost to overcome tablet-defect problems. For this reason, it is crucial to understand the mechanical properties of the materials that provide information about powder deformation behavior under stress conditions. In addition to this study, the ability of the powder bed to relieve entrapped air during the process of consolidation is also important to study in order to have better insight into the cause of tablet defects like capping and lamination.

Formulation scientists usually attempt to solve the problem by adjusting formulation and process variables. From the processing stand point, the incidence of capping and lamination may be reduced by using low compression forces, increasing the dwell time, changing shape of the tooling, and decreasing punch penetration (reduces the distance required for ejection of the tablet and decreases ejection forces) (14,15). From the formulation perspective, few practical remedies employed to reduce occurrence of defect includes, reducing percent fine particles in the formulation blend, using material deforming plastically, and increasing the binder concentration (16).

Attempts have been made to study the capping and lamination of tablets through the use of isotropic and homogenous polymer systems in the absence of granule porosity and high-speed compression (17), non-destructive predictive tools to evaluate cap value by the determination of the elastic property ratio (18) and a predictive tool to determine the capping index based on the residual die wall pressure in the ongoing tablet process (19). Even with technological advances, the question still arises about the probable chance of capping and lamination tendency of tablets in the preliminary stages of product development.

The objective of this study is to understand the cause of tablet defects, i.e., capping and lamination of tablets prepared from directly compressible powder blends using combination of analysis of powder properties of the powder blends and mechanical properties of the final tablets. The inability of powder blends to relief entrapped air, a cause of capping and lamination of tablets, has been measured and analyzed through powder properties and mechanical property of the tablets. The analysis of the powder blends involves the use of FT4 powder rheometer capable to characterize powders on the basis of dynamic, bulk, and shear properties. The evaluation of mechanical property involves compression of tablets of respective powder blends and determining breaking force required to crush tablets. The tablet tensile strength was determined using Eq. 3 from breaking force and has been further used to study tabletability of the powder blends.

MATERIALS AND METHODS

Materials

The two model drugs acetaminophen (APAP) and ibuprofen (IBU) were purchased from Fagron Inc. (Philadelphia, PA, USA) and were passed through a no. 30 mesh screen, prior to use. Microcrystalline cellulose (MCC, Avicel PH 101) was donated by FMC Corp. (Philadelphia, PA, USA) and was used for blending without any treatment. Magnesium stearate (MgSt) was purchased from Sigma Aldrich (St. Louis, MO, USA), respectively, and was further used without any treatment.

Methods

Preparation of Blends

Drug-excipient powder blends of APAP and IBU were prepared by blending each Active Pharmaceutical Ingredient (API) separately with MCC101 in concentrations ranging from 0% to 100% *w/w* in a turbula blender (Turbula® T2C, Glen Mills Inc., NJ, USA). All the blends were prepared at the scale of 200 g by mixing in a container of 500 g capacity for 7 min. Powder blends were further studied for the effect of lubrication by lubricating blends separately with 0.5% *w/w* of MgSt for 3 min. Freshly prepared powder blends were further analyzed in triplicates for powder properties and tablet mechanical property.

Measurement of Powder Properties

FT4 Powder Rheometer. Powder properties measurement of freshly prepared powder blends were performed using FT4 Powder Rheometer (Freeman Technology, Worcestershire, UK). Primarily, instrument was calibrated for force, torque, and height; aeration control unit was calibrated for air pressure and air velocity. Instrumentation vessel comprises of the split vessel assembly to ensure constant volume of sample for all the tests and for bulk density measurements. The powders were filled manually into instrument vessel for each test and subjected to conditioning cycle involving rotational and axial motion of twisted blade with helical angle of −5°. The process of conditioning gently displaces whole powder sample without exerting any stress to loosen and aerate the powder in order to construct homogenously packed powder bed. After completion of conditioning cycle, the powder bed was split and subjected to following tests.

Basic Flowability Energy (BFE) and Specific Energy (SE)

BFE and SE are the measure of dynamic flow properties of the powder. A 25-mm × 25-mL split vessel assembly and 23.5-mm twisted blade were used to perform these

measurements. BFE is the work done during downward anticlockwise movement of blade from top to bottom of the conditioned powder bed of precise volume by generating a compressive, a relatively high-stress flow mode. The blade moves in the powder bed with a tip speed of 100 mm/s at an angle of −5° helix. The energy required for the blade to move through the powder bed, was determined from the combination of force (measure of vertical resistance) and torque (measure of rotational resistance) for each millimeter traveled by blade and total energy is expressed in mJ. During this motion, particles in the powder tested are subjected to gravitational and inter-particulate forces.

SE is the work done during upward-clockwise motion of the blade from the bottom to top of the conditioned powder bed of precise volume by generation low stress flow mode due to gentle lifting of powder. The blade moves with the tip speed of 100 mm/s at an angle of +5° helix. In this measurement, powder particles are subjected to shear forces thus; SE is a direct measure of cohesiveness of the powder. It is calculated as the energy required per gram of powder blend during traverse upward motion of blade from bottom to top of the powder bed and expressed in millijoule per gram.

Permeability

Permeability is a bulk property and measured as the ability of powder to transmit fluid, i.e., air. This measurement was performed by filling prepared powder blends in 25-mm × 10-mL split vessel assembly followed by conditioning cycle with the blade of 23.5 mm diameter. The permeability testing process involves application of incremental normal stress as 1, 2, 4, 6, 8, 10, 12, and 15 kPa by a vented piston for predetermined period of time. Simultaneously, powder bed was aerated by aeration base in where aeration control unit supplies constant air at velocity of 2 mm/s. The response of this test was measured in terms of plot of pressure drop across the powder bed, i.e., powder resistance to the air flow against normal stress. The relative difference in air pressure between the bottom and top of the powder bed is pressure drop (ΔP) and is calculated using Darcy's law as follows (20):

$$k = \frac{q\mu L}{\Delta P} \tag{1}$$

Where,

k	Permeability (in square millimeter)
ΔP	Pressure drop (in pascal)
q	Air flow rate (in millimeter per second)
μ	Air viscosity (in pascal second) = 1.74×10^{-7} Pa.sec
L	Length of powder bed (in millimeter)

Compressibility

Compressibility is the bulk powder property which measures change in density of the powder as a function of applied normal stress. This measurement was performed using 25-mm × 10-mL split vessel assembly. Followed by conditioning cycle, the process of change in volume was measured by application of normal stress from 1 to 15 kPa to the powder bed. The normal stress was applied for predefined period with the help of vented piston head made of stainless steel mesh that allows entrapped air in the powder bed to escape uniformly from the bed surface. Compressibility is calculated from the change in volume given as,

$$\text{Compressibility} = \%\ \text{Change in volume after compression}$$

Or

$$\text{Compressibility index} = \frac{\text{Density after compression}}{\text{Conditioned bulk density}} \tag{2}$$

This property of powders takes into count factors like particle size distribution, cohesivity, particle stiffness, particle shape, and particle surface texture, thus, relating to many process environments such as storage in hoppers or super sacks, or behavior during roller compaction, etc.

Shear Cell Analysis

FT4 powder rheometer provides rotational shear cell assembly to measure the shear properties of the powders. The rotational shear cell analysis was performed with powder filled 50-mm × 85-mL split vessel and a shear head to induce rotational and vertical stresses. Initially, powder bed was subjected to conditioning cycle to form homogenous powder bed which is further consolidated to steady state using vented piston head followed by shearing sequence. A steady-state powder bed undergoes finite stress without continuous deformation. However, powder bed undergoes permanent deformation by flowing like fluid on application of shear force exceeding the shear strength of the powder bed. The point where flow occurs is maximum shear stress defined as "yield stress point" or "the point of incipient failure" (4,21).

The pre-consolidation of the powder bed was performed by vented piston through application of consolidation stress of 9 kPa followed by applying normal stress of 7, 6, 5, 4, and 3 kPa to relieve any entrapped air. On each applied normal stress, a sequence of pre-shearing process, i.e., over-consolidation of the powder at a maximum normal stress (pre-shear normal stress), to achieve steady-state shear stress and shearing processing, i.e., application of normal stress occurs (22). The data was collected as a plot of measured yield locus at each applied stress (σ) as shown in Fig. 1. The shear cell data was further analyzed with the help of FT4 data analysis software which uses Mohr's shear circle theory as shown in Fig. 1 to determine major principal stress (MPS), unconfined yield strength (UYS), cohesion (C), and flow function (FF or FF_c). Flow function is most commonly used parameter defining flowability of the powder as described by Jenike (23). It is defined as a ratio of MPS acting on the powder to the UYS of the powder at the MPS.

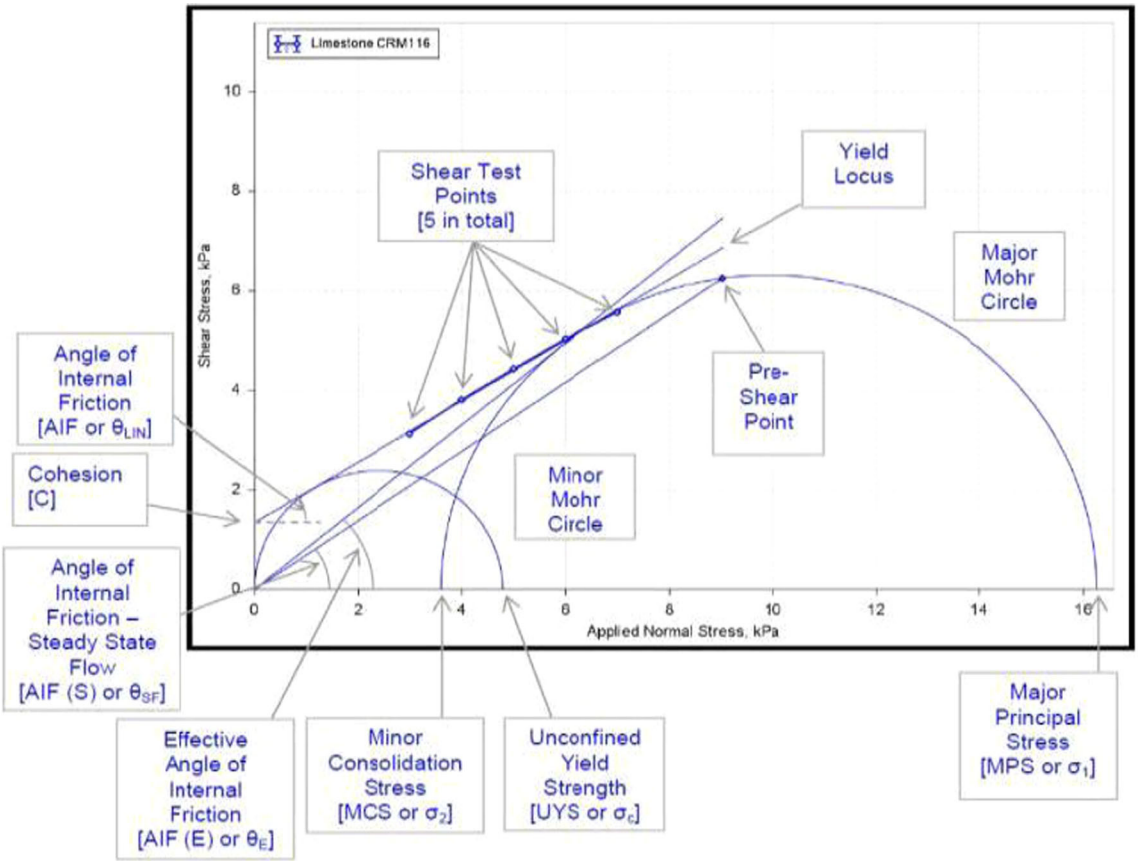

Fig. 1. Graphical representation of shear cell data analysis (Adapted from FT4 Powder Rheometer supplement: 'Additional Parameters Derived from Shear Cell Data')

Tablet Compaction

Tablet compaction process was performed using a single station Carver tablet press (Indiana, USA). A 14-mm flat-faced punch and die set were the tooling set for manufacturing of all the tablets. For each compression process, the tip of the punches and die (internally) were lubricated with 5% *w*/*v* of magnesium stearate suspension (prepared in ethanol) followed by air drying to avoid friction between tooling and ease ejection of tablets. Tablets ($n = 3$) weighing 750 mg (±10 mg) each were prepared from freshly prepared powder blends at varying compression force ranging from 1,000 to 5,000 lb with dwell time of 1 s. After manufacturing each tablet, dimensions of the tablets out-of-die were measured using Digital Vernier Caliper and were stored in desiccator equilibrated at 43% relative humidity condition (RH) at ambient temperature for 24 h. The purpose of storage of tablets for 24 h was to undergo stress relaxation. Before performing mechanical property analysis, i.e., breaking force required for crushing tablet, once again tablet dimension were measured.

Relative Humidity

The compacted tablets were subjected to 43% RH (±0.83) for 24 h. The RH condition was generated by holding saturated salt solution of potassium carbonate at ambient temperature (25 ± 2°C) in tightly sealed glass desiccator and equilibrated for 48 h before storing tablets. The RH in the chamber was measured using a digital hygrometer (VWR, Bridgeport, NJ, USA).

Measurement of Mechanical Property

Tablet Breaking Force. The breaking force of each tablet (F) was determined by application of transverse compression of 0.005 kg using TA-54 stainless steel probe (4 mm diameter) fitted to Texture Analyzer (Texture Technologies Corp., New York, USA) equipped with 50-kg load cell. The probe was fixed at a distance of 18 mm above the fixed platform set, where sample was held in position diametrically to minimize experimental variations. The pre-test speed of the probe was adjusted as 0.5 mm/s. As soon as the probe touches the surface of the tablet, the test was performed at the speed of 1 mm/s to travel a distance of 3 mm in the tablet core followed by post-speed (restores initial position) of 5 mm/s.

Tablet Tensile Strength. The breaking force of tablets defines 'Hardness' (24) and was determined by subjecting flat-faced round tablets to stress, its failure to tension on diametrical compression was indicated by splitting in halves. The breaking force was analyzed using TA-54 stainless steel probe attached to Texture Analyzer (Texture Technologies Corp., New York, USA). The tensile strength measurement

provides an insight of fundamental measure of the mechanical strength of the compacted material calculated using the breaking force with the following equation,

$$\sigma_T = \frac{2F}{\pi dh} \quad (3)$$

Where,

σ_T Tablet tensile strength (in macropascal)
F Tablet breaking force (in Newton)
d Diameter of tablet (in millimeter)
h Thickness of tablet (in millimeter).

Above Eq. 3 can be used to determine tensile strength of flat-facet round tablets only (25) and which fail under tension (26).

Particle Shape Analysis

Surface morphology and texture of pure API was conducted using Dino-Lite digital microscope Pro (BigC Dino Lite, Model: AM4815ZT, Torrance, CA, USA). The sample to be analyzed was prepared by spreading a thin layer of powder on the glass slide. The polarized microscopic images were captured by the means of an extended depth of field and extended dynamic range under the ×180–×220 optical magnification power. The images were reviewed using DinoCapture 2.0 software.

RESULTS

In this work, the cause of capping and lamination defect affecting final quality attributes of the tablets was investigated through analysis of the powder properties of un-lubricated and lubricated drug-excipient powder blends and mechanical property of their compacted tablets.

Powder Properties

BFE and SE

Table I shows the average BFE and SE values that were evaluated to understand the powder flow properties of the APIs and excipient with and without 0.5% MgSt. Figure 2a, c represents the measure of flowability energy and the measure of cohesiveness, respectively, of the un-lubricated and lubricated powder blends with the increasing addition of the APAP. Figure 2b, d shows the measure of flowability energy and specific energy, respectively, of the un-lubricated and lubricated powder blends with the increasing concentration of IBU.

Permeability

The property of powder to relieve air with an ease is of critical importance during the compression process. However, their inability to relief air can affect mechanical properties of the final compact leading to occurrence of capping or lamination of tablets during tableting process. The measurement of this property of powder blends with APAP and IBU are represented in Fig. 3a, b, respectively.

Compressibility

Figure 4a, b shows the percent compressibility change with the application of normal stress for the powder blends composed of increasing concentration of APAP with MCC 101 without and with 0.5% MgSt. Increase in the percent compressibility values was measured with the increasing concentration of APAP. The percent compressibility values of the powder blends composed of varying concentration of IBU with MCC 101 without and with 0.5% MgSt are shown in Fig. 5a, b, respectively.

Shear Cell Analysis

Tables II and III shows the cohesion and FF values of the APAP and IBU powder blends without and with 0.5% MgSt, respectively. Increase in the cohesion values and decrease in FF values was observed with the increase concentration of APAP in the powder blends while opposite trend was seen with increasing IBU concentration in the powder blends.

Mechanical Properties

Tablet Tensile Strength

Figure 6 shows the tablet tensile strength of the APAP and IBU powder blends without and with 0.5% MgSt lubricant.

Tabletability

Tabletability profiles with the increasing APAP concentration without and with lubricant are shown in Fig. 7a. Decrease in ability to form tablet of specific tensile strength

Table I. BFE Test: API and Excipient

	No lubricant		0.5% MgSt lubricant	
Material	BFE (mJ)	SE (mJ/gm)	BFE (mJ)	SE (mJ/g)
APAP	151.58 ± 4.33	9.09 ± 0.07	128.40 ± 6.85	7.49 ± 0.13
IBU	115.14 ± 2.33	5.19 ± 0.06	111.23 ± 8.36	3.88 ± 0.85
MCC101	109.60 ± 6.33	3.41 ± 0.09	72.85 ± 1.06	2.36 ± 0.18

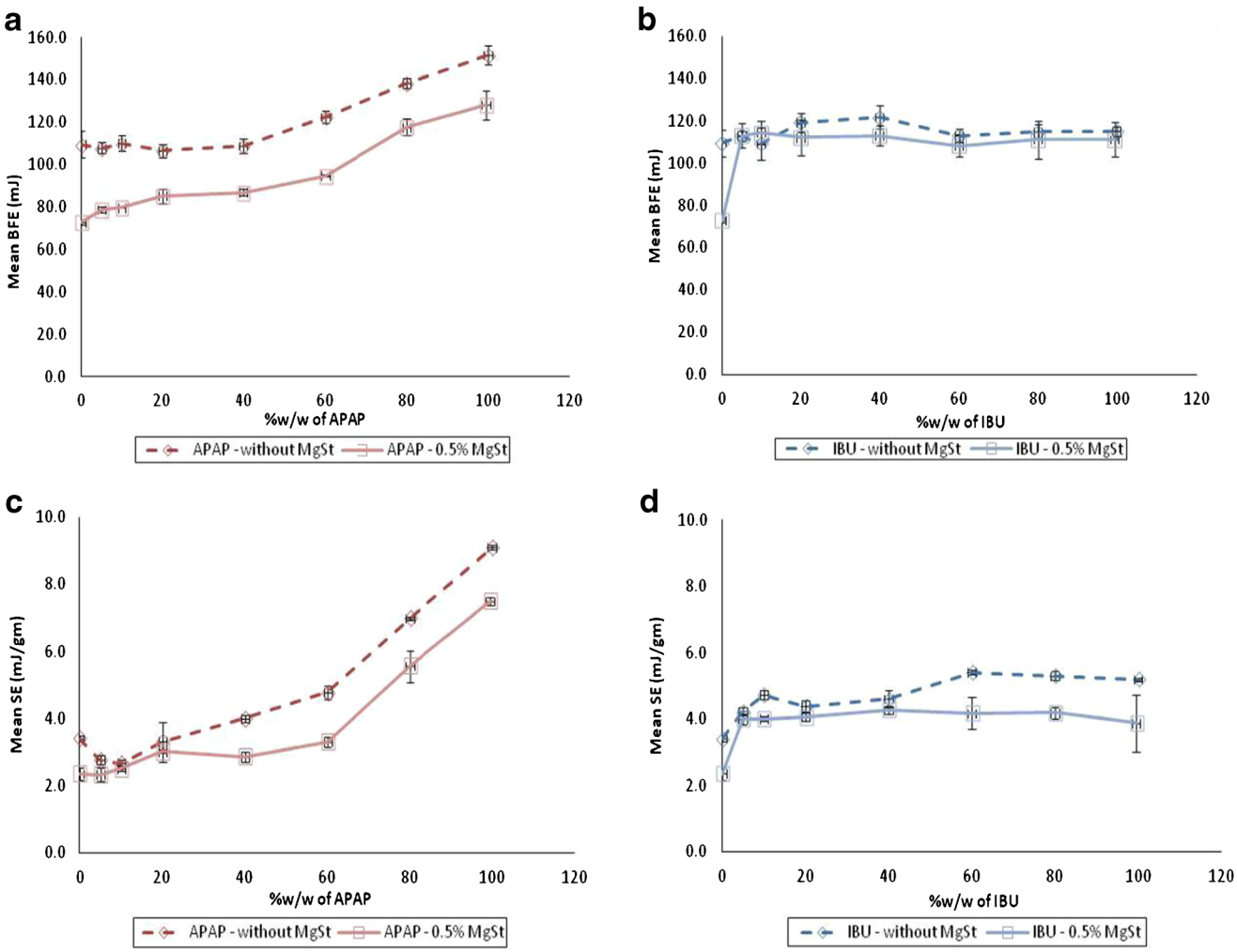

Fig. 2. Flowability energy of powder blends without and with 0.5% *w/w* of lubricant. **a** Mean BFE of powder blends with increasing addition of APAP. **b** Mean BFE of powder blends with increasing addition of IBU. **c** Mean SE of powder blends with increasing addition of APAP. **d** Mean SE of increasing addition of IBU

with the increasing compaction pressure was observed with increasing APAP concentration in the powder blend. Figure 7b represents the tabletability profiles of the increasing concentration of IBU in the powder blends without and with lubricant.

Particle Shape Analysis

Figure 8a, b represents the surface morphology and texture of the pure APAP and IBU, respectively.

DISCUSSION

Powder Properties

BFE and SE

In Table I, the high amount of energy required for blade to flow APAP powder presented high BFE value. This was observed due to APAP powder being composed particles having greater cohesive forces which form bulky mass thus, resisting motion of blade in the powder bed. Inter-particulate cohesive forces were measured in terms of 'Cohesion' defined by SE value. Cohesion of the powders is described based on the range of SE values as SE<5 with low cohesion, 5<SE<10 with moderate cohesion and SE >10 with high cohesion *(Adapted from FT4 Powder Rheometer Supplement: Specific Energy)*. SE value of APAP ranged on higher end of moderately cohesive region which may entrap high amount of air. However, IBU powder showed low BFE value as well as low SE value ranking IBU with minimal inter-particulate cohesive forces and projected better flow. MCC 101 composed of uniform particle size and shape was observed to have low BFE value with low SE value signifying low cohesion.

On lubrication of the API and excipients separately, further drop in BFE and SE values were observed as compared to un-lubricated API and excipients. Lubricants are incorporated in the pharmaceutical powder blends to improve flow of powder and reduce particle–particle friction (27). Impact of lubrication varies depending on the particle morphology. Pure APAP was observed to have irregular rough shape and existed in aggregates as observed in Fig. 8a thus; the amount of lubricant added did not reduce

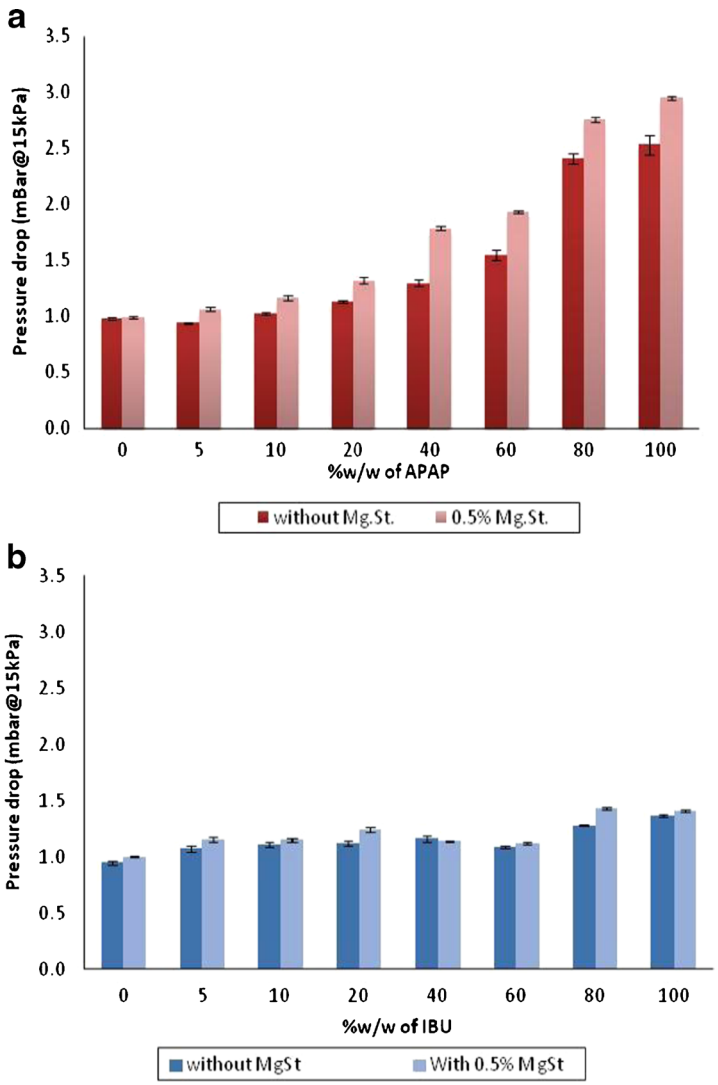

Fig. 3. Permeability test: Avg. Pressure Drop (mbar) at 15 kPa *versus* **a** increasing concentration of APAP blended with MCC101 without lubricant and with 0.5% *w/w* MgSt; **b** increasing concentration of IBU blended with MCC101 without lubricant and with 0.5% *w/w* MgSt

cohesiveness to a great extent. Figure 8b shows pure IBU particles with smooth rod shape which on addition of lubricant reduced -particle friction and resulted into low SE value. The effect of lubrication on MCC101 is observed to be similar like that on IBU.

Figure 2a, b shows the BFE values measured for the powder blends prepared with increasing addition of APAP and IBU, respectively. Addition of APAP to MCC 101without lubricant resulted in the increase in the BFE values due to cohesive nature acquired by the powder blend. At higher concentration of APAP in the powder blend, the powder adapts cohesive behavior similar to APAP and exhibit higher mechanical interlocking. During the motion of blade through the powder bed, the blade exhibits confined stress on the powder resulting flow or relatively localized stress transmission zone. Due to which the ability of the powder to resist the motion of the blade in the powder bed increases. Thus, the amount of energy required by the blade in order to generate flow pattern in the powder increases with the increase APAP concentration. Similar trend was represented by the powder blend with increasing addition of MCC101 with 0.5% *w/w* of MgSt. The difference in the BFE values of APAP blends with and without lubricant was due to ability of lubricant to coat the vessel and further reduce inter-particulate forces. Similar BFE values were measured with an increasing addition of IBU in the powder blends without and with 0.5% *w/w* MgSt. MCC 101with free flowing and non-cohesive nature (28) was measured with BFE value of 109.60 (± 6.34) mJ. The powders with non-cohesive nature generally have less number of air pockets and pack efficiently, which on motion of blade induces the powder flow by stress transmission, deep into the powder bulk. Thus, the blade requires less amount of energy to pass through the powder bed.

The cohesiveness of the powder blends prepared using APAP and IBU were measured by SE values and presented in Fig. 2c, d. The addition of higher concentration of APAP

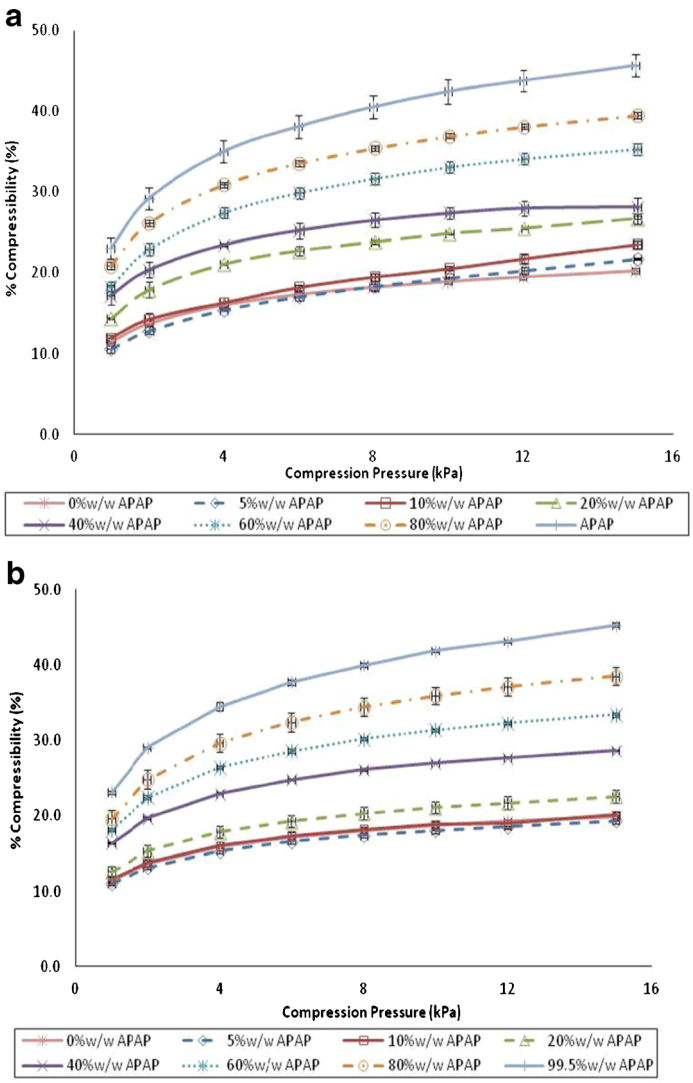

Fig. 4. Compressibility test: Avg.% Compressibility *versus* increasing Normal Stress (in kPa) for **a** increasing concentration of APAP blended with MCC101 without lubricant; **b** increasing concentration of APAP blended with MCC101 with 0.5% *w/w* MgSt

gradually layers itself on MCC101 particles and changes the behavior of powder from non-cohesive to cohesive. The cohesive nature of the powder blend is also contributed by the electrostatic nature of APAP particles. Thus, on further addition of the APAP (i.e. 70% *w/w* and 80% *w/w*), the powder blends were measured with moderate cohesion (i.e. 5–10 mJ/g). Similar rise in the SE values of the lubricated APAP blends was observed indicating addition of 0.5% *w/w* MgSt could not encounter the cohesive nature of the powder blends. The SE values measured for powder blends with increasing addition of IBU without and with 0.5% *w/w* lubricant in Fig. 2d, ranked all the powder blends with low to moderate cohesion.

Permeability

In the permeability test, the pressure drop measurements, i.e., pressure difference across the powder bed were performed by increasing application of normal stress up to 15 kPa using vented piston (at 90° helix angle without rotation) along with simultaneously supply of air with velocity of 2 mm/sec.

Increase in the pressure drop values was observed when plotted against increasing of concentration of APAP in the binary mixture prepared with MCC101 as seen Fig. 3a. Pure APAP with cohesive nature showed high pressure difference across the powder bed due to formation of bulky mass on the application of pressure thus, limiting the number of formation of channels in the powder bed. MCC101 pure showed lower pressure drop but, addition of APAP resulted in coating of individual MCC101 particles with APAP resulting into powder blend incapable of relief air supplied from the bottom of the powder bed. On addition of 80% *w/w* of APAP to the powder blend resulted into significant increase in the pressure drop as compared to 5%, 10%, 20%, 40%, and 60% *w/w* addition of APAP which shows linear increase in pressure drop values. Thus, 80% *w/w* APAP containing powder blend was expected to have probable chances of capping or

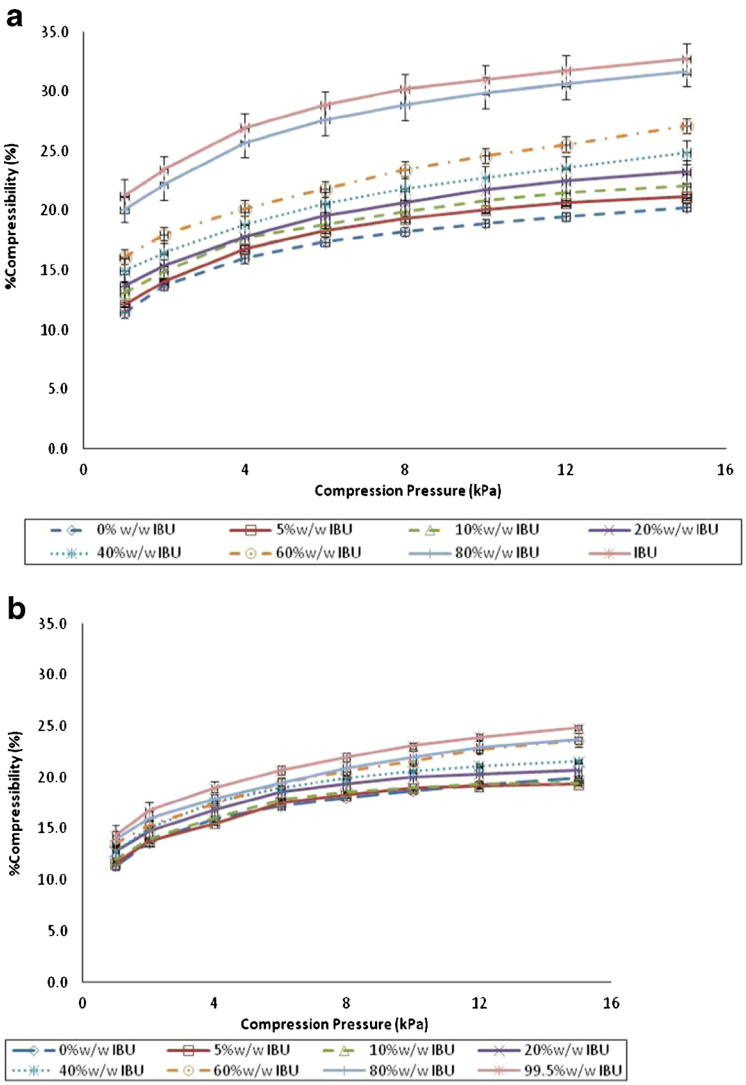

Fig. 5. Compressibility test: Avg.% Compressibility *versus* increasing Normal Stress (in kPa) for **a** increasing concentration of IBU blended with MCC101 without lubricant; **b** increasing concentration of IBU blended with MCC101 with 0.5% *w/w* MgSt

lamination of tablets in the manufacturing process. However, in case of binary mixture of IBU with MCC101 without lubricant, the values of pressure drop were in the range of 0.95 to 1.30 mbar at 15 kPa applied stress as seen in Fig. 3b.

Table II. Cohesion and Flow Function Values of Powder Blends Without Lubricant

	Acetaminophen		Ibuprofen	
%*w/w* API	Cohesion (kPa)	FF	Cohesion (kPa)	FF
0	1.37	5.86	1.37	5.86
5	1.64	4.72	1.19	5.89
10	1.82	4.53	0.59	6.73
20	1.69	4.66	0.71	6.87
40	1.83	4.62	0.23	7.37
60	2.13	3.61	0.38	7.70
80	2.41	3.41	0.57	7.96
100	2.72	2.88	1.01	8.43

Table III. Cohesion and Flow Function Values of Powder Blends with 0.5% *w/w* Lubricant

	Acetaminophen		Ibuprofen	
%*w/w* API	Cohesion (kPa)	FF	Cohesion (kPa)	FF
0	1.34	5.92	1.34	5.69
5	1.38	5.18	0.85	8.79
10	1.41	5.67	1.02	8.06
20	1.40	5.46	0.95	8.41
40	1.67	4.64	0.66	9.12
60	1.87	4.28	0.67	9.39
80	2.72	2.87	0.81	9.67
99.5	2.93	3.16	0.77	10.07

IBU blends were able to easily relieve air on incremental application of stress due to formation of uniform powder bed with higher number of channels in the powder bed. Also, visual observation was made distinguish APAP blends forming very compacted mass as compared to IBU blends.

On lubricating APAP blends with 0.5% *w/w* MgSt, showed further increment in the values of pressure drop. Powder blend composed of 80% *w/w* of APAP and 19.5% *w/w* of MCC101 on lubrication with 0.5% *w/w* of MgSt showed much higher pressure drop (Fig. 3a). However, on incorporation of lubricant in the IBU blends, there was very minimal change observed in the pressure drop values over increasing range of IBU concentration (Fig. 3b). The effect of lubricant on the powders with cohesive nature differs from powders with non-cohesive nature (27,29). Thus the effect of lubricant on the powder blends containing APAP, cohesive in nature and IBU, non-cohesive in nature was observed to be different due to difference in interaction with the powder blends. APAP powder blends formed cohesive powder blends containing increasing concentration of APAP which on lubrication bought about reduction in porosity of the powder bed on testing their permeability due to difference in particle–particle interaction of lubricant with the powder blends.

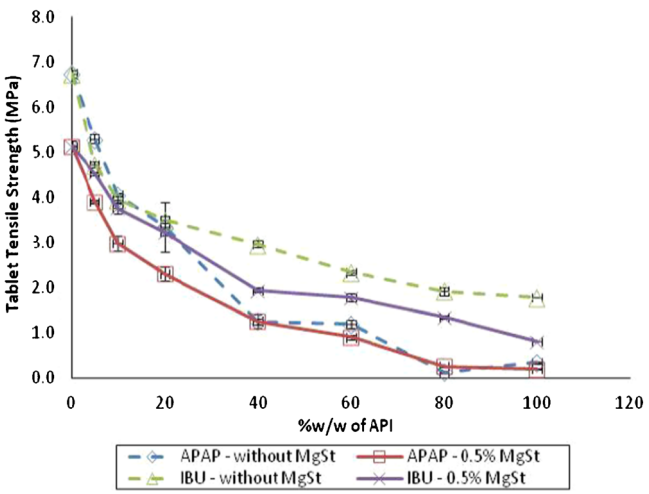

Fig. 6. Tensile Strength of the tablets of respective powder blends at 143 MPa

Compressibility

For the compressibility test, fresh sample of individual powder blends were subjected to incremental application of normal stress similar to permeability test, but powder beds were not aerated. The difference of change in volume on application of compression was studied through this test. This test takes into account powder characteristics such as particle size distribution, particle stiffness, and particle shape and particle surface texture to distinguish powders based on their cohesivity.

Increase in the values of percent compressibility with increasing concentration of APAP in the binary mixture prepared with MCC101 was observed in Fig. 4a. Pure MCC101 (non-cohesive in nature) under increasing stress showed no entrapment of air in the powder bed which rearranged uniformly due to stiff nature of particles and represented lower compressibility. While, APAP (cohesive in nature) shows significantly high compressibility due to high amount of entrapped air in the powder bed which was slowly relieved on application of stress and resulted into high change in the volume. At higher APAP concentration, the powder blends exhibited cohesive nature like pure APAP. Also, with increasing addition of APAP to the powder blend increase in the difference in between the initial and final volume was observed. Due to irregular surface of APAP, on addition of lubricant there was no change observed in the values of percent compressibility as seen in Fig. 4b.

Powder blends composed of IBU and MCC101, with increasing concentration of IBU the values of percent compressibility ranged from 20 to 35 kPa at the compression pressure of 15 kPa as seen in Fig. 5a. Incorporation of lubricant in the IBU powder blends resulted into further drop in the compressibility values explaining reduction in inter-particulate friction in the powder blend as seen in Fig. 5b.

Shear Cell Analysis

Analyzing shear properties of the powder is another means to directly measure powder flow properties and cohesiveness. In FT4 powder rheometer, the shear properties of the powder are analyzed using rotational shear cell and further FF and Cohesion values are determined based on Mohr's circle theory through data analysis software. Based on

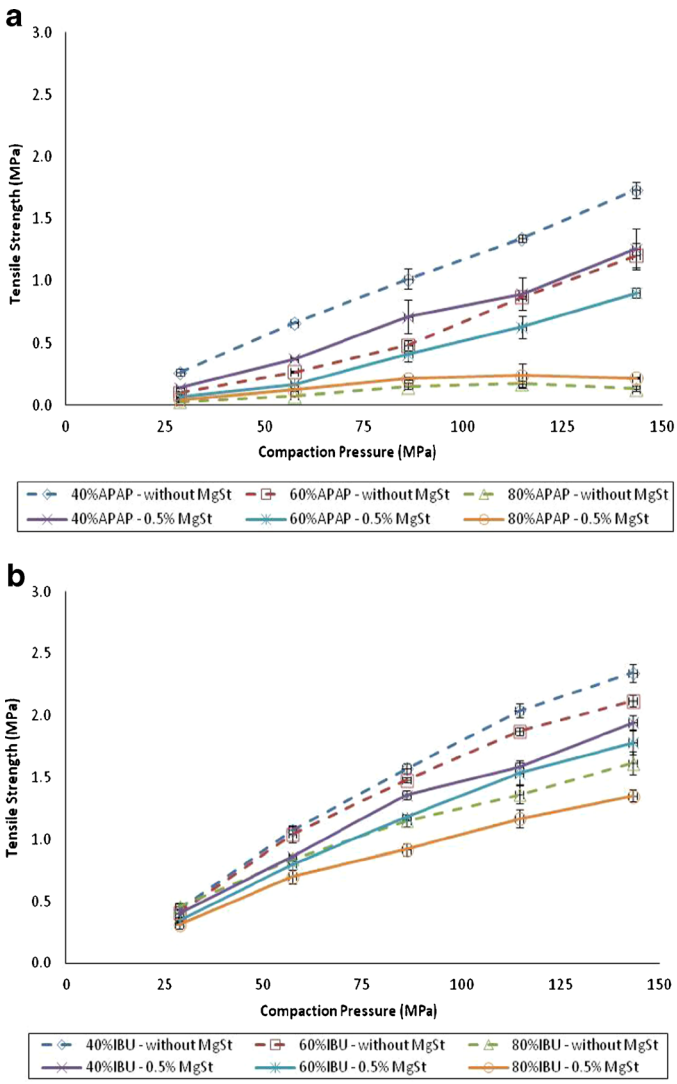

Fig. 7. Tabletability Profile of tablets composed of **a** APAP with MCC101 without and with 0.5% *w/w* MgSt; **b** IBU with MCC101 without and with 0.5% *w/w* MgSt

the FF values the powders are classified as: 10>FF "easy flowing", 4<FF<10 "free flowing", 2<FF<4 "Cohesive", and FF<2 "Very cohesive and non-flowing" (23).

With the increasing addition of APAP to MCC101 without and with 0.5% *w/w* MgSt resulted in increase in the cohesion values and decrease in FF values as seen in Tables II and III. The dynamic and bulk properties studied for the powder blends prepared by addition of APAP confirmed increasing cohesiveness of the powder blends with increasing concentration of APAP. As a result of increased cohesiveness in the powder blend, the inter-particulate and cohesive forces acting in the powder bed are higher which provide internal shear strength to the powder bed. Apart from internal forces, other factors such as particle–particle contact point and distance between them might also play important role (30). On the application of normal and shear stresses during the process of powder shear property analysis, the amount of shear strength required to initiate powder flow are higher as compared to powders shear strength. Thus, at higher concentration of APAP the powder blends exhibited high cohesion and low FF values classifying powder with cohesive nature.

In Tables II and III, the powder blends composed of IBU and MCC 101 without and with 0.5% *w/w* MgSt showed decrease in cohesion values with increasing FF values. The FF values for both un-lubricated and lubricated powder blends containing IBU ranged from 5 to 10, suggesting the free-flowing nature of the powder blends. The addition of IBU to MCC101 was observed to undergo moderate change in volume on application of normal stress during the compressibility test resulting in less number of true particle–particle contact points. The formation of compact mass may also be affected by the particle shape and structure (31). On lubrication of the powder blends, the contact points were further decreased due to property of lubricant to reduce inter-particulate friction (27). Hence, the powder flow initiated on application of low shear stresses and normal stresses resulting in better flow.

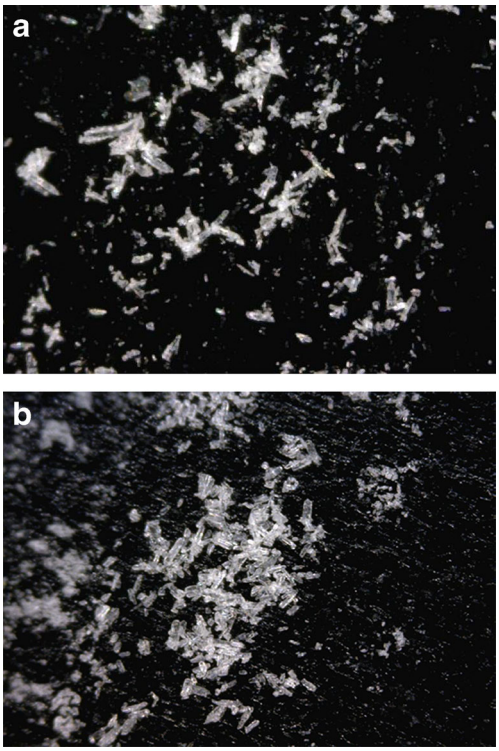

Fig. 8. Particle shape analysis of **a** pure APAP; **b** Pure IBU

Mechanical Properties

Tablet Tensile Strength

In Fig. 6, the tensile strength of the tablets calculated using Eq. 3 from breaking force applied to each tablet to break into halves for tablets were determined. Pure APAP on compaction, the out of die tablet due to entrapment of air representing low air permeability showed defect like cracks on the edge and fracture in the tablet body and also, APAP exhibits brittle nature (32). The tablets composed of un-lubricated powder blends with APAP as an API, increasing concentration of APAP showed significant drop in the tensile strength. Further decrease in tablet tensile strength was observed on introducing lubricant in the APAP powder blends. Lubrication of the powder blends causes negative effect on the tablet tensile strength (33). On 80%*w*/*w* of APAP load in the powder blend, the tablets out of die after manufacturing were observed to have fracture in the tablet bodies due to air entrapment on stress relaxation. Tablets manufactured of un-lubricated powder blends composed of increasing concentration of IBU, resulted the tablets with appropriate tensile strength without any tablet defects. Tablet tensile strength of lubricated powder blends prepared by addition of IBU were observed to be similar to that of the tensile strength of un-lubricated powder blends.

Tabletability

Tabletability profile is study of tablet tensile strength as a function of increasing compaction pressure for a given material (5,34). Evaluation of tabletability of given material gives an insight into the material behavior under stress, i.e., mechanical properties. It is also an useful tool to determine behavior of material in the high speed tablet press, as the ability of a material to form a compact mass under pressure is independent of speed (35). Figure 7a, b shows the plots of tablet tensile strength *versus* increasing compaction pressure, i.e., tabletability profile for un-lubricated and lubricated powder blends with different API loads.

In Fig. 7a, un-lubricated powder blends with increasing concentration of APAP resulted in drastic drop in the tensile strength. MCC101 undergoes plastic deformation under compaction pressure and forms true contact bonding points with final compact of specified tensile strength (28). At 80%*w*/*w* APAP load, the cohesive nature of the APAP entrapped air due to which the ability of MCC101 to form tablet of particular strength was completely ruled out by properties of APAP. Also, lowering of the tablet tensile strength was accompanied by the brittle nature of APAP, i.e., incapable of forming true contact bonding points and has high number of void spaces. Tensile strength of the tablets compacted from lubricated powder blend containing APAP was further observed to decrease. Lowering of tablet tensile strength for both the powder blends containing 80%*w*/*w* of APAP with increasing compaction pressure were studied explaining occurrence of tablet defects like capping and lamination and also, high-pressure drops were observed in Fig. 3a on subjecting these powder blends to permeability—a powder property test. Studies have been conducted showing negative effect of MgSt on the tablet tensile strength, especially when combined with plastically deforming material (36) and ability of fill surface voids differs depending on surface particle morphology (37). Thus the addition of MgSt to the powder blends containing lower APAP content and higher concentration of MCC101, a plastically deforming material shows significant drop in the tablet tensile strength. The lubricated powder blends with high APAP content was observed to further lower tablet tensile strength due to property of APAP. Tabletability profiles gradually decreased for un-lubricated and lubricated powder blends with increasing concentration IBU as seen in Fig. 7b. Lubrication of powder blend containing IBU resulted in lowering tablet tensile strength due to the addition of MgSt. The decrease in the tablet tensile strength on lubrication was a result of the negative effect of MgSt on the plastically deforming material. For each IBU powder blend, tabletability profile linearly increased with the increasing compaction pressure.

CONCLUSION

In this study, the ability of the powder blend to relieve entrapped air during the process of compression process which leads to formation of final tablets with tablet defects such as capping and lamination was successfully understood by analyzing dynamic, bulk and shear properties of the powder. Also, on conducting mechanical property study for the powder blends with ability to entrap air on compression showed drop in tablet tensile strength with increasing compaction pressure strongly signify occurrence of capping or lamination of tablets. From the study of powder properties and mechanical properties occurrence of capping and lamination of tablets containing 80%*w*/*w* APAP was analyzed. This study can help formulation scientist for early stage

determination of possible capping and lamination of tablets and help in preventing large-scale manufacturing failure or major market recalls.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors report no conflict of interest.

REFERENCES

1. Pavliv L, Cahill JF. Drug and biological development: from molecule to product and beyond. Formulation and Manufacturing. New York: Springer; 2007. p. 205.
2. Carlin BAC. Pharmaceutical dosage forms - tablets. Direct compression and the role of filler-binders. In: Augsburger SWHLL, editor. Informa. 2008. 173–216.
3. Lachman L, Lieberman HA, Kanig J. The theory and practice of industrial pharmacy. 3rd Indian ed. Compression and Consolidation of Powdered Solids. 1990. p 66–99.
4. Singh AP, Roye N, Hedman K. Powder rheology using a novel friction tool measuring system. In: Amercian Laboratory News. 2007. p. 1–2.
5. Maarschalk KV, Zuurman K, Vromans H, Bolhuis GK, Lerk CF. Porosity expansion of tablets as a result of bonding and deformation of particulate solids. Int J Pharm. 1996;140(2):185–93.
6. Joiris E, Di Martino P, Hermann AM, Guyot JC. Compression behavior of orthorhombic paracetamol. Pharm Res. 1998;15(7):1122–30.
7. Sun CQ, Grant DJW. Influence of crystal structure on the tableting properties of sulfamerazine polymorphs. Pharm Res. 2001;18(3):284–0.
8. Sun CC. Setting the bar for powder flow properties in successful high speed tableting. Powder Technol. 2010;201(1):106–8.
9. Nalluri VR, Kuentz M. Flowability characterisation of drug-excipient blend using a novel powder avalanching method. J Pharm Biopharm. 2010;74(2):388–96.
10. Mazel V, Busignies V, Diarra H, Tchoreloff P. Lamination of pharmaceutical tablets due to air entrapment: direct visualization and influence of the compact thickness. Int J Pharm. 2015;478(2):702–4.
11. Tanino T, Aoki Y, Furuya Y, Sato K, Takeda T, Mizuta T. Occurrence of capping due to insufficient air escape during tablet compression and a method to prevent it. Chem Pharm Bull. 1995;43(10):1772–9.
12. Allen T. Particle size measurement. 3rd ed. London: Chapman and Hall; 1983.
13. Chaudhari SP, Dave RH. To prepare and characterize microcrystalline cellulose granules using water and isopropyl alcohol as granulating agents and determine its end-point by thermal and rheological tools. Drug Dev Ind Pharm. 2015;41(5):744–52.
14. Garr JSM, Rubinstein MH. An investigation into the capping of paracetamol at increasing speeds of compression. Int J Pharm. 1991;72:117–22.
15. Allenspach CT, Zannou EA. Compaction of combination products. In: Celik M editor. Pharmaceutical powder compaction technology. 2 ed. Vol. 197. CRC Press; 2011.
16. Nystrom C, Glazer M. Studies on direct compression of tablets. XIII. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. Int J Pharm. 1985;23:255–63.
17. Fassihi AR, Parker MS. Formulation effects on capping tendencies. Int J Pharm. 1986;31:271–3.
18. Akseli I, Ladyzhynsky N, Katz J, He X. Development of predictive tools to assess capping tendency of tablet formulations. Powder Technol. 2013;236:139–48.
19. Sugimori K, Kawashima Y. A new practical index to predict capping occurring during the tableting process. Eur J Pharm Biopharm. 1997;44:323–6.
20. Durazo-Cardenas IS, Corbett J, Stephenson DJ. Permeability and dynamic elastic moduli of controlled porosity ultra-precision aerostatic structures. Ceram Int. 2014;40(2):3041–51.
21. Christensen RM. Defining yield stress and failure stress (Strength). 2011. p. 1–8.
22. Berry R, Bradley M, McGregor R. Brookfield powder flow tester—results of round robin tests with CRM-116 limestone powder. Proc Inst Mech Eng E J Process Mech Eng. 2014;10(3):40–58.
23. Jenike AW. Storage and flow of solids. University of Utah; 1964. p. Bulletin 123.
24. Table breaking force. United States Pharmacopeia and National Formulary (USP 32-NF 27). Vol. Ch. 1217. 2007, Rockville, MD. 726.
25. Newton JM, Haririan I, Podczeck F. The influence of punch curvature on the mechanical properties of compacted powders. Powder Technol. 2000;107(1–2):79–83.
26. Fell JT, Newton JM. Determination of tablet strength by the diametral-compression test. J Pharm Sci. 1970;59:688–91.
27. Li J, Wu Y. Lubricants in pharmaceutical solid dosage forms. Lubricants. 2014;2(1):21–43.
28. George RE. Avicel® PH microcrystalline cellulose, NF, Ph Eur., JP, BP. FMC Corporation; 2000. p. 1–14.
29. Faquih AMN, Mehrotra A, Hammond SV, Muzzio FJ. Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials. Int J Pharm. 2007;336:338–45.
30. Hou H, Sun CC. Quantifying effects of particulate properties on powder flow properties using a ring shear tester. J Pharm Sci. 2008;98:4030–9.
31. Almaya A, Aburub A. Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants. J Am Assoc Pharm Sci. 2008;9(2):414–8.
32. Prasad KV, Sheen DB, Sherwood JN. Fracture property studies of paracetamol single crystals using microindentation techniques. Pharm Res. 2001;18(6):867–72.
33. Van Veen B, Bolhuis GK, Wu YS, Zuurman K, Frijlink HW. Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose. Eur J Pharm Biopharm. 2005;59(1):133–8.
34. Armstrong NA, Palfrey LP. The effect of machine speed on the consolidation of four directly compressible tablet diluents. J Pharm Sci. 1989;94(3):465–72.
35. Tye CK, Sun C, Amidon G. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J Pharm Sci. 2005;94:465–72.
36. Wang J, Wen H, Desai D. Lubrication of tablet formulations. Eur J Pharm Biopharm. 2010;75(1):1–15.
37. Morin G, Briens L. The effect of lubricants on powder flowability for pharmaceutical application. J Am Assoc Pharm Sci. 2013;14(3):1158–68.