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Research paper

Compaction behavior of roller compacted ibuprofen

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Abstract

The effect of roller compaction pressure on the bulk compaction of roller compacted ibuprofen was investigated using instrumented rotary tablet press. Three different roller pressures were utilized to prepare granules and Heckel analysis, Walker analysis, compressibility, and tabletability were performed to derive densification, deformation, course of volume reduction and bonding phenomenon of different pressure roller compacted granules. Nominal single granule fracture strength was obtained by micro tensile testing. Heckel analysis indicated that granules prepared using lower pressure during roller compaction showed lower yield strength. The reduction in tabletability was observed for higher pressure roller compacted granules. The reduction in tabletability supports the results of granule size enlargement theory. Apart from the granule size enlargement theory, the available fines and relative fragmentation during compaction is responsible for higher bonding strength and provide larger areas for true particle contact at constant porosity for lower pressure roller compacted granules. Overall bulk compaction parameters indicated that granules prepared by lower roller compaction pressure were advantageous in terms of tabletability and densification. Overall results suggested that densification during roller compaction affects the particle level properties of specific surface area, nominal fracture strength, and compaction behavior.

Keywords: Ibuprofen; Roller compaction; Heckel analysis; Compressibility; Tabletability; Compaction behavior

1. Introduction

Pharmaceutical powders are often pretreated with particle modification process before compaction. Generally, this pretreatment is a granulation step in which the primary drug(s) and/or the excipient particles are agglomerated into larger secondary particles (granules or agglomerates), usually of a higher porosity than the primary ones [1]. Roller compaction is a commonly used unit process for production of tablets by dry granulation process and is especially useful in case of heat and moisture sensitive products. Particle modification processes lead to change in materials' deformation and densification behavior under pressure, which ultimately affects the mechanical strength of the tablets [2,3].

There are a number of literature reports on the effect of slugging on the compaction behavior of the materials [2–5]. Work hardening caused by the roller compaction increases the resistance to permanent deformation of materials with the amount of deformation that the material is subjected to. The reduction in the compressibility of the blends containing microcrystalline cellulose and dicalcium phosphate was attributed to the work hardening [6]. Therefore the change in tabletability after dry granulation is an example of how processes can affect performance of formulations. Sun et al. proposed the reduced tabletability of roller compacted granules as a result of granule size enlargement for plastic materials. It was further suggested that hardening of the particles affects plastic deformation

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of granules but should not significantly affect bonding strength which is primarily determined by molecular interaction between two adjacent surfaces over a unit area of bonding and not the concentration of defects [3]. The plastic deformation encountered during primary compression during roller compaction can also affect the further deformation during tableting. Insensitivity of compaction properties of brittle granules to size enlargement by roller compaction has also been reported [5]. Therefore, roller compaction alters the densification as well as deformation properties.

The present study assesses the effect of roller compaction pressure on the bulk compaction phenomenon using an instrumented rotary press. The effect of associated processing like fragmentation and fracture of the roller compacted ribbons during desizing and sieving on overall compaction behavior are also investigated. Heckel analysis, Walker analysis, compressibility, and tabletability have been used to describe the course of densification, volume reduction and bonding phenomenon.

2. Materials and methods

2.1. Materials

Racemic (±) ibuprofen ($C_{13}H_{18}O_2$) (IBN) was received as a gift sample from Arbro Pharmaceuticals Ltd., New Delhi. Sample exhibited plate shaped crystal habit and melting point of 75–78 °C.

2.2. Methods

2.2.1. Roller compaction

Ribbons of IBN were prepared using a roller compactor (Clit Mini Roller Compactor, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India). The roll speed was kept at 12 rpm and the feeder speed was 50 rpm. A hopper with a 2.5 L volume having bore diameter of 19 mm was used for charging the powder. Corrugated rolls of 100 mm in diameter and 25 mm in width were used for roller compaction. Different roll pressures i.e., 77.3, 126.6 and 175.8 kgf/cm^2 were utilized for preparation of ribbons and these ribbons were designated as batch R1, batch R2, and batch R3, respectively. Large ribbons were manually broken into smaller pieces and subsequently passed through BSS # 16 and those retained on BSS # 20 were used for tablet compaction. The granules obtained after sieving from 77.3, 126.6 and 175.8 kgf/cm^2 roller compaction pressure were designated as batch G1, batch G2, and, batch G3, respectively.

2.2.2. True density and tablet weight measurements

The true density was determined in triplicate by helium pycnometry (Pycno 30, Smart Instruments, Mumbai, India) at ambient conditions. Compact weight of each material was determined by digital analytical balance (AG285, Mettler Toledo, Switzerland).

2.2.3. Particle size distribution and specific surface area measurement

Particle size distributions of granules were determined by collecting the different sieve fractions. Particle size of corresponding sieve fraction was determined by optical microscopy by measuring diameter along the longest axis (DMLP microscope, Leica Microsystems, Wetzlar, Germany).

Specific surface area of three different batches of roller compacted IBN was determined using nitrogen gas sorption. Prior to measurements, weighed samples were regenerated by degassing to remove moisture and contamination. The regenerated sample was dipped in liquid nitrogen and the quantity of the adsorbed gas (70% Nitrogen + 30% Helium) was measured using thermal conductivity detector and then integrated using electronic circuit in terms of counts. The instrument was calibrated by injecting known quantity of nitrogen. The measured parameters were then used to calculate surface area of the sample by employing the adsorption theories of Brunauer, Emmett and Teller (BET).

2.2.4. Single granule fracture strength

The measurement of single granule nominal fracture strength was performed using a texture analyzer which was calibrated for both the distance and the load cell. All experiments were done with 5 kg load cell and 2 mm flat faced probe. The force required to travel a specified distance was measured as the fracture force of an individual particle. Instrument parameters were fixed as pre test speed of 0.4 mm/s, test speed of 0.2 mm/s (fracture speed), and post test speed of 0.6 mm/s; and the data acquisition rate was 200 points per second using fully integrated data acquisition and analysis software – Texture Expert. A stainless steel support was kept on platform to support the test granule so it could be axially aligned to the probe. The probe was moved down vertically on single granule until fractured. Fracture strength of twenty single granule from each batch of roller compacted granules was measured at ambient conditions.

2.2.5. Tableting and data acquisition

Rotary tablet press (Mini II, Rimek, Ahmedabad, India) was equipped at one of the 8 stations with 8 mm D-tooling with flat punch tip. Feed frame was used for uniform die filling and blind dies were used at all other positions. Precompression rollers were set out of function. Tablets of each material were compressed at constant volume. Humidity (40 ± 5% RH) and temperature (25 ± 5 °C) conditions were monitored through out the study. Tablet weight was kept at 202 ± 3 mg and applied force was leveled by moving the pressure roller with a hand wheel. Each of the three batches of roller compacted granules were compressed at, 7.9 ± 0.4 kN. The compaction pressure was calculated from punch face area and compaction force.

Data were acquired by Portable Press Analyzer™ (PPA) version 1.2, revision D (Data Acquisition and Analyzing

System, PuuMan Oy, Kuopio, Finland), through an infrared (IR) telemetric device with 16-bit analog-to-digital converter (6 kHZ). Force was measured by strain gauges at upper and lower punches (350 Ω, full Wheatstone bridge; I. Holland Tableting Science, Nottingham, UK), which were coupled with displacement transducers (linear potentiometer, 1000 Ω). Upper and lower punch data were recorded and transmitted on separate channels by individual amplifiers ("Boomerangs"). The amplifiers truncated the raw data from 16 bit to 12 bit after measuring to check IR transmission (data transmission rate-50 kbaud; Internal data buffer–1024 measurement points). Analysis of compaction data was carried out by PPA Analyse software (version 1.2, revision D). Accuracy of force and displacement transducers was 1% and 0.02%, respectively. The suitability of the data acquisition system has previously been reported [7].

2.2.6. Calculation of tablet porosity and tensile strength

The porosity, ε of the compacts was calculated by the equation,

$$\varepsilon = 1 - \rho_c/\rho_t \quad (1)$$

where ρ_c is the density of the compact which was calculated from the weight and volume of the resulting compact. ρ_t is the true density of compact. Breaking force of the tablets was measured using a tablet hardness tester (Tablet hardness tester, Erweka, USA). Tablet dimensions were measured with a digital caliper (Digimatic Mitutoyo Corporation, Japan). To eliminate the undesirable effect of variable tablet thickness on measured breaking force, tensile strength was calculated using the equation.[8]

$$\sigma = 2F/\pi dt \quad (2)$$

where σ is the tensile strength (MPa), F is the observed breaking force (N), d is the diameter (mm), and t is the thickness of the compact (mm).

3. Results and discussion

3.1. Characterization of ibuprofen

True density value ($n = 3$) was found to be 1.116 ± 0.0003 g/cm^3 the values of specific surface area of batch G1, batch G2, and batch G3 were 0.525, 0.517, and 0.465 m^2/g, respectively. The results of particle size distribution showed that lower pressure roller compacted granules showed the higher percentage of smaller sized particles than higher pressure roller compacted granules.

3.2. Single granule fracture strength

A distinct force maximum in force–displacement profile was observed that corresponds to the point at which the test granule fractures (Fig. 1). The nominal fracture strength, (τ_{0s}) for each granule was calculated from the maximum force using the following expression [9],

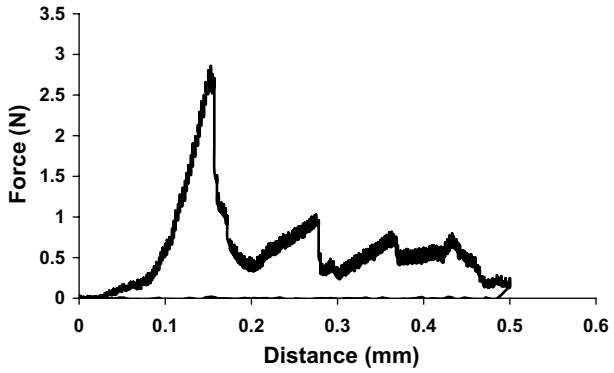

Fig. 1. Representative force–displacement plot for calculating the nominal fracture strength by micro tensile testing on texture analyzer. Peak value was taken for calculations of nominal fracture strength.

$$\tau_{0s} = 0.4 * F_{max}/\pi d^2 \quad (3)$$

where F_{max} is the maximum observed fracture force, and d is the diameter of the particle undergoing test. Average nominal fracture strength varied from 0.074 N/mm^2 for batch G1 granules to 0.185 N/mm^2 for batch G3 granules (Table 2). The granules obtained from higher roller compaction pressure yield at higher force than of lower roller compacted granules. The specific surface area difference between all three batches also supported the effect of primary densification on the fracture tendency of the granules. A higher specific surface area available per gram in granule of batch G1, made them more prone to crack initiation, under applied load as compared to granules of batches G2 and G3.

3.3. Compaction data analysis

3.3.1. Heckel analysis

The Heckel model provides a method for transforming a parametric view of the force and displacement signals to a linear relationship for materials undergoing compaction. The equation is based on the assumption that the dependence of densification on pressure is of first-order [10,11]

$$\ln[1/1 - D] = KP + A \quad (4)$$

Table 1
Particle size distributions of different sieve cuts of three batches of roller compacted ibuprofen

Sieve cut (μm)	Percentage particle distribution		
	Batch G1	Batch G2	Batch G3
1616–1784	9.6	11.3	36.4
1428–1514	28.9	33.2	36.9
1039–1148	34.7	37.1	13.4
904–1022	9.7	8.0	5.5
625–724	3.2	1.5	0.8
494–596	4.6	2.9	2.0
300–356	1.9	1.1	1.0
<<109–165	5.2	3.0	1.6

Table 2
Nominal fracture strength of granules having particle size of 1100–1700 μm and specific surface area for different batches of ibuprofen

Batch	Nominal fracture strength range (N/mm^2)	Average nominal fracture strength (N/mm^2)	Specific surface area (m^2/g)
Batch G1	0.060–0.093	0.074 (0.011)	0.525
Batch G2	0.118–0.135	0.120 (0.009)	0.517
Batch G3	0.154–0.260	0.185 (0.034)	0.465

Values in parentheses indicate standard deviations.

where D is the relative density of the tablet (the ratio of tablet density to true density of powder) at applied pressure P, and K is the material-dependent constant i.e., the slope of the straight line portion of the Heckel plot and the reciprocal of K is the mean yield pressure. In-die measurements of the tablet thickness give apparent mean yield pressure (Py). The one third of the reciprocal of slope obtained from Heckel equation is used to calculate yield strength (σ_0) of the material undergoing compaction cycling. Constant A gives densification of the powder due to initial particle rearrangement (D_a). A being the sum of two densification terms:

$$A = \ln[1/1 - D_0] + B \tag{5}$$

where $\ln[1/1 - D_0]$ is related to the initial die filling and B gives densification due to slippage and rearrangement of primary and fragmented particles (D_b). D_0 is defined as the densification due to die filling or initial powder packing.

$$D_a = 1 - e^{-A} \tag{6}$$

$$D_b = D_a - D_0 \tag{7}$$

For studying the effect of roller compaction on three batches of IBN linear regression was done on straight line portions of the Heckel plot (Fig. 2). The parameters obtained from Heckel analysis of the three roller compacted batches, at 7.9 ± 0.4 kN force, are summarized in Table 3. Values of slopes derived from the Heckel plots

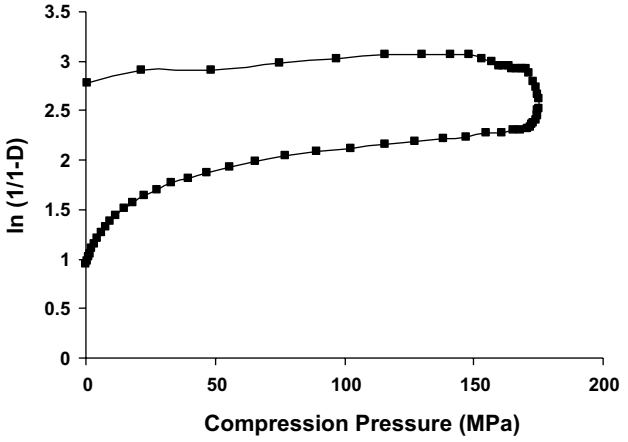

Fig. 2. In-die Heckel plots for batch G3 granules of ibuprofen compressed at 7.9 ± 0.4 kN. Initial curvature at low pressure corresponds to particle rearrangement, while the linear part of the curve indicates the ability of the material to deform plastically. At higher pressures curvature was observed due to strain hardening (work hardening). In-die elastic expansion after removal of force leads to decompression phase of Heckel plot.

decreased as we move from batch G1 to batch G3. This indicated that higher pressure was needed for batch G3 to attain the same densification. This can be attributed to higher pressure during roller compaction, which increased the relative density for a given compression pressure. Hence, a higher degree of densification was exhibited by the higher pressure roller compacted granules as compared to lower pressure roller compacted granules (batch G3 vs. batch G1), therefore values of Py and the derived yield strength (σ_0) decreased from batch G3 to batch G1. Py describes the resistance against densification under applied force and the granules of batch G3 showed higher resistance against densification. Results of densification resistance of the batch G3 granules were also supported by the experimentally observed higher yield strength from Heckel plot as well as micro tensile testing of the granules on texture analyzer. This fact can also be explained by the relative difference in dwell-time of three bathes. During roller compaction and actual tableting condition on rotary tablet press, batch G3 granules underwent higher pressure cycle than the other two batches.

The values of D_0, D_a and D_b obtained from initial region decreased in the order batch G1 > G2 > G3, thereby indicating a higher propensity for particle rearrangement and/or fragmentation in case of lower pressure compacted granules. Lower values of D_a, D_0, and D_b for batch G3 granules (lower propensity towards particle rearrangement/fragmentation) are due to the higher yield strength of batch G3 granules which resist the particle fragmentation at low force. Also the higher observed yield strength of batch G3 granules inhibits the crack propagation under low applied force [12].

3.3.2. Walker analysis and tablet compressibility

The compression data were analyzed by Walker equation [13] in order to study the course of volume reduction. The Walker equation is based on the assumption that the rate of change of pressure with respect to volume is proportional to the applied pressure. Walker proposed equation in terms of the percentage relative volume as the dependent variable.

$$100 * (V'/V_0) = -W \log P + C \tag{8}$$

$$100 * V = -W \log P + C \tag{9}$$

where V_0 is the volume at zero porosity and V' is the volume at pressure P. The relative volume is $V'/V_0 = V = 1/D$. W (compressibility coefficient) expresses the percent change in volume of the material when the pressure is increased on

Table 3
Apparent mean yield pressure (Py), yield strength (σ_0), densification due to initial particle rearrangement (D_a), densification due to initial die filling (D_0), and densification due to slippage and rearrangement of primary and fragmented particles (D_b) obtained from in-die Heckel analysis of batch G1, G2 and G3 at compression forces of 7.9 (0.4) kN. Compressibility coefficient (W) was calculated from the linear regression transformation of 100 V versus log P. Each value represents an average of four tablet measurements with their standard deviations in parentheses

Compression force (kN)	Batch	Py (MPa)	σ_0 (MPa)	D_a	D_0	D_b	W	Pressure range for W (MPa)
7.9 (0.4)	G1	55.9 (9.8) ($R^2 > 0.9927$)	18.63	0.842 (0.004)	0.710 (0.005)	0.132 (0.006)	16.66 (0.29) ($R^2 > 0.9899$)	4–148
	G2	71.1 (5.4) ($R^2 > 0.9890$)	23.70	0.836 (0.004)	0.702 (0.008)	0.131 (0.002)	17.02 (0.23) ($R^2 > 0.9866$)	3–159
	G3	90.2 (6.5) ($R^2 > 0.9923$)	30.07	0.758 (0.002)	0.630 (0.005)	0.128 (0.005)	25.26 (0.58) ($R^2 > 0.9940$)	2–170

log scale, and is considered as a measure of the irreversible compressibility of the compact; C is a constant. Table 3 represents the results of compressibility coefficient, W from the linear regression analysis of $100^{*}V$ vs. log P. Results indicate that higher pressure roller compacted granules (Batch G3) showed lower values of W as compared to lower pressure roller compacted granules (Batch G3). The compressibility coefficient, W which describes the percentage change in volume on logarithmic scale of applied pressure. The lower change in volume in case of lower pressure roller compacted granules can be attributed to lower densification during roller compaction and higher porosities.

Compressibility parameter for each batch of granules is represented as a plot of compression pressure versus in-die tablet porosity (Fig. 3) [14]. For batches G1, G2, and G3, the values of porosity attained after 100 MPa compression pressure were about 3.7%, 5.6%, and 19.4%, respectively. At 150 MPa, the observed values of porosity were 1.8%, 4.5%, and 18.4%, for batches G1, G2, and G3, respectively. This indicated around 50%, 24%, and 5% reduction on tablet porosities when pressure is raised from 100 to 150 MPa. These observations suggest that granules from higher pressure roller compacted batch showed lower compressibility. Hence, increase in compressibility of granules from lower pressure roller compacted batch could be derived from an increase in densification during compression. The higher percentage reduction in porosity is attributed to the greater

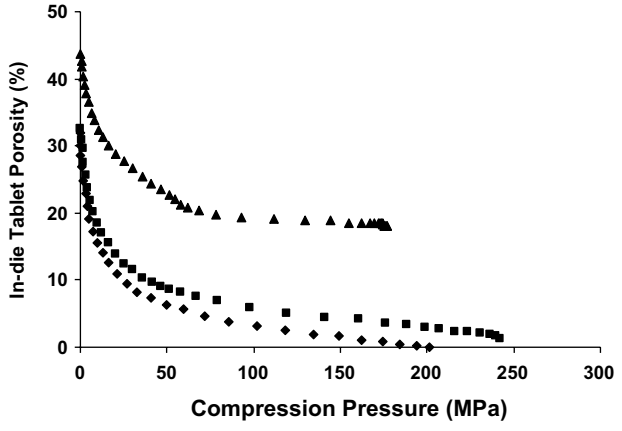

Fig. 3. Plot showing the in-die tablet porosity of batches – G1 (♦), G2 (■), and G3 (▲) as a function of increasing compression pressure.

fragmentation and initial particle rearrangement that can lead to formation of smaller particles which play a void filling role, further decreasing the percentage porosity. Also the new available surfaces formed during fragmentation allow more homogenous pore distribution, which further reduces the porosity of compact. This fact can also be confirmed during Heckel analysis where granules from higher pressure roller compacted batch showed more resistance to densification (higher yield strength at given pressure) which ultimately affects the compressibility. Also, the lower specific surface area of batch G3 granules is responsible for the resistance in porosity reduction.

3.3.3. Tabletability

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compaction pressure and is represented by a plot of tablet tensile strength against compaction pressure [14]. From the results of compression pressure and the resultant tensile strength, it was observed that IBN powder showed higher tensile strength at all compression pressure studied as compared to roller compacted granules. When comparing the results of tablet tensile strength and compression pressure of roller compacted granules, no significant difference was observed in tensile strength at very low compression pressure (up to 53 MPa) and little difference was observed even at high compression pressure (above 250 MPa) (Fig. 4). These can be attributed to insufficient densification at very low applied force, which does not result in sufficient deformation and subsequent interparticulate bond formation. But at intermediate compression pressure (90–200 MPa) there was a significant difference between the tabletability of the roller compacted batches. Among the studied roller compacted granules, the higher pressure compacted granules (batch G3) showed lower tensile strength than lower pressure compacted granules (batch G1). The difference in tabletability (at intermediate pressure) of the various roller compacted granules can be attributed to strain hardening of the higher pressure roller compacted granules which increases the resistance to permanent deformation of materials with increased amount of deformation. Rees and Rue demonstrated work hardening using sodium chloride and suggested that increased numbers of dislocations are produced at

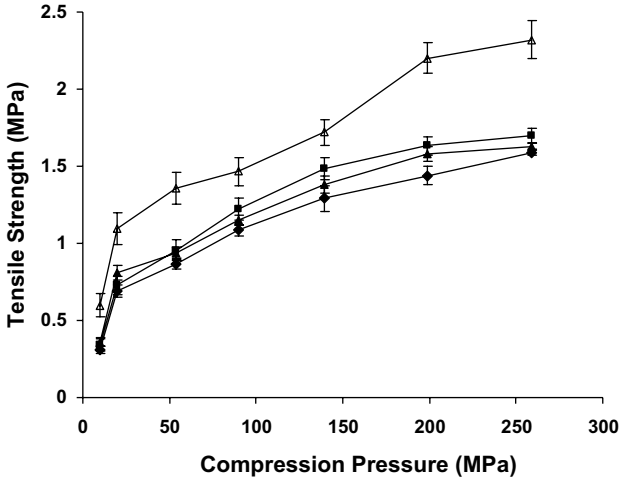

Fig. 4. Tablet tensile strength of batches – G1 (♦), G2 (■), G3 (▲), and ibuprofen (Δ) as a function of increasing compression pressure.

weak points on increasing compaction pressure [6]. The increase in dislocation density increases the potential energy of the dislocation lattice. This phenomenon makes it more difficult to produce further dislocations during second compression. It can be suggested that raised energy levels of dislocations already present, render the material more resistant to further deformation.

The results of Heckel analysis showed that batch G3 exhibited greater yield strength as compared to batches G1 and G2. From the results of particle size distribution (Table 1), it was apparent that lower pressure roller compacted granules showed higher percentage of fines as compared to higher pressure roller compacted granules. Therefore particles different in size but identical in plasticity and hardness (or yield strength) can have different yield pressure obtained from Heckel analysis. It has been reported that *Py* was found to increase with increasing particle size for L-lysine monohydrochloride [15]. The decrease in *Py* value for paracetamol due to larger particle size has also been reported [16]. The derived yield pressure is affected by the series of factors like interparticulate rearrangement, friction between particles and die-wall, fracturing of the particles, elastic and plastic deformation, resistance against deformation, strain hardening and pressure course. Sonnergaard critically evaluated Heckel equation and reported that Heckel model is practically linear at low densities and at high density (near zero porosity) Heckel transformation tends to infinity [17]. Therefore, had it been the work hardening phenomenon behind reduced tabletability, one would assume the decrease in tabletability over entire pressure range instead of 90–200 Mpa pressure range.

Ibuprofen crystals have been reported as more plastic than brittle [18,19]. The reduction in tabletability of granules after roller compaction could be attributed to the size enlargement because larger particles tend to pack less efficiently for materials that do not undergo extensive fragmentations. For similar type of tooling and compaction parameters, tablets made up of larger particles give higher porosity value. This fact can also be visualized in the plot of in-die tablet porosity vs. compaction pressure as batch G1 gave lowest porosity (Fig. 3). The available contacts points present per unit area between the particles are higher for smaller sized particles.

The particle size distribution data of granules showed decreasing trend in fines and increasing trend in higher sized particles from lower to higher pressure roller compacted granules (Table 1). The available fines can act as contact point between the particles. Therefore both reduced total contact points and effective bonding area reduce the tablet tensile strength. Additionally, the fragmentations during the compaction and fines generated during compaction can affect the tabletability. As indicated in Table 2, granules picked up from higher pressure roller compacted pressure showed higher average nominal fracture strength than lower pressure roller compacted granules for 1100–1700 μm size range. The average nominal fracture strength had direct consequence on fragmentation during compaction as from the Heckel analysis, it was apparent that lower pressure roller compacted granules showed greater fragmentation propensity (Higher values of D_a, D_b, and D_0; Table 3) than higher pressure roller compacted granules. This phenomenon enhances the formation of true contacts and subsequent bond formation. The higher percentage of available fines and available surface area resulting from fragmentation during compression, leads to increased tensile strength for lower pressure roller compacted granules as compared to higher pressure roller compaction. This finding was further supported by the relative higher specific surface area available to enhance the interparticulate bonding, thereby adding to the greater fracture strength of the batch G1 granule (Table 2).

4. Conclusions

The bulk compaction parameters exhibit different trend in densification and volume reduction depending on the pressure utilized during the roller compaction. Heckel analysis showed that granules prepared from higher roller compacted pressure had lower tendency for fragmentation, initial particle rearrangement and gave higher yield strength. The bulk compressibility profiles of roller compacted IBN were affected by the particle level properties like granule fracture strength, particle size distribution and granule specific surface area. Bulk compaction parameters indicate that granules prepared by lower roller compaction pressure are advantageous in terms of easy processibility in the subsequent unit operations.

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