A comparison of industrial lactose obtained by roller compaction with spray dried lactose and α-lactose monohydrate using compression analysis techniques.

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Original Article

ABSTRACT

The aim of this study was to develop a lactose excipient using a production-scale roller compactor suitable for use in the pharmaceutical industry. The physical properties and compression behavior of the roller compacted lactose were investigated using Kawakita analysis and force-displacement (F-D) techniques. α-lactose monohydrate and spray dried lactose were used for comparison purposes. Kawakita analysis of the aforementioned powders showed that roller compaction produced lactose powder with characteristics similar to those of spray dried lactose with some additional improvements. Compression and profile analysis of the F-D curve confirmed that the roller compacted lactose has similar flow behavior to spray dried lactose with the advantage of a lower level of compression energy. Drug preparations utilizing compacted lactose showed no effect, for example hindering, on drug dissolution. Consequently, using industrial scale roller compactor is suitable to turn α-lactose monohydrate into a direct compression (DC) excipient equivalent to spray dried lactose. This outcome can be accomplished in the context of in-house and commercial processing of lactose products.

KEY WORDS: Roller compaction, α-lactose monohydrate, spray dried lactose, Kawakita analysis, force-displacement curve, compression work, dissolution

INTRODUCTION

Lactose is the most widely used filler-diluent in the formulation of solid dosage forms. The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, availability, bland taste, low hygroscopicity, excellent physical and chemical stability and water solubility (1). On an industrial scale, α-lactose monohydrate is obtained by crystallizing highly concentrated whey lactose solutions at low temperatures, separating the crystals from the mother liquor by centrifugation and subsequently drying off the adhering moisture from the crystal mass (2). Crystalline α-lactose monohydrate exhibits relatively poor binding properties and consolidates mainly through fragmentation due to its "brittleness". On the other hand, amorphous lactose is known to be more compressible than its crystalline form and it yields tablets of higher tensile strength than crystalline lactose (3, 4). Different techniques, such as freeze drying, spray drying and roller compaction, have been used to develop a semi-crystalline lactose in order to improve its compressibility (5, 6).

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Spray dried lactose is produced by spray drying a lactose slurry. The final product contains a mixture of α-lactose monohydrate crystals and spherical agglomerates of small crystals held together by glass or amorphous material. The former contributes fluidity and the latter enforces the compressibility to the product. It has excellent flow and binding properties. It deforms plastically compared with α-lactose monohydrate particles of the same size (7). The amorphous portion of the spray-dried lactose is responsible for the improved binding and plastic deformation properties. Compressibility is affected if it is allowed to dry below a level of 3% w/w moisture. Spray-dried lactose discolors when the active pharmaceutical ingredient (API) contains an amine group. It has been reported that the spray-dried lactose produces harder, less friable tablets, that were more susceptible to color changes following storage at elevated temperatures than those containing native lactose (8).

Different modified or co-processed forms of lactose can result from the use of different techniques other than spray drying. For example, roller compaction is regarded as a cost- and labor-effective technique, especially when using direct compression (9-12). Roller compaction is widely employed for the production of free-flowing agglomerates and as an alternative to wet granulation in solid dosage manufacturing (13-19). Gereg and Capolla (15) investigated the use of roller compaction to improve the particle properties of α-lactose monohydrate. The study addressed the effect of the compaction process on the size and shape of the lactose particles but did not refer to the possible effect of compaction on crystallinity. Spray dried lactose was used as a reference material, since it is considered to have good flow and compressibility properties. Al-Akayleh *et al.* (9) investigated the roller compaction of α-lactose monohydrate co-processed with Mg silicate using a bench-top roller compactor operating at a maximum pressure of 10 MPa. They reported that compaction improved the compressibility and compatibility of α-lactose monohydrate. The effect on powder crystallinity, however, was not reported. Abu Fara, *et. al.* (6) investigated the use of roller compaction to prepare a directly compressed lactose excipient using crystalline α-lactose monohydrate comparing its crystallinity with commonly used industrial spray-dried lactoses. From their results it can be concluded that roller compaction reduced the crystallinity of α-lactose monohydrate and that the resulting compacted lactose is similar to spray dried lactose in behavior. Roller compaction introduced preferable characteristics to the raw α-lactose monohydrate by inducing changes in crystallinity and particle morphology. Roller compaction did not cause changes in the chemical configuration of the lactose material via isomerization, but did affect the morphology of the α-lactose monohydrate which enhanced the flowability of the powder. Freeman, *et. al.* (20) examined the correlation between the roller compaction process variables and the rheological characteristics of the lactose granules produced. They reported a good correlation between the compaction pressure and the flow characteristics of the granules, as assessed by the flow rate index and the aeration energy.

It is essential to characterize the behavior of the powder during the tablet compression process and correlate that behavior to the intrinsic and new properties of the powder. It is known that the quality of the dry granulate has significant impact on the downstream tableting process which has been shown to be governed by the rheological properties of the feed granules (21-23). Particle size distribution was the primary basis used to characterize the quality of the granules in many studies (24, 25). Other studies also showed that powders with same particle size can differ largely in their flow behavior due to the effect of other properties such as particles shape and surface texture (26-28).

Different methods can be used to analyze tablet compression processes of pharmaceutical solid dosages. Several compressibility models have been developed to describe changes in the relative density of a powder bed as a function of the applied compression pressure. Heckel and Kawakita equations are the most commonly employed mathematical models used to characterize powders based on true and bulk densities respectively (29-32). Antikainen and Yliruusi (33) investigated the compression behavior of several pharmaceutical excipients through analysing

the force displacement compression profile. The results showed a mathematical correlation for plastic deformation and elasticity of the material during compression quantifying their dependence on the compression pressure. Their results showed that plastic flow, fragmentation, and elastic recovery could be determined through a detailed analysis of the different stages of the compression process. Roopwani and Buckner (34) proposed a principal component analysis (PCA) technique to evaluate quantitatively the behavior of materials during the compression process using the original force and displacement data without relying on a particular model's parameter.

Studying the work of compression, which involves computing the energy input during different stages of compression could elucidate the flow behavior of the powder during compression which certainly determines the development of tablet microstructure and morphology and hence the tablet physical properties.

The objective of this work was to compare an industrial lactose obtained using roller compaction at different conditions with an industrial commonly used spray-dried lactose and an original α-lactose monohydrate. The study employs the Kawakita equation and the compression energy represented by the force-displacement curve in order to characterize the powder and its flow behavior in the compression process. The comparison is also performed through the application of the above mentioned three forms of lactose in conjunction with ibuprofen as drug model.

MATERIALS AND METHODS

Materials

Crystalline α-lactose monohydrate (Pharmatose® 200M) was supplied by DFE Pharma (Veghel, the Netherlands). Spray-dried lactose (Foremost #316 Fast Flo) was obtained from Foremost Farms (Rothschild, WI 54474, USA). The purity of the lactose powders complied with USP 31 (35) specifications. Ibuprofen, fine powder, batch number 19014 12061, was obtained from Shasun Pharmaceuticals Limited (Chennai, India). Sodium Lauryl Sulfate, lot number K425720, catalogue number 8170341000, assay (two-phase titration) >85.0%, was from Merck kGaA (Darmstadt, Germany). Primojel® was obtained from DFE Pharma (Foxhol, the Netherlands).

Methods

Roller compaction

5 kg of pure crystalline α-lactose monohydrate was compacted using a production scale roller compactor (TFC-520 Roller Compactor, Vector Corporation, Freund Group Company, Marion, IA 52302 USA). The following compaction parameters were investigated to assess their effect on the characteristics of the compacted lactose: compaction pressure, number of compaction repetitions as well as the ratio of screw speed to roller speed (SR). These parameters are the main processing variables which affect the possible changes or modifications in the processed powder material (36-38). The parameters were alternatively changed in order to obtain the most suitable transferred powder utilizing the available compaction pressure ranges (5000 to 20000 kPa). Compaction was repeated using the same sample up to 4 times. The effect of the ratio of screw to roller speed was studied from 3 to 10. The produced sheets were initially collected in a container then transferred manually to a Quadro mill (Vector Corporation, Freund Group Company, Marion, IA, U.S.A) equipped with a 2000 μm sieve. Milling was run continuously for 15 – 20 minutes until all the roller compacted material had been ground into a powder. Analyses was performed on the materials collected downstream of the sieve.

The experimental compaction runs are summarized in Table 1.

Compression process

Samples of 100 to 150 mg α-lactose were compressed using a Gamlen Tablet Press (Gamlen Tableting Ltd., Biocity Nottingham, UK). This was achieved without lubricating the upper or lower punches or the die. The punch speed was kept constant at 60 mm/min.

Table 1 Roller compaction experiments and conditions

RUN	COMPACTION PRESSURE (kPa)	Nº OF COMPACTION REPETITIONS	RATIO OF SCREWSPEED TO ROLLER SPEED (RS)
Lac - Mono			
Lac - SD			
5K - 1C - 3 RS	5000	1	3
10K - 1C - 3 RS	10000	1	3
15K - 1C - 3 RS	15000	1	3
20K - 1C - 3 RS	20000	1	3
20K - 3C - 3 RS	20000	3	3
20K - 1C - 7 RS	20000	1	7
20K - 1C - 10 RS	20000	1	10
20K - 3C - 5 RS	20000	3	5
20K - 4C - 5 RS	20000	4	5

Different compression forces ranging from 100 kg to 500 kg were applied. Three tablets were prepared to ensure reproducibility. The tablets were flat, round with a 6 mm diameter. Compression runs were performed for samples of crystalline α-lactose monohydrate, spray-dried lactose and roller compacted lactose.

Bulk density

The powder bulk density was determined by gently pouring the powder into a 100 mL graduated cylinder up to volume. The weight of the 100 mL powder was recorded. The bulk density was then calculated by dividing the mass of the powder by 100.

Dissolution test

In vitro drug release of tablets was evaluated from tablets using ibuprofen as a model drug (50% w/w) and either α-lactose monohydrate, spray-dried lactose or compacted lactose (at 47.9 % w/w) in addition to a solubilizer (0.1% w/w SLS) and a disintegrant (2% w/w Primojel®). 50 g of the powder was prepared by mixing ibuprofen with the other constituents for 10 minutes using an Erweka cube mixer (KB 155, Langen, Germany). The mixtures were directly compressed into 13 mm circular tablets (400 mg tablet mass) using a single punch tableting machine. The applied compression pressures were adjusted to obtain tablet crushing strength values of 2 MPa ± 0.5. For dissolution testing, the United States Pharmacopoeial (USP) method was adopted whereby the dissolution medium was made up of phosphate buffer solution (pH 7.8) on the basis of the high solubility of ibuprofen attained at pHs above its pKa value (i.e. 4.4) (35, 39). Each tablet was dropped in a vessel containing 500 mL of the phosphate buffer solution. Stirring was maintained at a paddle speed of 50 RPM and at a temperature of 37±0.5°C. At predetermined time intervals, 5 mL of the medium was sampled and filtered through a 0.2 μm filter. The withdrawn sample was immediately replaced with an equal amount of fresh dissolution medium. The filtered samples were analyzed using a UV 3000+ (Labindia, Maharashtra, India) at a wavelength of 268.5 nm using a 2 nm spectral bandwidth and 1 cm quartz cells. UVWin 5 software was used to control and record the absorbency of the measured samples. The *in vitro* dissolution was concurrently performed using two different reference tablets. First, by compressing ibuprofen powder into tablets of the same weight and at the same compression conditions of the test tablets, however, without adding any of the other excipients. The Second reference drug was commercially available Advil® 200 mg tablets (Pfizer, NY, USA).

Treatment of data

Kawakita analysis was used to compare the compression properties of the crystalline α-lactose monohydrate, spray dried lactose, and lactose samples processed by roller compaction at conditions shown in Table 1.

The Kawakita equation is usually used to linearize the non-linear pressure-porosity relationship provided by the Heckel model into a linear pressure-volume reduction relationship. Therefore, the Kawakita equation (Equation 1) is dependent upon the initial powder bulk density instead of the true density of the powder as in the case of the Heckel equation (40-42).

$$C = \left[\frac{V_0 - V}{V_0}\right] = \frac{abP}{1+bP} \qquad \text{Eq. 1}$$

Where, C is the degree of volume reduction of the powder column under the applied pressure, P. The constant a is the minimum porosity of the material

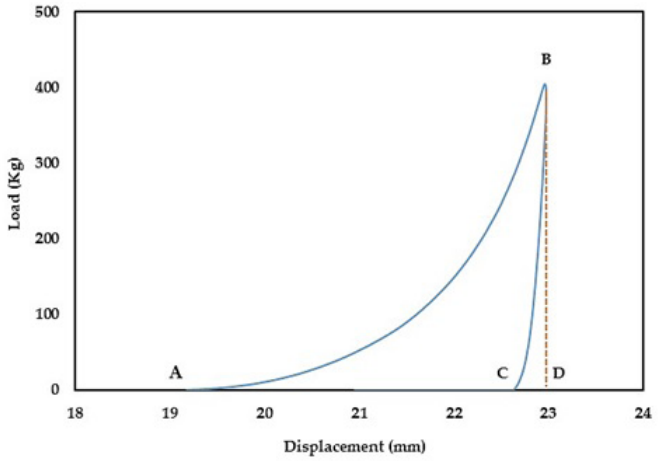

Figure 1 A typical force-displacement curve of the compression process

before compression, while constant b relates to the amount of plasticity of the material. The reciprocal of b or P_k defines the pressure required to reduce the powder bed by 50% (30, 31).

Equation 1 can be rearranged in a linear form as shown in Equation 2:

$$\frac{P}{C} \quad \frac{P}{a}+\frac{1}{ab} \qquad \text{Eq. 2}$$

Compression evaluation

The work of compression was calculated for each compression run from the force-displacement curve. A representative curve is shown in Figure 1. The compression work is given by the area under the O-B curve whereas the area under the curve B-C gives the elastic recovery work exhibited by the compressed powder. The two analysis techniques complement one another so that a complete characterization of the powder and its flow behavior during compression is obtained.

Statistical analysis

A one-tailed T-test of the null hypothesis was used to determine whether values of the investigated parameters and hence the properties of the original α-lactose monohydrate, spray dried lactose and the roller compacted lactose differed significantly from each other. Results were considered significant at a P-value <0.05 (43).

RESULTS AND DISCUSSION

Figure 2 shows typical linear Kawakita plots of Equation (2) for some selected compression runs of uncompacted and compacted lactose. The Kawakita constants a, b, ab, $1/b$, and 1-a were calculated from the slope and intercept of the fitted linear equations as shown in Table 2.

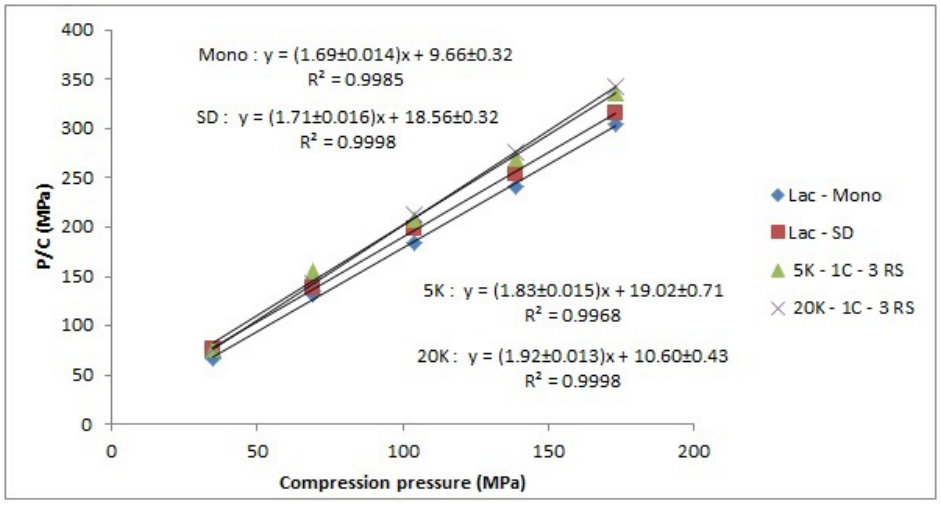

Figure 2 A typical Kawakita plot for α-lactose mono hydrate, spray dried lactose, and selected runs of roller compacted lactose.

Table 2 Kawakita parameters for the different experimental runs

RUN	*a*	1/*b* (MPa)	*ab* (MPa^{-1})	1-*a*	Bulk density (g/cm^3)
Lac - Mono	0.591 ± 0.0048	5.705 ± 0.235	0.104 ± 0.003	0.409 ± 0.004	0.543
Lac - SD	0.581 ± 0.005	10.405± 0.112	0.053 ± 0.0002	0.419 ± 0.005	0.573
5K - 1C - 3 RS	0.547 ± 0.0049	10.405 ± 0.381	0.053 ± 0.002	0.453 ± 0.0048	0.607
10K - 1C - 3 RS	0.541 ± 0.0043	9.291 ± 0.196	0.058 ± 0.001	0.463 ± 0.0043	0.614
15K - 1C - 3 RS	0.537 ± 0.0051	10.092 ± 0.231	0.054 ± 0.0025	0.460 ± 0.005	0.630
20K - 1C - 3 RS	0.522 ± 0.0047	10.292 ± 0.243	0.051 ± 0.003	0.478 ± 0.005	0.647
20K - 3C - 3 RS	0.455 ± 0.005	10.405 ± 0.198	0.045 ± 0.002	0.545 ± 0.0045	0.697
20K - 4C - 3 RS	0.427 ± 0.0048	14.989 ± 0.253	0.034 ± 0.004	0.573 ± 0.0048	0.756
20K - 1C - 7 RS	0.483 ± 0.0047	6.226 ± 0.217	0.075 ± 0.003	0.517 ± 0.0038	0.652
20K - 1C - 10 RS	0.463 ± 0.0045	6.764 ± 0.315	0.068 ± 0.002	0.537 ± 0.004	0.679
20K - 4C - 5 RS	0.427 ± 0.005	12.692 ± 0.251	0.034 ± 0.004	0.573 ± 0.005	0.756

Each Kawakita parameter for spray-dried lactose was significantly different from its counterpart for α-lactose monohydrate. At least one Kawakita parameter ($1/b$) for spray-dried lactose was not significantly different from its counterpart from the following roller compacted lots: 5K-1C-3RS, 15K-1C-3RS, 20K-1C-3RS and 20K-3C-3RS.

The effect of roller compaction on Kawakita parameter *a* is shown in Figure 3. The value of parameter *a* decreased upon inducing high mechanical stress by further processing of lactose through increasing either the compaction pressure, or compaction repetition, or the compaction relative speed as shown in Figures (3-a, 3-b, 3-c) respectively. The implication of increasing the ratio of the relative speed of the feeding screw to the roller speed may be that it intensifies the energy induced into the material in the compaction process by increasing the shear force on the material. A decrease in the maximum volume reduction *a* reflects the lower inter-particle volume due to becoming denser upon roller compaction. This was evident by the increase in bulk density of all powders subjected to mechanical compression as shown in Figure 3.

The value of *a* and the bulk density are inversely proportional. Regardless of the magnitude, the value of *a* for spray dried lactose and roller compacted lactose is significantly smaller than that of the α-lactose monohydrate. Accordingly, the particles of the compacted and spray dried lactose undergo lesser displacement upon compression. In contrast, α-lactose monohydrate showed the highest *a* values which may result in a larger displacement of the particles upon compression. Furthermore, increasing the roller compaction effect by compaction repetition or, to a lesser extent, by increasing the compaction relative speed, significantly increased the bulk density with a concomitant significant decrease in *a*. Such an effect is likely to influence the flow behavior of the powder during tablet compression. This effect of compaction repetition and compaction relative speed on *a* could be attributed to higher energy induced in the powder.

Figure 4 presents the $1/b$ parameter measured for α-lactose monohydrate, spray dried lactose and lactose compacted at different operational conditions. As parameter $1/b$ is a measure of the pressure needed to cause ½ volume reduction, it is a measure of the resistance of granules to applied pressure. The greater the $1/b$ parameter, the harder the granules, most probably, due to the lesser extent of plastic deformation taking place upon compression (44). Accordingly, the granules of compacted lactose were significantly as hard as that of spray-dried lactose, with the exception of lots 10K-1C-3RS , 20K-1C-7RS and 20K-1C-10RS. The granules of spray dried lactose and those of all the roller-compacted lots were significantly harder than those of α-lactose monohydrate. This may be due to a larger extent of particle consolidation in spray-dried

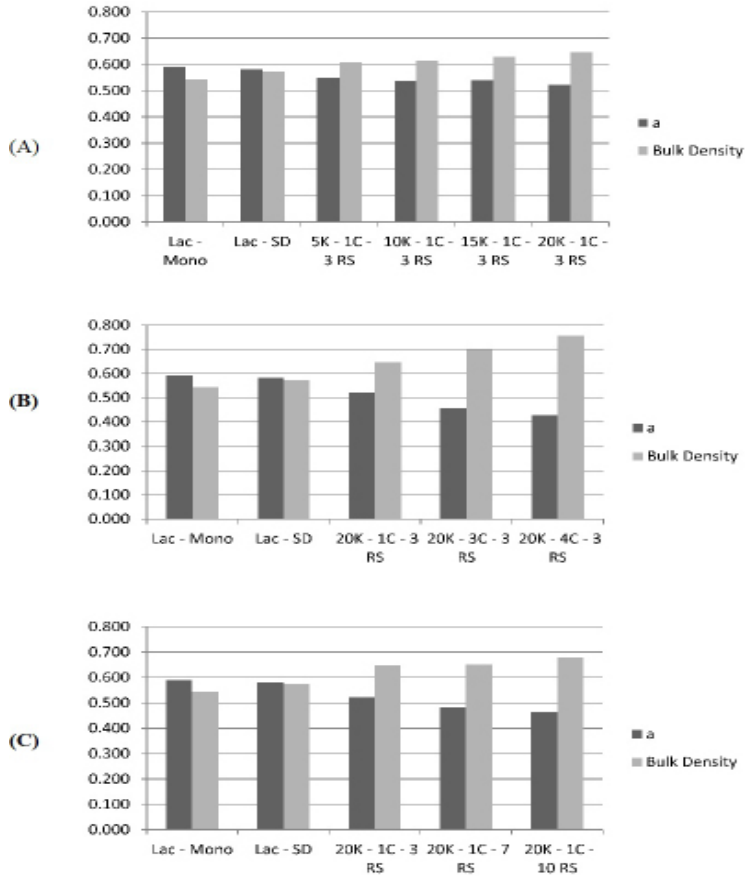

Figure 3 The effect of compaction on parameter *a* and bulk density: compaction pressure (A), compaction repetition (B), compaction relative speed (C).

and roller compacted lactose compared to α-lactose monohydrate leading to a higher resistance against the applied compression force. For a given compaction pressure (20K) and RS (3), increasing the number of compaction cycles significantly increased the granule hardness. The hardest granules were obtained at the highest compaction pressure (i.e., 20K) and at 4 cycles of compaction of α-lactose monohydrate. On the other hand, for a given compaction pressure (20K) and one compression cycle, increasing the RS from 3 to 7 or 10 significantly decreases $1/b$ such that it becomes significantly lesser than of spray-dried lactose. This may be explained by visualizing the effect of compaction pressure and compaction repetition as applying a net force vector in the direction of gravity on the powder particles causing increased van-der-Waals bonding between particles and hence resulting to more compact and hard granules. However, when the relative speed of roller compaction is increased, the powder particles are subjected to a net force vector perpendicular to the direction of gravity equivalent to a high shear force which could break some of formed van-der-Waals bonds between particles, which in turn, could result in lower hardness and strength (45).

The effect of roller compaction process on the Kawakita parameter *ab* is demonstrated in Figure 5. This parameter reflects the particle rearrangement upon powder compression. Compared to α-lactose monohydrate, significantly lower *ab* values were obtained through spray drying and roller compaction. The results in Figure 5-A show that compaction process under different compaction pressures and one compression cycle produced a powder with particle rearrangement similar to that obtained by spray dried lactose. On the other hand, as shown in

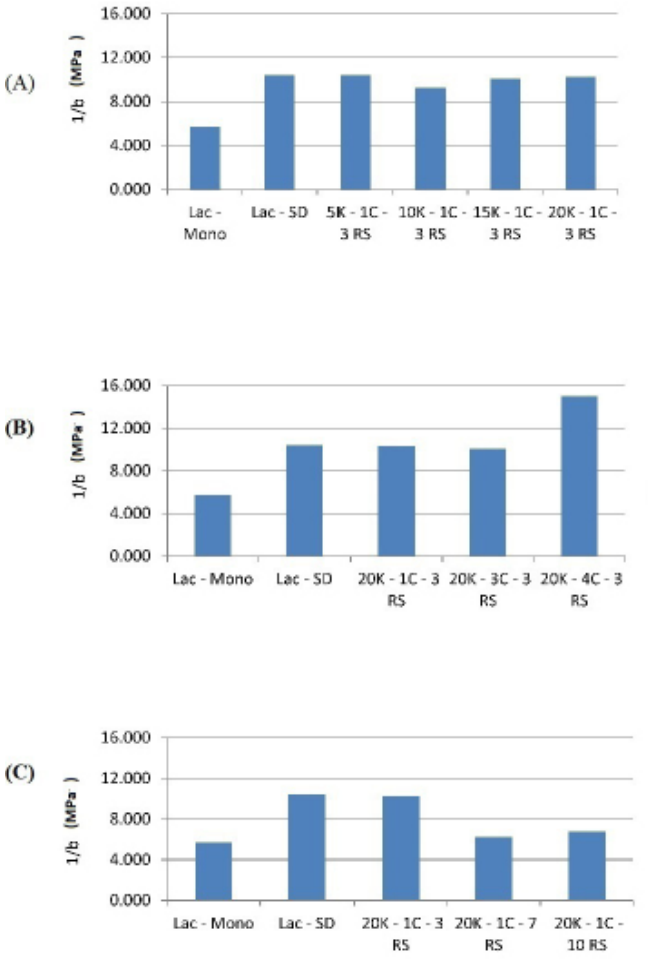

Figure 4 The effect of compaction on parameter 1/b for compaction pressure (A), compaction repetition (B) and compaction relative speed (C).

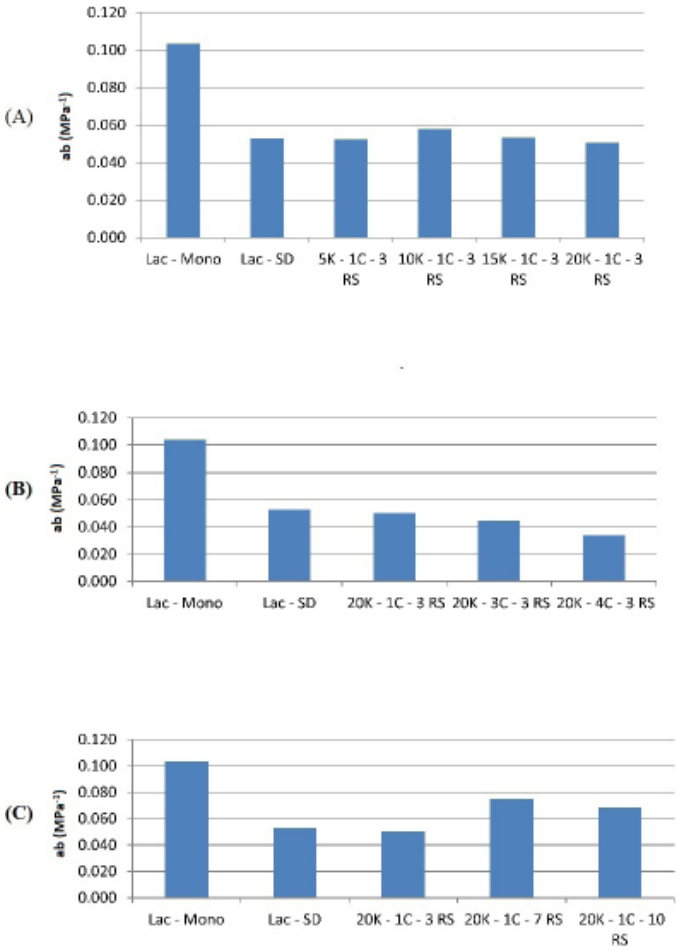

Figure 5 The effect of compaction on parameter ab for compaction pressure (A), compaction repetition (B) and compaction relative speed (C).

Figure 5-B, repetition of compaction at a similar RS produced a powder with decreasing values of *ab* significantly lesser than that of the spray dried lactose. This could be indicative of a lesser capability for particle rearrangement due to a more compact powder structure. Regarding the effect of compaction relative speed at a given pressure and for a constant number of compression cycles, as the RS increased, the less compacted powder was produced whose value of *ab* was significantly larger than that of spray dried lactose. Consistent with the observations for the value of *a* and *1/b*, the effect of the relative speed appeared to be dominant in inducing higher shear stress in the powder relative to inducing compaction.

The initial relative density represented by the parameter *1-a* increased by the action of roller compaction as seen in Figure 6. This parameter is analogous to the bulk density. Again, such an increase is consistent with trends observed for volume reduction *a* and granule strength *1/b*. Taken together, the results indicate that optimized roller compaction can improves flow during compression

The correlation of the Kawakita parameter *1/b* to the granule hardness was validated by measuring tablet hardness at different compression forces. At compression forces between 20-50 kN, the crushing strength of tablets made from roller compacted lactose

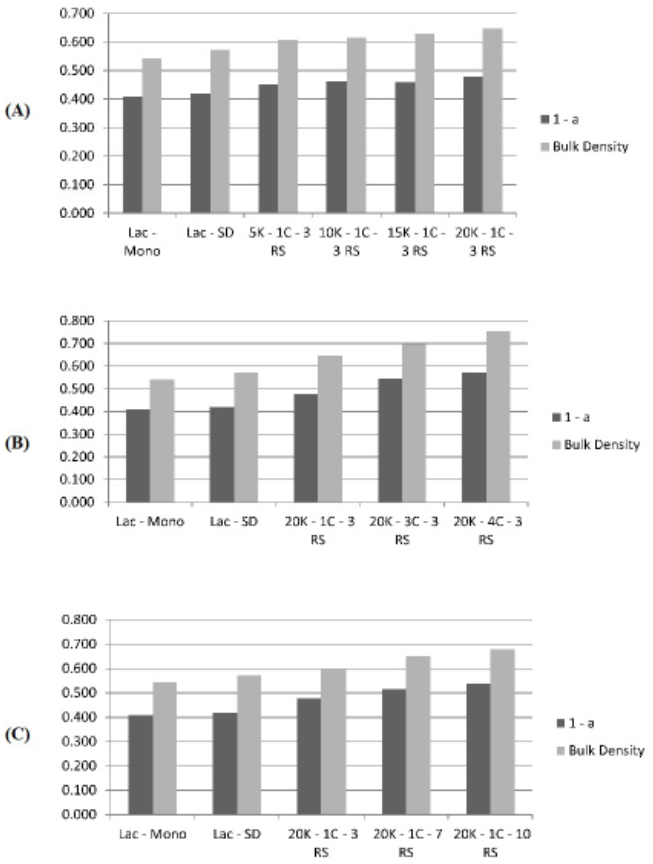

Figure 6 The effect of compaction on parameter 1-a and bulk density for compaction pressure (A), compaction repetition (B) and compaction relative speed (C).

was greater than those of tablets made from spray-dried lactose. Tablets from both types of processed lactose showed, as expected, a crushing strength greater than those of tablets made from α-lactose monohydrate (Figure 7).

Subsequently, the crushing strength as a function of compression pressure was compared for the three types of lactose separately mixed with ibuprofen at a drug: excipient ratio of 1:1 (Figure 8). For compression forces between 20 and 35 kN the crushing force of ibuprofen tablets followed the relationship roller compacted lactose > spray-dried lactose > α-lactose monohydrate. The tablet crushing force increased for all types of lactose up to a compression force of 35 kN, above which the crushing force underwent a sharp decrease. For ibuprofen tablets made with compacted lactose and α-lactose monohydrate, the crushing

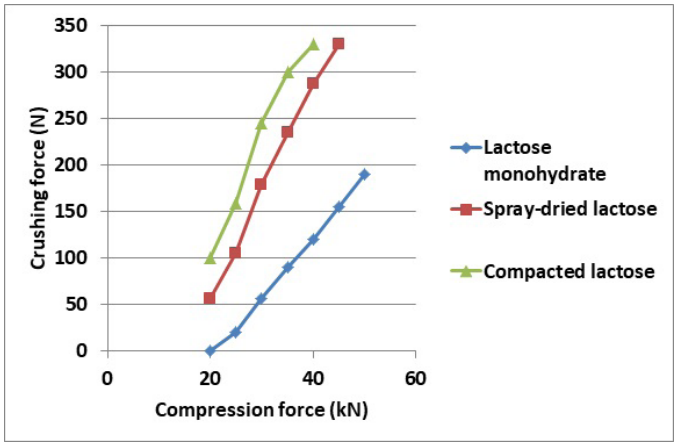

Figure 7 Crushing strength of tablets made from α-lactose monohydrate, spray dried lactose and roller compacted lactose.

force increased up to 40 kN compression force then decreased above 45 kN. This decrease in crushing force was larger for ibuprofen tablets made with spray-dried lactose. The decrease in tensile strength above a specific compression force may be due to a counter effect to lactose van-der-Waals binding resulting from the highly fragmenting nature of ibuprofen (46). Accordingly, such drug fragmentation became excessive above this specific compression force due to a greater surface coverage of lactose with a drug with binding properties.

It should be noted that no attempt was made to compare the particle size and size distribution of the α-lactose monohydrate, spray dried lactose and the various lots of milled roller compacted lactose.

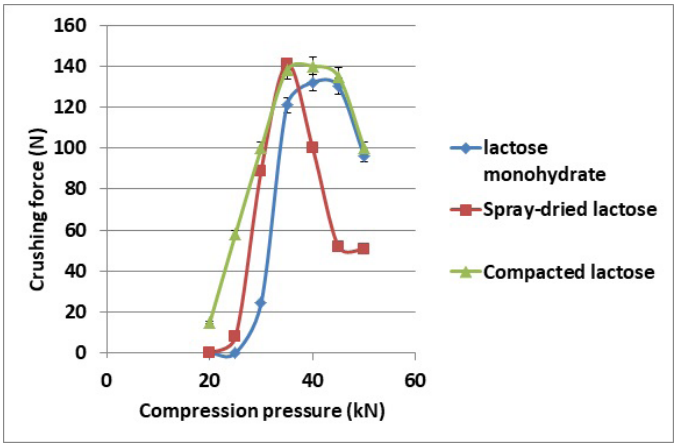

Figure 8 Crushing strength of tablets made from α-lactose monohydrate, spray dried lactose, and roller compacted lactose with ibuprofen as API.

Therefore, it cannot be definitively concluded whether the changes in the Kawakita parameters were due to differences in particle size distribution or to differences in morphology, amorphization or surface free energy upon roller compaction. Since all the particles of the roller compacted lactose were below 500 μm with a particle size distribution likely to be dissimilar to that of either the spray-dried lactose or the α-lactose monohydrate, this study cannot definitively rule out the possibility that a similarity in particle size distribution alone may impart favorable characteristics to α-lactose monohydrate, similar to that of roller compacted lactose.

Compression work analysis

The movement of the powder into the die is visualized as a combination of both plug flow of the powder bed and shear flow (Couette flow) of particles relative to each other. The magnitude of the compression work reflects the total energy consumed in the linear movement of the powder bed as well as the Couette flow (shear flow) of the particles. The rate of compression (the shape of the force-displacement curve) reflects the ratio between the plug flow and shear flow, and consequently, the microstructure characteristics affecting this ratio. For an acceptable compression process, it is desirable to have an optimum combination between plug and shear flow to achieve an acceptable degree of compaction. Generally, a greater degree of compaction results in an improved mechanical integrity of the tablet.

Figure 9 shows compression at different compression forces for α-lactose monohydrate, spray dried lactose and lactose roller compacted at different conditions (see Table 1). There is a significant difference between the compression work of the spray dried lactose and the other samples. It can be seen that the sample closest to the spray dried one in terms of the work of compression is 20K-4C-5RS.

The flow behavior of the powder during the compression process is presented in Figure 10a. Although there is a major difference in magnitude, the flow behavior of the spray dried lactose and the compacted sample (20K-4C-5RS) are similar. Consequently, it can be concluded that roller compaction can produce a direct compressed lactose powder similar in behavior to the commercial spray dried lactose whilst employing a lesser compression force.

The linear displacement of the powder bed of a

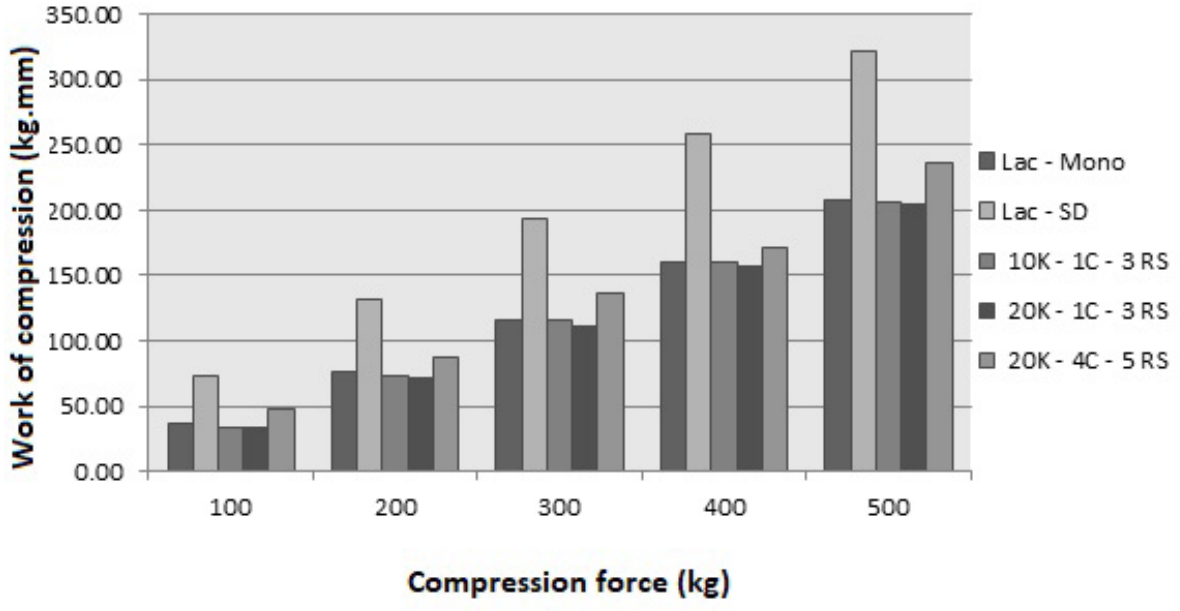

Figure 9 Compression work at different compression forces for lactose monohydrate, spray dried lactose, and compacted lactose at different conditions.

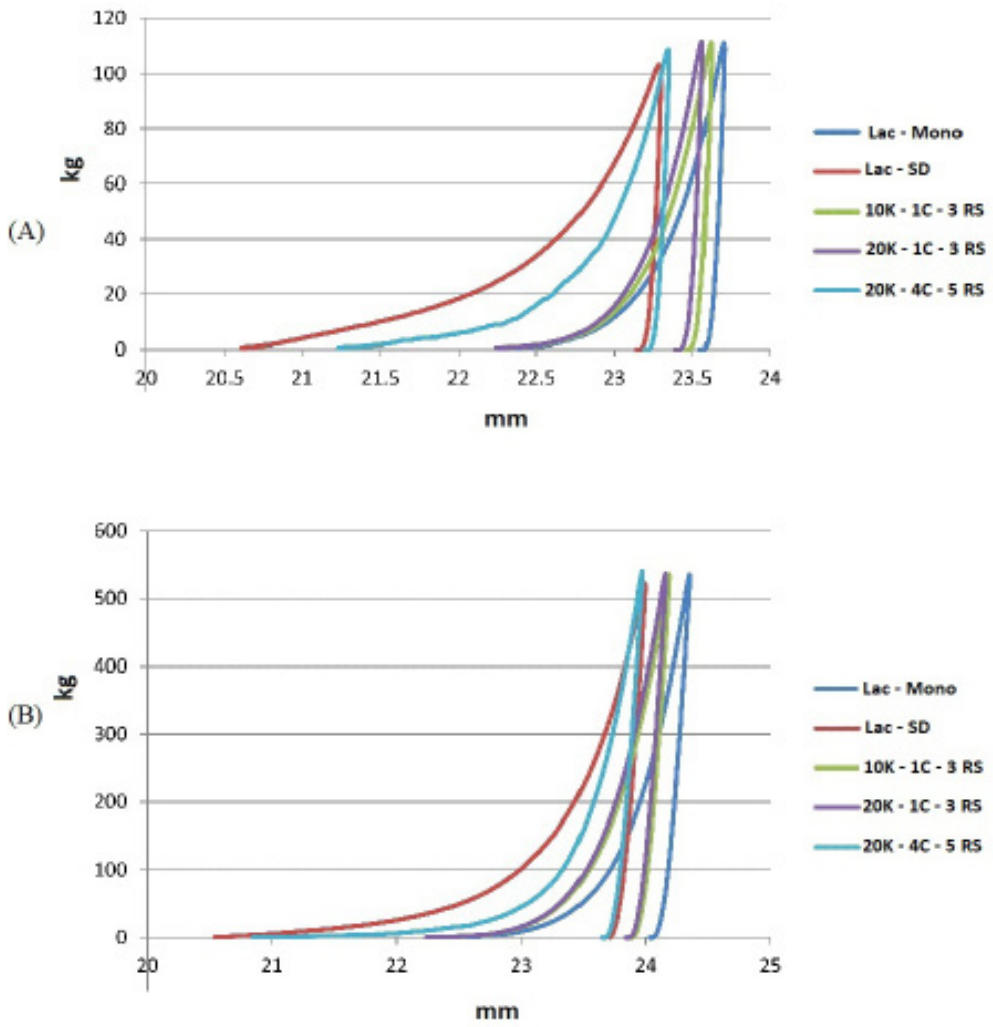

Figure 10 Compression profile for lactose monohydrate, spray dried lactose, and compacted lactose at different conditions: (A) at 100 kg compression force, (B) at 500 kg compression force.

crystalline material is larger at the beginning of the compression cycle because the force is not large enough to introduce disorder in the material structure. On the other hand, toward the end of the compression cycle, some disorder and deformation of the material structure has occurred, but there is not enough time for rearrangement flow of the powder particles.

In examining the force-displacement (F-D) curves for compacted and spray dried lactose and comparing them with α-lactose monohydrate, it can be seen that the displacement profiles (compression and decompression) of the two processed lactose excipients precede that of α-lactose monohydrate (Figure 10b). This corresponds to a lower linear displacement and higher compression force for the processed excipients when they undergo compression. This behavior is consistent with the results from the Kawakita analysis of the powders whereby processed lactose showed lower a and higher $1/b$ values when compared to α-lactose monohydrate. In other words, the lesser volume reduction for a higher applied force needed upon compression of the processed compared to the unprocessed excipients indicated that a higher energy is needed to compress the processed lactose powders into tablets. This higher energy input could be attributed to the Couette flow of particles in the radial direction resulting in a better tablet homogeneity.

This greater energy input was also responsible for the harder compacts of processed excipients compared to α-lactose monohydrate.

The ibuprofen tablets were also subjected to a dissolution test. Figure 11 shows that no more than 20% of drug was released from tablets containing only the drug, i.e., without excipients. The drug release of a commercial product (Advil® 200 mg tablets) presented a typical immediate release profile whereby 80% of ibuprofen was released at 60 minutes. When the ibuprofen tablets (200 mg drug) were prepared using physically mixed lactose (either compacted at stage G, or α-lactose monohydrate, or spray dried lactose), a disintegrant (2% w/w) and a solubilizer (0.1% w/w SLS) at a ratio of 1:1 drug:total excipients, the dissolution profile showed a typical immediate release pattern. The dissolution of ibuprofen tablets containing all types of processed or unprocessed lactose excipients showed almost identical profiles whereby more than 85% of the drug was released in less than 30 minutes (USP 31). Hence, the ability of the lactose to disintegrate and release the drug is independent of its powder physical nature. The release of water insoluble drugs is not expected to be changed using roller compacted lactose.

CONCLUSIONS

It can be concluded from the Kawakita analysis of the compression data that roller compaction of the α-lactose monohydrate at optimum compaction pressure, number of compaction cycles and RS yielded a processed powder similar in its characteristics to the commercially used spray dried lactose.

The analysis of the compression work and profile demonstrated that the roller compacted lactose had a similar flow behavior as spray dried lactose with an advantage of a decreased level of compression force for a given crushing strength.

Tablets made from roller compacted lactose exhibited a greater crushing strength than those made from spray dried lactose or α-lactose monohydrate.

Roller compaction of lactose powder improved the physical properties of the powder and that of the compressed tablets without decreasing the dissolution and release of the incorporated API. Consequently, it is suggested that industrial scale roller compaction can convert α-lactose monohydrate into a lactose excipient that is equivalent in physical properties and compaction behavior to spray dried lactose.

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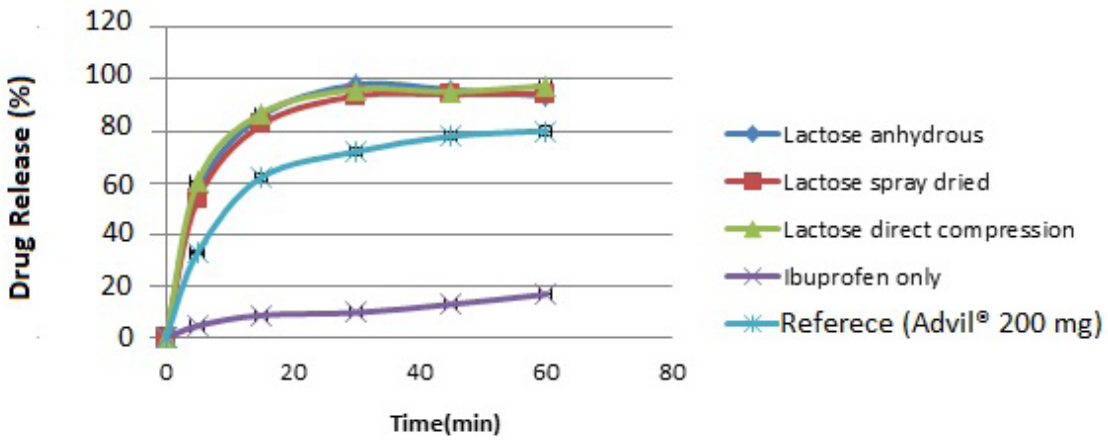

Figure 11 Release of ibuprofen from different types of lactose.

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