Original Research Article

Effect of compression pressure on inhalation grade lactose as carrier for dry powder inhalations

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Abstract

Introduction: This study focused on the potential effects of compression forces experienced during lactose (InhaLac 70, 120, and 230) storage and transport on the flowability and aerosol performance in dry powder inhaler formulation. **Materials and Methods:** Lactose was subjected to typical compression forces 4, 10, and 20 N/cm². Powder flowability and particle size distribution analysis of un-compressed and compressed lactose was evaluated by Carr's index, Hausner's ratio, the angle of repose and by laser diffraction method. Aerosol performance of un-compressed and compressed lactose was assessed in dispersion studies using glass twin-stage-liquid-impenger at flow rate 40-80 L/min. **Results:** At compression forces, the flowability of compressed lactose was observed same or slightly improved. Furthermore, compression of lactose caused a decrease in *in vitro* aerosol dispersion performance. **Conclusion:** The present study illustrates that, as carrier size increases, a concurrent decrease in drug aerosolization performance was observed. Thus, the compression of the lactose fines onto the surfaces of the larger lactose particles due to compression pressures was hypothesized to be the cause of these observed performance variations. The simulations of storage and transport in an industrial scale can induce significant variations in formulation performance, and it could be a source of batch-to-batch variations.

Key words: Aerosolisation, compression pressure, dry powder inhalation, lactose, particle size

INTRODUCTION

Dry powder inhalers (DPI) are commonly used to treat respiratory diseases such asthma, bronchitis, emphysema and chronic obstructive pulmonary disease. In DPI, the deposition of the drug at the target site is maximum.[1] An aerosolized drug will be deposited either in the extrathoracic region (mouth, throat, and oropharynx) or within the lungs where drug particles can deposit in the bronchial region (also called central deposition) and in the alveolar region of the lung (known as peripheral deposition). Lung deposition studies determine the quantity of an aerosolized drug.[1] The study provides information on the regional distribution of the inhaled compound within the lungs, which could be expressed as the ratio of central to peripheral deposition.[2] Dry powder drug particles, designed for respiratory delivery, require a small aerodynamic diameter to avoid impaction in the throat and upper airways.[3] However, micronized particles of this size tend to be highly cohesive, and thus, a much larger nontherapeutic carrier particle is typically incorporated in DPI formulations to reduce drug particle agglomeration, improve aerosol redispersion, and facilitate dose metering.[4]

Pharmaceutical formulations have therapeutic doses in the microgram range (e.g., 200-400 μg) and cannot be metered without the addition of a diluent. Lactose as a diluent used for specific formulation type, which are generally referred to as carrier-based formulations and the powder blend contains an ordered mix of drug particles, uniformly adhered to the larger

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carrier, throughout the powder bed.[5,6] On aerosolization, the drug particles should be liberated from the carrier so that they can pass into the respiratory tree while the carrier material impacts in the throat and is swallowed. To complicate matters, the carrier may have a wide size distribution and contain excipient particles with a similar diameter to the drug material. In these cases the physics of a simple ordered mix is complicated as "fine" excipient particles may alter the effective lactose surface and/or form complex multi-particulate agglomerated systems.[7-9]

Empirical observations and theoretical models for drug aerosolization in these systems are complicated by the plethora of physico-chemical variables of the carrier. For example, carrier roughness,[10,11] carrier shapes,[11] surface energy,[12] and mild compression force[13] are variables that have been shown to influence aerosol performance. Inevitably the study of one physico-chemical property in isolation is difficult, since the modification of one variable generally results in a change in other variables in the system such as changing carrier size alters roughness or changing polymorphic form alters surface chemistry and shape. Previous studies have reported carrier size to be a dominating factor for drug aerosol performance. For example, Guenette *et al*.[14] studied a range of multimodal carrier size distributions whose size distributions spanned 2-200 μm and using, principle component analysis, reported fine and course fine distributions influenced the performance of the drug salbutamol sulfate. Donovan and Smyth[15] studied the influence of carrier size on the aerosolization behavior of budesonide from blends across a wide range of size classifications (30-300 μm). The reported data larger lactose carriers (250-355 μm) to perform poorly when compared to smaller lactose carriers (32-45 μm), attributing this to carrier-drug (budesonide and sodium cromoglycate) kneading processes during blending. Interestingly, the group also reported that such observations were dose-dependent and attributed this to variations in roughness and variations in "force distribution" on the carrier. In another study, Islam *et al*.[7] studied the aerosolization of salmeterol xinafoate from lactose carriers across a range of diameters (22-157 μm) and observed that aerosol performance decreased with increased lactose size. The group found that the aerosol performance was dominated by both size and roughness. For example, anhydrous lactose samples showed a rank decrease in performance as size was increased, while granulated lactose showed a rank increase in performance over the same size range. More recently, Ooi *et al*.[16] suggested that higher energy processes drive aerosolization, this is likely to be due to the number of impaction event, associated frictional and rotational forces rather than the actual collision velocity. Since the larger carrier had increased momentum and drag forces. In isolation of other variables, as carrier size increases, a concurrent decrease in drug aerosolization performance is observed. The small pressures can cause much larger localized pressures on the carrier particle surfaces which can then cause substantial deformation in surface and loose fines. The amount of loose and surface fines is hypothesized to have been the major source of variation in dry powder inhalation properties. Likewise, Marek *et al*.[13] studied the effect of compression of lactose fines

on to the surface of larger lactose particles due to mild procession pressures and observed decrease DPIs performance; suggested simulation of storage and transport in a hopper can induce variation in formulation.

Carrier based DPIs have shown to be relatively inefficient delivering only about 10-20% of the total dose to the lungs. The poor efficiency of DPIs is related to the complex physiology of respiratory track as well as to characteristics of powder formulation (carrier size and roughness) for inhalation and their inhalation devices. Dispersion of micronized drug particles in respiratory delivery will be dependent on the drug cohesive and adhesive properties to the carrier in the powder formulation. Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPI's. Dose uniformity is a challenge in the performance of DPI's. This is a greater concern with powders than with liquids because of the size and discrete nature of the particulates.[17] Particulate interaction occurs in a mixture of micronized drugs because particle detachment forces favour cohesion or adhesion. Thus micronized particles interact with themselves to produce agglomerates and with other surfaces including excipient to form interactive units. Effective respiratory delivery requires the dispersion of drug from agglomerates and interactive units using energy generated by inhalation devices.[7] Compression of lactose prior to blending caused a decrease in *in vitro* aerosol dispersion performance.[13]

Batch-to-batch variation in excipients can cause significant performance differences, even when standard physical characterizations indicate that the batches are not different.[18-24] Similarly, dual sourcing has been shown to cause performance differences as well,[18-28] which makes supply-chain interruptions even more devastating to pharmaceutical companies. However, there is very little information in the literature about the origin of these variations in lactose performance. Typical standardized tests include particle size distribution, X-ray powder diffraction, differential scanning calorimetry, and other compendial methods; however, variations between different types of lactose are detectable, but not between different batches of the same lactose type.[29] Surface energy[23] and low-frequency dielectric spectroscopy[22] have been able to distinguish between some lactose batches, though these processes are time intensive and restricted to very small sample sizes, thus providing little industrial relevance as they are unsuited to high throughput screening. Accordingly, a rapid test to predict lactose performance prior to the completion of the manufacturing process would be ideal. For aerosols, the physical instability is more important, because agglomeration may be irreversible and lead to an inability to generate aerosol particles of respirable size.[29] Although they may not reach equilibrium during transit, susceptible aerosol particles may be subject to hygroscopic growth, which increases particle dimensions and affects lung deposition.[29] The purpose of this study was to assess the potential effects of mild compression conditions, mimicking typical pressures experienced during long-term and short-term storage while storage, transportation as well as powder processing. Specifically, the effects of these treatments on particle sizes,

morphologies, flow properties, surface areas, and aerosolization performance were examined. The report indicates the potential significance of processing of carrier on both batch-to-batch variability and intra-batch variability.

MATERIALS AND METHODS

Materials

The different grades of lactose used specifically in DPIs formulation InhaLac 70 (INHL 70), InhaLac 120 (INHL 120) and InhaLac 230 (INHL 230) were supplied by Meggle Excipients and Technology (Germany). Micronized salbutamol sulfate was supplied by OREX Pharma Pvt. Ltd. (Dombivali, Mumbai). Isopropyl alcohol and hydrochloric acid were supplied by Merk (Mumbai, India). Water was purified by reverse Osmosis (Milli Q, Mumbai, India).

Preprocessing of lactose

The lactose samples INHL 70, INHL 120 and INHL 230 were subjected to compression to simulate possible conditions experienced during the storage/transportation of bulking agent use in DPI formulations. Prior to testing the lactose were stored at 45% RH and 25°C, 10 g of each placed into die (5 cm × 5 cm × 1.5 cm) of stainless steel and compression pressure of 4, 10 and 20 N/cm^2 was applied for 60 days.[30]

Particle size analysis

The particle size distributions were measured by laser diffraction method using Malvern Mastersizer 2000, Malvern (Worcestershire, UK). Approximately, 1 g of compressed and un-compressed lactose were dispersed in 800 ml isopropyl alcohol and sonicated for 5 min prior analysis. An aliquot of the suspension was then transferred to the small dispersion cell of the Malvern particle sizer until an obscuration between 2% and 5% was achieved. Each measurement was based on 2000 sweeps and all samples were analyzed in a singlet.

Optical microscopy

The morphology of the uncompressed and compressed lactose INHL 70, INHL 120, and INHL 230 samples were studied by using Motic microscopy (DMWB1-223 ASC, Canada).

Powder flow

The uncompressed and compressed lactose (INHL 70, INHL 120, INHL 230) were analysed for bulk density (BD), tapped density (TD), Carr's index (CD) Hausner's ratio (HR), angle of repose (AR) as per procedure described by Lachman *et al*.[31]

Preparation of blend

Salbutamol sulfate was geometrically blended with the lactose (uncompressed and compressed separately) in the ratio of 1:250 followed by mixing in an air tight zip-log bag at 46 rev/min for 30 min. The blends were then stored in tightly sealed containers at 45% RH and 25°C, for 24 h. Content uniformity of each blend was tested according to the method described in British Pharmacopoeia 2010. These blends were filled into the capsules (50 mg/capsule) on filling machine (Electrolab, India). The weight variation should not exceed 5%.[32]

In vitro aerosol performance analysis

The influence of uncompressed and compressed lactose as a carrier on the aerosolization efficiency of salbutamol sulfate was studied using a glass twin-stage-liquid-impinger as per USP specification inlet port (TSLI; Copley's scientific, Denmark, UK). Since the driving force behind the efficient separation of drug from carrier is air flow-rate (and thus the energy imparted into the system), the performance was evaluated as a function of flow rate of 60-80 L/min. Prior testing, 15 ml of distilled water was added to stages 1-2. The flow rate (60-80 L/min) was set using high compression pressure 5 rotary vane vaccume pump (Erweka GmbH, Heusenstomm, Germany) and (TSLI 3063, TSLI Instruments Ltd., Buckinghamshire, UK). 50 mg of the prepared blend was then placed in Rotahaler TM DPI device (GlaxoSmithKline, Uxbridge, UK) and the device was then kept in mouthpiece adaptor of the inlet port. The TSLI was operated so that 4 L of air was drawn through the device. All stages of TSLI were washed into suitable volumetric for ultraviolet analysis to determine salbutamol mass recovery. All the experimental procedures were carried out under the controlled environment of humidity (45% RH) and temperature (25°C) and samples were randomized for both carrier diameter and flow rate.

RESULTS AND DISCUSSION

Particle size analysis

Particle sizing performed using laser light scattering yielded the D(0.1), D(0.5), and D(0.9) of the lactose INHL samples [Figure 1a-c]. The D(0.1) values provided evidence of the loss of fines with the highest compressed particles. Particle size distribution of the INHL 70, INHL 120 and INHL 230 compressed at 4, 10, and 20 N/cm^2 analyses suggested that increase in particle size as compared to uncompressed. Specifically D(0.1), D(0.5), and D(0.9) values 70.63, 150.12, and 265.55 µm for un-compressed INHL 70; 71.51, 151.63 and 266.85 µm for compressed INHL 70 at $4N/cm^2$; 75.57, 153.58, and 274.47 µm for compressed INHL 70 at 10 N/cm^2; 78.36, 155.04, and 274.76 µm for compressed INHL 70 at 20 N/cm^2 respectively. Similarly D(0.1), D(0.5), and D(0.9) values 61.93, 132.21 and 220.24 µm for un-compressed INHL 120; 62.49, 132.09, and 220.59 µm for compressed INHL 120 at 4 N/cm^2; 65.76, 142.04, and 225.64 µm for compressed INHL 120 at $10N/cm^2$; 68.78, 142.04, and 232.20 µm for compressed INHL 120 at 20 N/cm^2 respectively. Likewise, D(0.1), D(0.5), and D(0.9) values 53.10, 110.18 and 159.25 µm for un-compressed INHL 230; 54.34, 115.20 and 163.11 µm for compressed INHL 230 at 4 N/cm^2; 58.69, 121.40 and 174.21 µm for compressed INHL 230 at 10 N/cm^2; 61.90, 128.64 and 181.36 µm for compressed INHL 230 at 20 N/cm^2, respectively. Particle size distribution analysis suggests the increase in particle size of compressed lactose as compared to uncompressed.

Optical microscopy

Motic microscopy was used to determine whether compression caused any visible surface changes to the lactose. The uncompressed lactose samples were irregular, slightly crystalline in nature and within the size range described by the particle size analysis. Furthermore, all the samples appeared to have a rough surface. Micrographs of the compressed lactose showed the compression of fines onto the surfaces. Again, the larger compression pressures caused a more dramatic and more frequent change in the lactose surface.

Powder properties

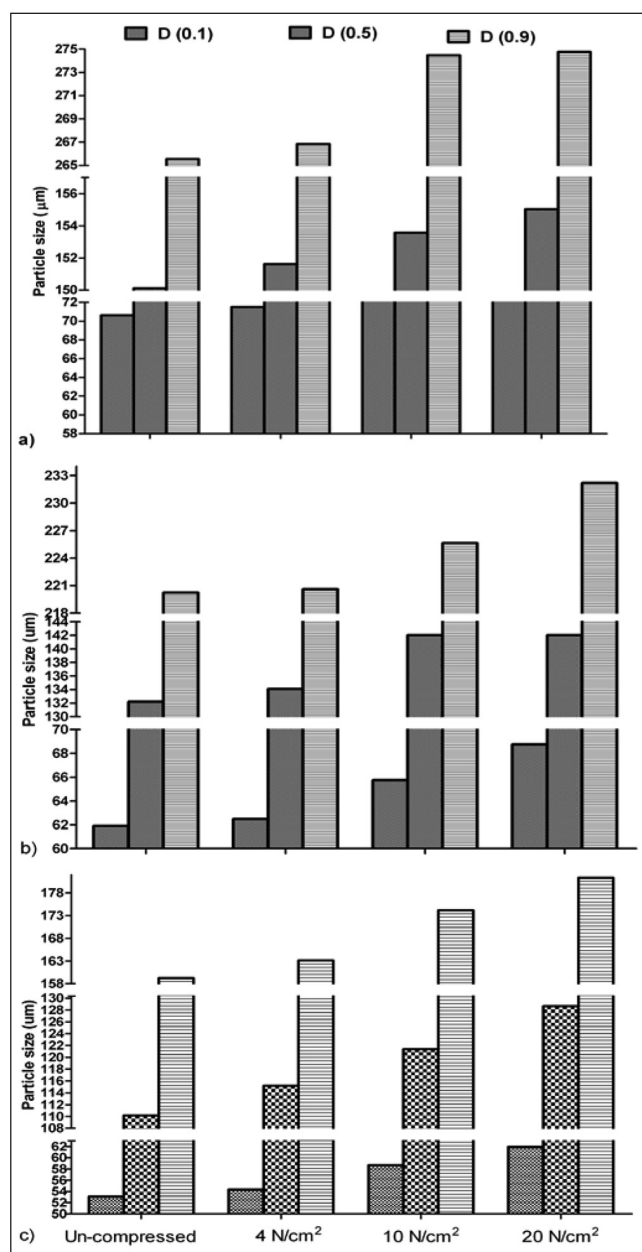The BD and TD of compressed lactose was observed decreases as compared with un-compressed. As shown in Figure 2,

BD of INHL 70 uncompressed and compressed at 4, 10 and 20 N/cm^2 was found to be 0.9354, 0.731, 0.7375, and 0.7673 g/ml, respectively. Similarly, TD was found to be 1.16, 0.8333, 0.8446 and 0.8825 g/ml, respectively. The BD of INHL 120 lactose uncompressed and compressed at 4, 10 and 20 N/cm^2 was found to be 0.8477, 0.8055, 0.7894, and 0.7612 g/ml, respectively. Likewise, TD was found to be 0.9570, 0.8787, 0.8423 and 0.8137 g/ml respectively. The BD of INHL 230 lactose uncompressed and compressed at 4, 10 and 20 N/cm^2 was found to be 0.8680, 0.8787, 0.9354, and 0.8705 g/ml respectively. Similarly, TD was found to be 0.9353, 0.9090, 0.9504, and 0.8969 g/ml respectively. The compressed lactose samples had significantly lower the BD and TD compared to uncompressed lactose. Differences in BD and TD between lactose samples are possibly a consequence of different crystalline nature or different particle size (as, for the same material, small particles have a different density from larger particles).[33] The smaller the BD and TD for compressed lactose powders indicate a lower number of contact points between
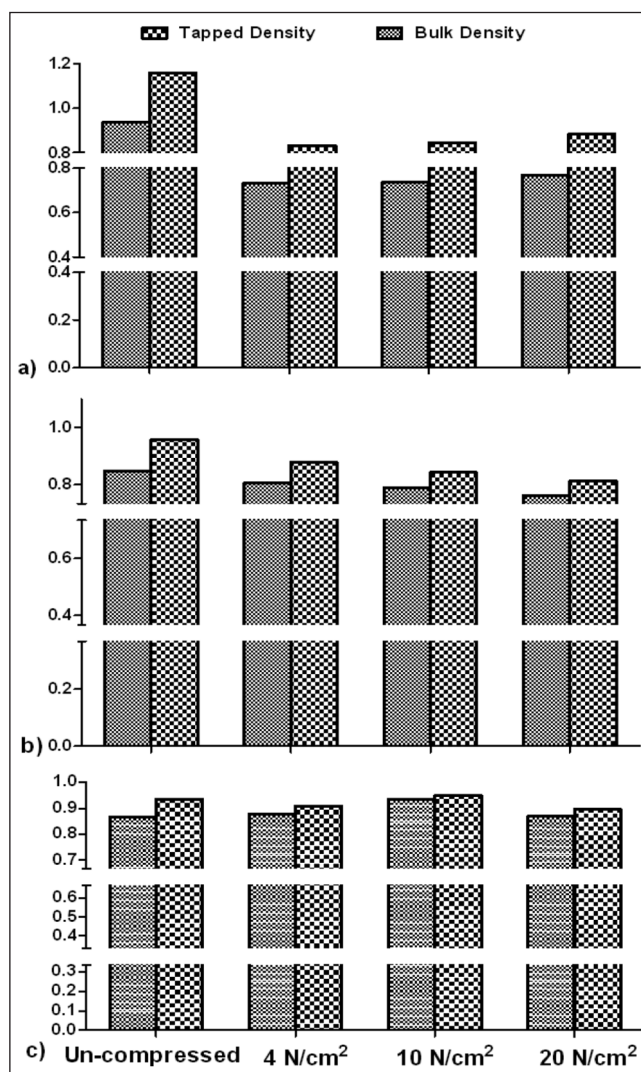

Figure 1: Particle size distribution (D[0.1], D[0.5], and D[0.9]) of lactose for the un-compressed and compressed at 4, 10 and 20 N/cm^2 of (a) InhaLac 70, (b) InhaLac 120 and (c) InhaLac 230

Figure 2: Bulk density and tapped density of un-compressed and compressed at 4, 10 and 20 N/cm^2 of (a) InhaLac 70, (b) InhaLac 120 and (c) InhaLac 230

particles within these powders compared to those present in uncompressed lactose. The irregular shape and higher surface roughness of the compressed lactose samples will contribute to the good flow properties, lower BD and TD due to increased interlocking propensity and frictional forces between the particles. In addition, the comparatively larger particles present in the compressed batches will also lead to better powder flowability. The compressed lactose samples had significantly lower the BD and TD compared to uncompressed lactose.

The Carr's index data of INHL 70 lactose uncompressed and compressed at 4, 10 and 20 N/cm^2 was observed as 16.01%, 13.99%, 14.52% and 15.01% respectively, suggests good flowability. The HR for both uncompressed and compressed INHL 70 was found to be 1.24, 1.24, 1.14, and 1.15, indicates coarse particles that showed good flowability. At the same time, AR from uncompressed and compressed lactose 21.19°, 21.19°, 20.52,° and 20.66° shifted to lower value exhibited better flowability. The Carr's index, HR and AR data showed certain variations in the powder flow properties of compressed lactose INHL 70 at 4, 10 and 20 N/cm^2. Similarly, AR decreases from 21.19° to 20.52° at 20N/cm^2 compression observed in Figure 2 indicates better flowability. These data might be related with a slight change in particle size due to compression results into increase in flowability. The Carr's index of INHL 120 lactose was found to be 12.89 % for uncompressed and 9.08, 6.70 and 6.89% for compressed at 4, 10, and 20 N/cm^2, respectively which showed good flowability. Similarly, HR was found to be 1.12, 1.12, 1.06 and 1.06 and AR was 24.03°, 23.56°, 23.89° and 22.70° suggests good flowability. The Carr's index and HR suggests an increase in flow property of compressed INHL 120 as compared to un-compressed. Similarly, AR decrease from 24.03° to 22.70° at 20 N/cm^2 compression observed indicates better flowability as per the pharmacopoeia specifications. The Carr's index of INHL 230 lactose was found to be 7.74% for uncompressed and 3.44, 1.60, and 3.03% for compressed at 4, 10, and 20 N/cm^2 respectively which showed good flowability. Similarly, HR was found to be 1.07, 1.07, 1.01 and 1.03 and AR was 27.42°, 26.59°, 26.59° and 25.28° suggests good flowability. The Carr's index, HR and AR data showed certain variations in the powder flow properties of compressed lactose INHL 230 at 10 N/cm^2 and 20 N/cm^2. The Carr's index and HR suggest increase in flow property of compressed INHL 230 as compared to uncompressed. Similarly, AR decrease from 27.42° to 25.28° at 20 N/cm^2 compression observed in Figure 3 indicates better flowability as per the pharmacopoeia specifications. These data might be related with slight change in particle size due to compression results into increase in flowability.

The Carr's index, HR and AR data showed certain variations in the powder flow properties of compressed lactose INHL 70, INHL 120 and INHL 230 at 4, 10 and 20 N/cm^2. The Carr's index and HR suggests increase in flow property of compressed lactose as compared to un-compressed. A lower compressibility index for compressed lactose powders confirms the increased cohesiveness (due to higher inter-particulate forces). Carr's index
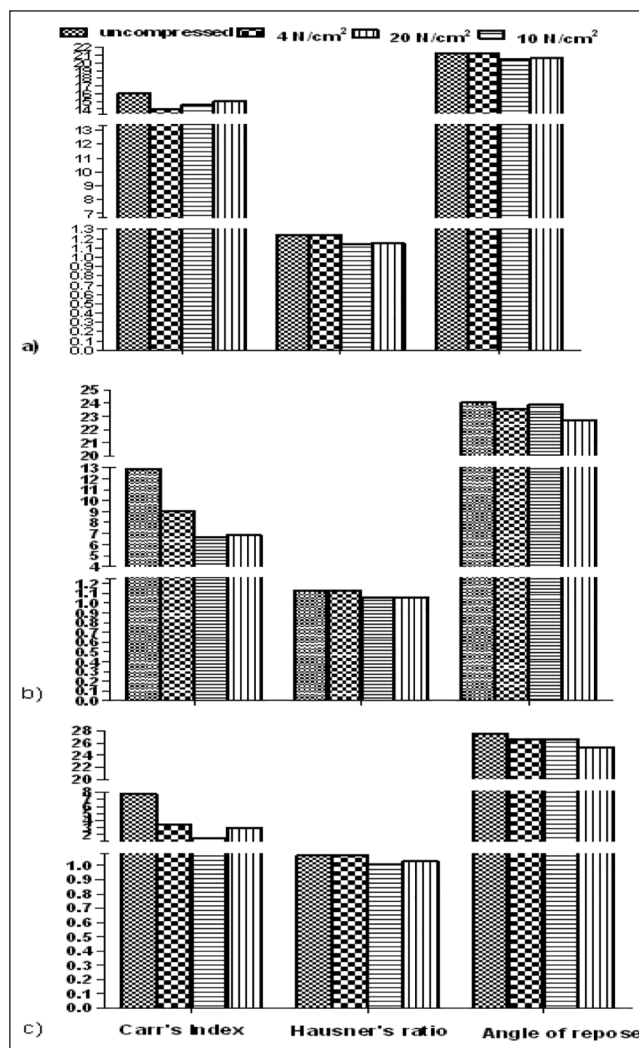

Figure 3: Carr's index, Hausner's ratio and angle of repose of uncompressed and compressed at 4, 10 and 20 N/cm^2 of (a) InhaLac 70, (b) InhaLac 120 and (c) InhaLac 230

of lactose powder could be directly correlated to lactose particle and inversely correlated to lactose particle surface roughness. The changes in densities of resultant lactose with different compression forces could be attributed to the fact that the different pressure influences the amounts of intrinsic fine particle lactose content and this in turn influences average contact points between particles within compressed lactose powders. Indeed, the increased BD, TD, and Carr's index suggested compression causes adhesion of fines on larger particles of lactose and enlarges it which prevents the friction of fine on the funnel surface improved the flowability of compressed lactose as compared with uncompressed lactose.

In vitro aerosol performance analysis

Aerosol dispersion performance studies from INHL 70, INHL 120, and INHL 230 are shown in Figure 4a-c for the different compression prior to blending with salbutamol sulphate. Compression of lactose prior to blending inhibited drug dispersion relative to the uncompressed, followed by the
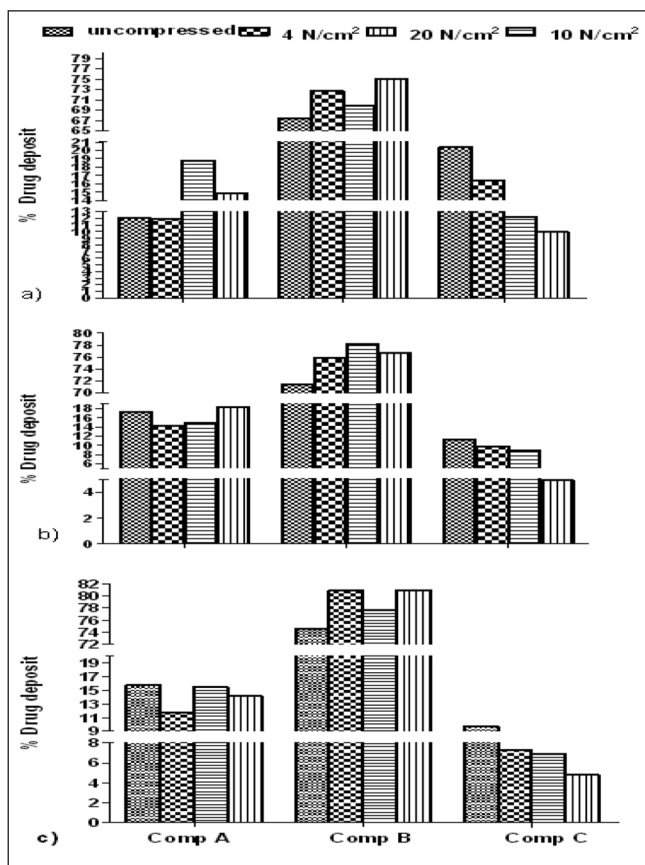
Figure 4: Percentage deposition of drug blended with un-compressed and compressed at 4, 10 and 20 N/cm² of (a) InhaLac 70, (b) InhaLac 120 and (c) InhaLac 230 lactose in compartment A (mouth), B (throat) and C (lungs)

significantly lower performance of lactose compressed at 4, 10 and 20 N/cm². The percentage deposition of drug at target site from INHL 70 of un-compressed and compressed at 4, 10 and 20 N/cm² in lungs was found to be 20.43%, 16.42%, 12.25% and 10.02%, respectively. The effect of compression pressure on INHL 70 lactose suggested that when mechanical stress over the lactose increases the force of cohesion between lactose particle might be decreased leads to slight decreased in particle size, whereas the force of adhesion between lactose and drug decreased or might be due to less moisture which was required for adhesion affects the adherence of drug on INHL 70 lactose carrier, associated with lesser drug deposition in lungs.

The percentage deposition of drug at target site from INHL 120 lactose of uncompressed and of uncompressed and compressed at 4, 10 and 20 N/cm² in compartment C (Comp C) represents lungs was observed as 11.19%, 9.86%, 8.85% and 4.94% respectively. The effect of compression pressure on INHL 120 lactose suggested that when mechanical stress over the lactose increases the cohesion between lactose particles also increased as per particle size analysis. The force of adhesion between lactose and drug was considerably increased. The carrier that is INHL 120 lactose size increases leads to more deposition in compartment A (Comp A) represents mouth and compartment

B (Comp B) represents throat as compared with compartment C represents lungs, resulted lesser drug deposition at target site lung. The percentage deposition of the drug at the target site from INHL 230 lactose of uncompressed and compressed at 4, 10 and 20 N/cm² in lungs was observed as 11.19, 9.86, 8.85, and 4.94% respectively. The effect of compression pressure on INHL 230 lactose suggested that when mechanical stress over the lactose increases the cohesion between lactose particles also increased as per particle size analysis. The increase in particle size might be related to moisture presence in INHL 230 that leads to accumulation/aggregation or clumping of lactose particle. The force of adhesion between lactose and drug was considerably increased. The carrier that is INHL 230 lactose size increases leads to more deposition in mouth and throat as compared with lungs, resulted a smaller amount of drug deposition at target site lung. INHL 70, INHL 120 and INHL 230 compressed at 4, 10 and 20 N/cm² showed a decline in drug deposition at target site lungs as compared with uncompressed lactose. The proportion of fines differs in all used grades of lactose studied by particle size analysis may be associated with variation in aerosol performance. The percentage deposition of drug from formulation with uncompressed and compressed at 4, 10, and 20 N/cm² of INHL 70 observed decrease as compression pressure increases. Analogous observations were obtained from INHL 120 and INHL 230. In comparison the lowest aerosol performance was observed at 10 and 20 N/cm² (<10%). The influence that lactose fines exert on the aerosol performance of DPI formulations has been extensively investigated in the literature, with numerous studies noting their ability to improve aerosol performance.[7,34-38] However, the mechanism by which lactose fines modulate performance remains ambiguous. One hypothesis speculates that lactose fines occupy the high energy sites on the surface of the carrier particles, allowing the active pharmaceutical ingredient (API) to adhere to lower energy sites on the carrier surface, mitigating the adhesion force between the drug and carrier and thereby facilitating the detachment.[36,38] Alternatively, other studies have cited the formation of aggregates, termed multiplets, between the lactose fines and the micronized API.[7,34,35] The larger surface area of the multiplets, relative to nonaggregated drug particles, increases their susceptibility to the aerodynamic detachment forces of the inhalation flow stream. By contrast to previous studies focusing on the influence of lactose fines, where experimental DPI formulations were prepared by either adding a specified concentration of fines to form ternary blends or intentionally removing the fine particle population through either Air-jet sieving or dissolution, the present study employed crystalline inhalation grade lactose where the fine particles were compressed onto the surface. It is speculated that the compression of the lactose may strongly adhere the fines onto the surface of the larger carriers, hindering their ability to migrate to higher energy sites on the carrier surfaces during blending, or from forming multiplets with the micronized API particles. The results indicate that the performance of the lactose population with a significant fines concentration was significantly influenced by the compression. The precise mechanism by which the mild pressures hinder drug dispersion remains obscure, as the

compression can result in both increasing the adhesion strength between lactose fines and larger carriers, and compressing the lactose fines into aggregates, either of which would disrupt the fines from migrating to high energy sites and/or forming multiplets with the API particles. However, the results agree with the published studies indicating the ability of lactose fines to significantly influence aerosol performance. The implications of these findings on processing DPI formulations are many-fold. However, the processing history of inhalation grade lactose is important, particularly if the lactose contains a relatively high concentration of fines. If processes that exert pressure on the lactose powder, even mild pressures far below the mechanical strength of lactose, are not controlled, performance may vary from batch-to-batch. Finally, it may also be expected that variation will occur within batches due to the unequal pressures that powders experience depending on their location in containers.

CONCLUSION

It has been shown here that very slight amounts of pressure are able to cause significant variations in intra-batch performance. The compression can result in both increasing the cohesion strength between lactose carriers of different grades and compressing the lactose fines into aggregates, either of which would getting accumulated to each other when higher amount of pressure (20 N/cm^2) was applied. These pressures were well within those which may occur during storing of lactose in containers during the transportation and processing of DPIs. Batch-to-batch variability may arise from processing or manufacturing effect, which may be associated with the potential effect of compression forces experienced during powder storage, transport and manufacturing on flowability and aerosol performance of lactose are DPI formulated. Furthermore, compressed INHL 120 and INHL 230 lactose showed an increase in particle size that is, increase in carrier size, decreased aerosol performance associated with lesser drug deposition in targeted site lungs. Thus, the compression of the lactose fines onto the surfaces of the larger particles due to compression pressure was hypothesized to be the cause of observed performance variations. From the above study it was conclude that compression pressure experienced during storage and transport in an industrial scale can include significant variation in formulation that affects drug deposition at target site, and it was speculated that this could be a source of batch-to-batch variation.

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Conflicts of interest
There are no conflicts of interest.

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