International Journal of Pharmaceutics 390 (2010) 134–141

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Characterisation and functionality of inhalation anhydrous lactose

Chonladda Pitchayajittipong[a], Robert Price[a,*], Jagdeep Shur[a], J. Sebastian Kaerger[b], Stephen Edge[c]

[a] Pharmaceutical Surface Science Research Group, School of Pharmacy and Pharmacology, University of Bath, Bath, UK
[b] Aeropharm GmbH, Rudolstadt, Germany
[c] Novartis Pharma AG, Basel, Switzerland

ARTICLE INFO

Article history:
Received 17 September 2009
Received in revised form 13 January 2010
Accepted 19 January 2010
Available online 25 January 2010

Keywords:
Dry powder inhaler
Anhydrous lactose
Powder fluidisation

ABSTRACT

The relationships between the physicochemical properties and functionality in dry powder inhaler (DPI) performance was investigated for inhalation grade anhydrous lactose and compared to monohydrate grades. The excipients were characterised using a range of techniques including particle size analysis, moisture sorption and powder rheometry. The inhalation anhydrous lactose grades were readily characterisable. The aerosolisation performance of capsule based DPI formulations containing budesonide (200 μg) and different grades of lactose evaluated using inertial impaction measurements produced fine particle doses of budesonide ranging from 24 to 49 μg. There were no apparent relationships between aerosolisation performance and excipient characteristics, such as particle size and powder density. However, formulations containing lactose grades which exhibit higher powder fluidisation energy values resulted in higher fine particle doses of budesonide.

1. Introduction

Commercially available dry powder inhaler (DPI) products are designed to deliver therapeutic agents to the lungs by using the patient's inspiration action to liberate the medicament from a formulation *via* a device. The formulation typically consists of the therapeutic drug(s) and an excipient, which is contained within a reservoir, capsule or a blister. Such formulations are produced by physically mixing micronised drug particles and larger-sized excipient 'carrier' particles, namely lactose monohydrate. In addition to imparting essential functional characteristics to formulations, such as blend uniformity and flow, excipients also facilitate the delivery of the drug to the lungs (Telko and Hickey, 2005). The process of detachment of drug particles from excipient particles, and their deposition in the airways, is crucial to the performance of DPI products and is largely dependent on the balance of the microscopic and macroscopic interfacial forces acting between components of the formulation (Jones et al., 2008). Such forces, which also exist in conventional solid dosage forms, are affected by powder characteristics, such as particle size distribution (PSD), surface chemistry, topography, environmental conditions and mechanical stresses, both during manufacture, shelf life and during the inhalation manoeuvre by the patient (Hickey et al., 2007a, 2007b).

It is generally accepted that the aerosolisation performance of DPIs can be improved by changes in the PSD of excipients and drugs and *via* the addition of ternary excipients, for example leucine and fine lactose particles of similar geometric size as the drug particles (Lucas et al., 1998; Jones and Price, 2006). Even though there are many reports describing the performance of DPI formulations of excipients and inhalation drugs, from blending to aerosolisation, the number of excipients used in marketed DPI products is limited, with lactose monohydrate being the excipient of "choice". Commercially, non-lactose based excipients, typically carbohydrates, have been used in only a limited number of DPI products and DPI development programs, as well as in many academic studies (Tee et al., 2000; Steckel and Bolzen, 2004; Hooton et al., 2006). In view of this limited number of regulatory approved DPI excipients, excipient suppliers are increasing their range of products, albeit based on lactose, for use in DPI applications. For example, agglomerated, anhydrous and micronised lactose are now commercially available. However, the relationships between the apparent excipient functionality and DPI performance of such available grades have, as yet, to be reported.

Recently, new inhalation grades of anhydrous lactose have been launched. Even though anhydrous lactose is used in a marketed DPI product, namely Asmanex® Twisthaler®, the use of any new excipient in a DPI development program would require the full characterisation and understanding of the functionality of the excipient, both as a material, and in formulations (Edge et al., 2008). Importantly, an understanding of excipient grade, and supplier, inter-changeability may allow more flexibility in development programs and supply chains. This is especially true for inhalation excipients due to the complex nature of DPI products where the performance is, in part, a consequence of surface phenomena.

* Corresponding author. Tel.: +44 (0) 1225 383644; fax: +44 (0) 1225 386114.
E-mail address: r.price@bath.ac.uk (R. Price).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.01.028

In carrier-based formulations, a critical step in generating a DPI therapeutic aerosol is the 'fluidisation' and entrainment behaviour of a powder (Shur et al., 2008). This process of powder fluidisation is primarily governed by the packing properties of a powder, which can be related to physicochemical properties, powder characteristics, such as PSD, environmental conditions and interfacial interactions (Valverde et al., 1998; Crowder et al., 1999; Castellanos, 2005). In terms of DPIs, the effect of PSD, of both the excipient and drug, on product performance must also, to some degree, be related to the history of the formulation, for example, during blending and manufacturing and capsule or blister environment.

The stresses experienced by the formulation are obviously much less in a final product, where at rest, masses of the order of grams, or even milligrams in the case of a capsule based product, will be close to their bulk density. Even though basic evaluation of powder properties such as bulk and tapped density and angle of repose can afford valuable insights into powder behaviour (Carr, 1965), newer techniques such as powder rheometry are being investigated (Freeman, 2007). The evaluation of such powder characteristics may afford additional insights into the relationships between excipient grades and apparent DPI performance.

The aim of this study was to characterise the physicochemical properties of several different grades of inhalation lactose to further understand the relationships between lactose functionality and DPI formulation performance, with particular emphasis on new commercial inhalation grades of anhydrous lactose in a capsule based formulation.

2. Materials and methods

Micronised budesonide (Sicor, Santhia, Italy), lactose monohydrate (Respitose ML001[1], DMV-Fonterra Excipients, Germany; Lactohale LH200[1], Friesland Foods Domo, The Netherlands; Monohydrate 120M[1], Sheffield Pharma Ingredients, USA) and anhydrous lactose (SuperTab 21AN, DMV-Fonterra Excipients, Germany; Anhydrous 120MS[1], Sheffield Pharma Ingredients, USA; Lactopress Anhydrous, Friesland Foods Domo, The Netherlands), acetonitrile (AR grade, Fisher Chemicals, UK), hexane (laboratory grade, Fisher Chemicals, UK) and silicone oil (Acros Chemicals, UK) were used as supplied. Water was purified by reverse osmosis using an Elix-S system (Millipore, Molsheim, France).

2.1. Sieving

Lactose samples were initially dry sieved through a 750 μm sized sieve (Endecotts Ltd, London, UK) using an Analysette 3 Pro vibratory sieve shaker (Fritsch, Idar-Oberstein, Germany) to remove any large aggregates and to aerate the materials.

2.2. Bulk and tapped density

The bulk density of blends was determined by pouring a sample of the powder (*ca.* 80 mL) into a 100 mL measuring glass cylinder and measuring the powder volume. The tap density was determined after tapping the 100 mL cylinder using a jolting volumeter (J. Engelsmann, Ludwigshafen, Germany). The powder volume was measured after successive 500 tap cycles until the volume was constant and the tapped density determined. The compressibility index was calculated from the bulk and tapped densities (United States Pharmacopoeia, 2009).

[1] Inhalation grade excipients.

2.3. Surface area analysis

The specific surface areas of the lactose samples were determined using a Gemini 2360 surface area analyser (Micromeritics Instrument Corporation, Norcross, USA). A five-point BET nitrogen adsorption analysis was performed in triplicate after degassing the samples for 24 h in a FlowPrep 060 degasser (Micromeritics Instrument Corporation, Norcross, USA).

2.4. Particle size analysis

Particle size analysis (dry state) was performed using a Sympatec HELOS (Sympatec GmbH, Germany) laser diffraction system. Approximately, 33 mg of powder was loaded into a measuring vial, which was dispensed using the ASPIROS (Sympatec GmbH, Germany) micro-dosing unit. The powder was then dispersed into the HELOS system using the RODOS (Sympatec GmbH, Germany) dry disperser pre-set at 2.0 bar. Particle size analysis was performed using WINDOX 4.0 software (Sympatec GmbH, Germany). Particle size distributions were performed in triplicate and determined using Fraünhofer theory. Micronised budesonide was determined to exhibit a median equivalent volume diameter of 1.62 ± 0.03 μm, with 95% of particles less than 5.0 μm.

2.5. Preparation of DPI formulation blends

Binary DPI formulations containing 0.8% (w/w) budesonide (200 μg dose) and the different grades of lactose were prepared. Each binary formulation contained 0.032 g budesonide and 3.968 g lactose, and was prepared by geometric mixing and further blended using a Turbula T2F (Willy A Bachofen AG, Switzerland) at 46 rpm for 40 min. The resulting formulation blends were passed through a 250 μm sized sieve (Endecotts Ltd, UK) to remove any large agglomerates.

2.6. High performance liquid chromatography (HPLC) and content uniformity analysis of budesonide

The HPLC system consisted of a pump (Jasco PU-980, Jasco Corp., Japan) coupled to a UV detector (Jasco UV-975) set at 248 nm. The mobile phase was 60:40 water:acetonitrile by volume. The pump flow rate was set to 1.5 mL min^{-1} through a 5 μm Hypersil MOS C8 column (Jones Chromatography Ltd, UK). Following blending, the drug content uniformity of all the formulations was assessed using ten random samples of 25 ± 1 mg from each blend. Powder formulations were dissolved in 100 mL of mobile phase. The relative standard deviation (RSD) of the drug content of formulations of budesonide exhibited acceptable drug content uniformity, with RSDs of less than 5%.

2.7. Inertial impaction testing of prepared blends

Each blend (25 ± 1 mg) was accurately weighed into size three hydroxypropylmethyl cellulose capsules (HPMC, Shionogi Qualicaps SA, UK). The filled capsules were stored at 44% RH for 24 h prior to *in vitro* performance testing. Aerosolisation testing was performed using a Next Generation Impactor (NGI) with pre-separator, which was connected to a vacuum pump (GE Motors). Prior to testing, the pre-separator was filled with 15 mL of mobile phase and the cups of the NGI cups were coated with 1% (v/v) silicone oil in hexane to eliminate particle bounce. For each experiment, two individual capsules of the same formulation were discharged into the NGI at 90 L min^{-1} for 2.8 s *via* a Cyclohaler® (TEVA Pharmaceuticals, The Netherlands) DPI device. Following aerosolisation, the NGI apparatus was dismantled and the inhaler, capsules and each part of the NGI was washed down into known volumes of HPLC mobile

Table 1
Physicochemical characteristics of lactose excipients.

Lactose grade	Bulk density ($g\,cm^{-3}$)	Tapped density ($g\,cm^{-3}$)	Compressibility index[a] (%)	Loss on drying (%)	Water content (%)	True density[b] ($g\,cm^{-3}$)	Surface area ($m^2\,g^{-1}$) (±Range)
Respitose ML001	0.56	0.84	33	0.21	5.15 ± 0.02	1.543	0.88 ± 0.02
Lactohale LH200	0.39	0.65	40	0.21	5.14 ± 0.02	1.543	0.57 ± 0.02
Monohydrate 120M	0.57	0.81	29	0.22	5.19 ± 0.03	1.543	0.82 ± 0.01
Anhydrous 120MS	0.60	0.79	23	0.12	0.28 ± 0.01	1.584	0.43 ± 0.01
Lactopress Anhydrous	0.70	0.85	18	0.12	0.28 ± 0.01	1.588	0.47 ± 0.02
SuperTab 21AN	0.70	0.86	19	0.12	0.24 ± 0.01	1.586	0.48 ± 0.01

[a] Calculated according the United States Pharmacopoeia, 2009.
[b] (±Range = 0.004).

phase. The mass of drug deposited on each part of the NGI was determined by HPLC. This protocol was repeated three times for each blend, following which, the emitted dose, mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle dose (FPD) and fine particle fraction of the nominal (loaded) dose (FPF_{LD}) were determined. The FPD represented the mass of drug less than 5 μm.

2.8. Scanning electron microscopy

Powder morphology was investigated using scanning electron microscopy (SEM, Jeol 6310, Tokyo, Japan) at 10 keV. Samples were mounted on carbon sticky tabs and gold-coated (20 nm thickness) before imaging (Edwards Sputter Coater, UK).

2.9. Differential scanning calorimetry

The thermal properties of the different grades of lactose were investigated using a differential scanning calorimeter (DSC 2910, TA Instruments, UK) calibrated with indium and tin standards. Approximately 3–6 mg of sample was accurately weighed into an aluminium pan and crimped with a lid to form a hermetic seal. The sample and reference (an identical, but empty, hermetically sealed pan) were heated at a rate of 10 °C min^{-1} from 30 to 350 °C. The calorimeter head was flushed with nitrogen gas at 25 mL min^{-1} during all measurements.

2.10. X-ray powder diffraction

X-ray powder diffraction (XRPD) was used to determine the crystal structures of the different grades of lactose. XRPD diffractograms were obtained using a Phillips analytical X-ray powder diffractometer (Cambridge, UK) with a Cu Kα source (λ = 1.5418 Å) operated at 40 kV and 25 mA. A single sweep between diffraction angles (2θ) 5° and 30° was employed for each measurement.

2.11. Dynamic powder flow and permeation analysis

A FT4 Powder Rheometer (Freeman Technology, UK) was used to investigate the flow properties of the excipients (without drug) under aerated conditions as previously described (Shur et al., 2008). In each case, *ca.* 20 mL of sample powder was analysed in a 25 mm bore borosilicate glass cylinder. The powders were evaluated using an automated aeration programme that runs a sequence of tests at increasing levels of air velocity through the powder sample (0–14 mm s^{-1}), with a conditioning cycle before each test cycle. The samples were conditioned using a 23.5 mm blade, which was moved down a clockwise helical path with a helix angle of 5° at a velocity of 20 mm s^{-1}. This provides a gentle displacement of the powder, which removes the packing history of the powder and any operator influence thereby generating a homogenised or uniform low packing stress in the powder. Following conditioning, the blade traverses axially into the powder whilst axial and rotational forces are measured as different air velocities were passed through the powder. From these measurements, the total flow energy of the powders was determined at different air flow velocities. Upon fluidisation, the flow energy of the powders plateau at a defined air flow velocity from which the fluidisation energy was determined.

Powder permeability studies were conducted at a constant airflow velocity of 2 mm s^{-1} through the powder bed, with varying normal stress between 1 and 20 kPa being applied to the sample. The pressure drop across the powder bed was measured as a function of the applied normal stress. This provides information regarding the resistance of the powder bed to air permeation which is related to the fluidisation behaviour of a powder. In all cases measurements were performed in triplicate.

2.12. Statistical analysis

Linear regression analysis was used for the assessment of HPLC calibration. Statistical analysis between different populations carried out using one-way analysis of variance. Comparison of the mean values was performed by Tukey's multiple comparison. All statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc, USA). Error bars in graphical representations of data show ±1 standard deviation in all cases.

3. Results and discussion

The various lactose grades were characterised in terms of their physicochemical characteristics, powder flow properties and their effect on the *in vitro* aerosolisation performance of 200 μg dose budesonide blends (25 mg).

3.1. Physicochemical characteristics of inhalation grades of lactose

The physiochemical characteristics of inhalation grades of lactose are presented in Table 1 and were typical for anhydrous lactose and lactose monohydrate. For example, the inhalation grades of anhydrous lactose exhibit higher true densities than inhalation grade lactose monohydrate. Additionally, and as expected, differential scanning calorimetry (DSC) thermograms, presented in Fig. 1, exhibited endothermic thermal events typical for lactose monohydrate, at *ca.* 120–150 °C (dehydration) and *ca.* 205 °C (melting) and for anhydrous lactose, at *ca.* 230 °C (melting). Powder X-ray diffraction patterns (not shown), of the respective inhalation grades were also typical for lactose monohydrate and anhydrous lactose.

3.2. Scanning electron microscopy

Typical SEMs of inhalation grades of anhydrous lactose and lactose monohydrate are shown in Fig. 2. As expected, the lactose monohydrate samples (Fig. 2A, C, D) exhibited distinct particle shapes, the surfaces of which contained finer lactose monohydrate particulates. Anhydrous lactose (Fig. 2B, E, F) consists of particles

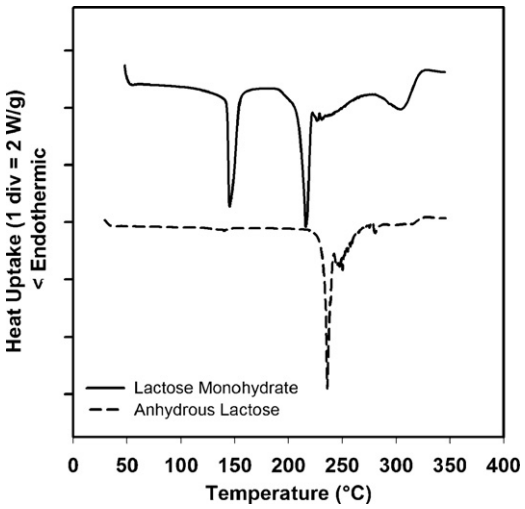

Fig. 1. Typical differential thermal calorimetry data for inhalation lactose anhydrous (Anhydrous 120MS) and monohydrate (Lactohale LH200).

which exhibit greater roughness, which reflects the roller dryer method of manufacture, which results in the formation of microcrystallite assemblies rather than distinct crystals.

3.3. Particle size distribution

One of the most important characteristics of any 'carrier' excipient, and indeed drug, is the particle size distribution. In general, fine excipient particles tend to improve *in vitro* performance and a certain level of larger particle sized material is required for robust manufacturability. The PSDs of the various lactose grades are presented in Table 2. It can be seen from Table 2 that the excipients exhibit a range of particle size distributions and, importantly, fines contents, with ML001 containing the highest level of fines.

3.4. Water content

The loss on drying and water content of the inhalation lactose grades, as determined by Karl Fisher, were typical for lactose monohydrate and anhydrous lactose and were within the regional pharmacopoeial requirements (see Table 1). As expected, the water

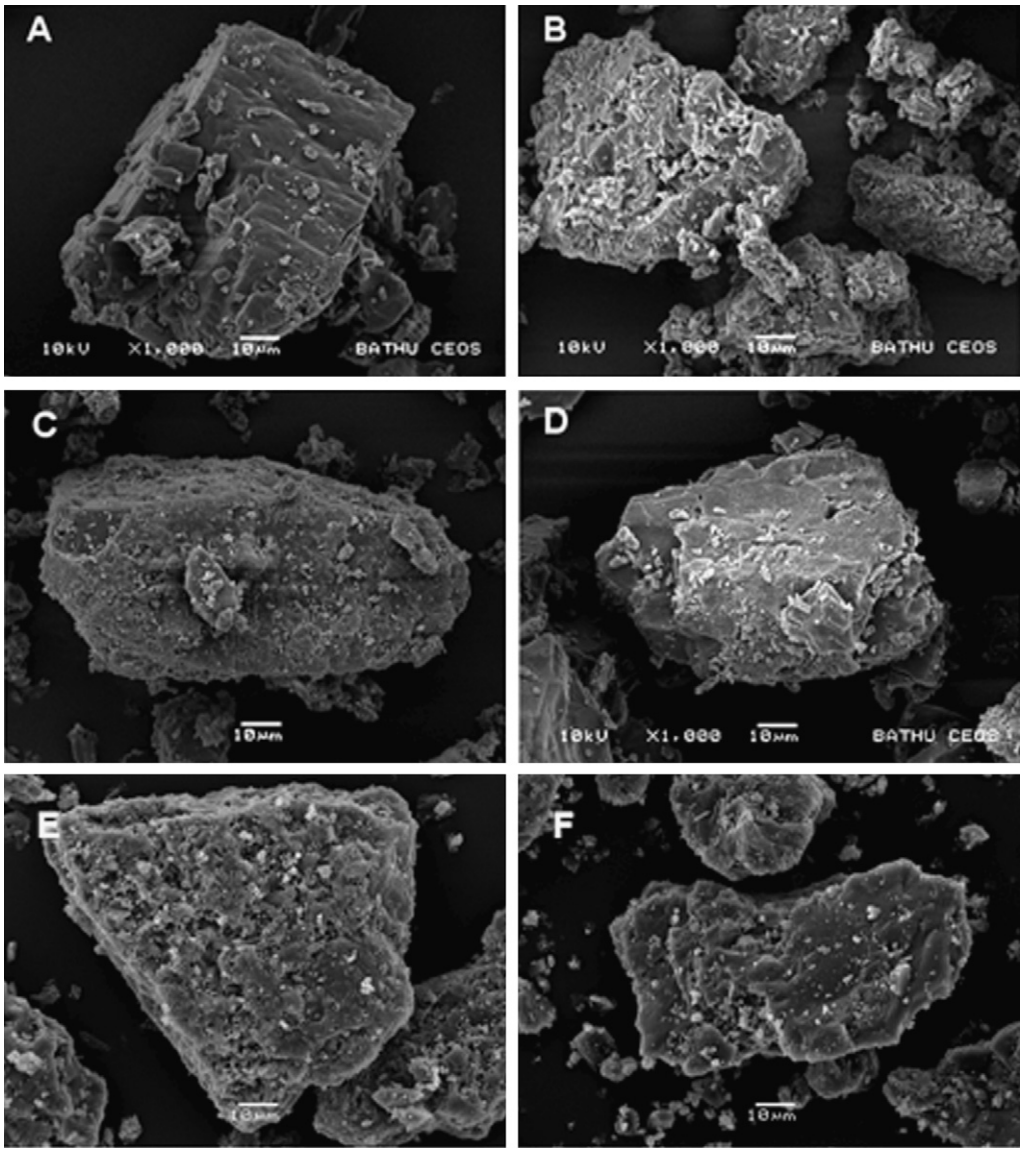

Fig. 2. Representative SEM images of inhalation grades of, A: lactose monohydrate (Lactohale LH200), B: anhydrous lactose (Anhydrous 120MS), C: lactose monohydrate (Respitose ML001), D: lactose monohydrate (Monohydrate 120M), E: anhydrous lactose (SuperTab 21AN), and F: anhydrous lactose (Lactopress Anhydrous).

Table 2
Particle size distributions of lactose excipients. $n = 3$.

Lactose grade	Particle size analysis (±Std Dev)		
	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
Respitose ML001	2.62 (0.04)	40.66 (0.80)	138.17 (1.11)
Lactohale LH200	16.15 (0.32)	85.11 (1.23)	147.22 (1.21)
Monohydrate 120M	11.01 (0.48)	61.01 (0.99)	144.67 (0.99)
Anhydrous 120MS	7.25 (1.28)	83.54 (1.58)	185.01 (0.94)
Lactopress Anhydrous	30.25 (1.08)	153.54 (1.98)	255.32 (1.84)
SuperTab 21AN	10.25 (0.28)	103.37 (0.98)	185.01 (1.98)

content of the anhydrous grades, of <1%, confirmed the 'anhydrous' nature of these materials. The water content, in conjunction with loss on drying data, provides an approximation of the level of lactose monohydrate present in the anhydrous lactose grades of *ca.* 3%. Such levels of lactose monohydrate in anhydrous lactose confirm that lactose grades, like many excipients, should be considered, and studied, as composite materials rather than chemically pure substances.

3.5. Dynamic vapour sorption

Of particular relevance for the performance of inhaled drug products is the moisture sorption properties of formulations, and their components. Indeed, lactose is one of the most studied excipients in view of its degrees of association with water. Even though there are numerous reports describing the water sorption properties of amorphous lactose and lactose monohydrate, there are few documenting anhydrous lactose. Typical dynamic vapour sorption (DVS) data for inhalation grades of lactose monohydrate and anhydrous lactose is shown in Fig. 3. Both materials exhibit relatively low moisture sorption at relative humidities (water activities) of less than 70%. As expected, anhydrous lactose absorbs relatively more water at higher water activity than lactose monohydrate which is a consequence of the conversion of anhydrous lactose to the monohydrate form. Upon de-sorption, the apparent increase in mass of the anhydrous lactose is mostly due to the presence of lactose monohydrate. However, to become fully hydrated, anhydrous lactose should attain an approximate 5% mass increase. It is clear that the timescales of any DVS experiment used to study complex transformations should reflect the materials science and thermodynamics of such events. Even though lactose monohydrate is the most stable form of lactose, it is apparent that conversion to this form may not be 'rapid'. Indeed it has been reported that full conversion requires storage for 4 weeks at 97% RH, a condition which a drug product would not encounter (Shah et al., 2008).

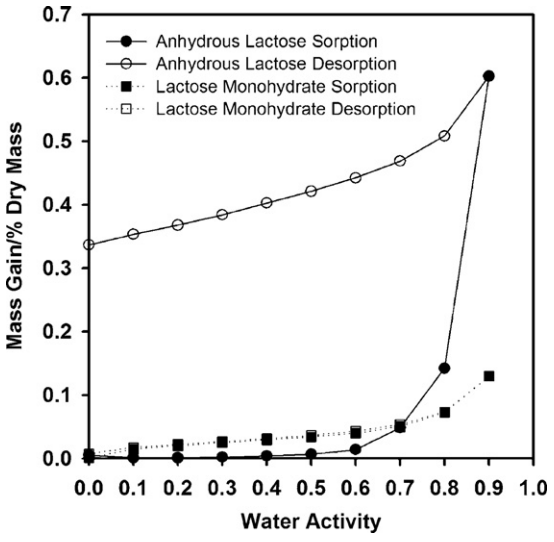

Fig. 3. Typical DVS sorption and de-sorption profiles for inhalation lactose anhydrous (Anhydrous 120MS) and lactose monohydrate (Lactohale LH200). Lines are for clarity.

Even though 'anhydrous lactose' is a pharmacopoeial excipient, its compendial descriptions can, as for many excipients, be misleading. Anhydrous lactose, like many excipients, is a composite material, and typically contains approximately 80% beta lactose and 20% alpha lactose, together with a small amount of lactose monohydrate, as also suggested by the previously mentioned Karl Fischer and loss on drying data (Edge et al., 2009). However, it is not clear to what degree these alpha and beta forms exist as discrete entities and so-called 'mixed crystals', which have been identified in, for example, DSC studies (Lerk et al., 1984). The material may also contain a small amount of amorphous lactose, especially if milled. In terms of the interaction of anhydrous lactose with water (moisture), it would be expected that the surface of anhydrous lactose contains some lactose monohydrate. However, when considering how anhydrous lactose sorbs moisture, it unclear how such molecular transportation would occur. The initial interaction of water with the surface of anhydrous lactose would produce the hydrated form in the surface. The surface would then consist of lactose monohydrate, the most stable form of lactose. It is not clear how water becomes incorporated into the crystal structure of lactose units beneath the hydrated surface, which is suggested by DVS data. One possibility is *via* diffusion through the stressed crystalline lactose monohydrate since the true density of lactose monohydrate is less than anhydrous lactose. Additionally, such changes in structure would be expected to introduce stresses into the material, again producing free space, and new anhydrous lactose surfaces. This 'free' space could facilitate water transportation into the anhydrous lactose, allowing hydration to occur, albeit at relatively slow rates which may be important considering the importance of surface interaction in DPIs (Price et al., 2002).

3.6. Powder flow

An understanding of the flow properties a formulation during formulation, manufacturing and aerosolisation is critical to the successful, and reproducible, production of a drug product and to ensure pharmaceutically consistent performance of each batch of the product. In addition to bulk and tapped density measurements, the compressibility, permeability and fluidisation properties were studied using a powder rheometer. The relationships between powder characteristics and aerosolisation performance were also investigated.

Bulk and tapped density measurements are a standard approach for gaining an insight into the performance of powders during processing. The bulk and tapped densities, together with the compressibility indices, of the lactose excipients are given in Table 1. The excipients exhibit a range of bulk and tapped densities. In general, low bulk density tends to indicate poor powder flow. The relationship between bulk and tapped density can be used as a descriptor of flow, for example *via* the calculation of the Hausner ratio or a compressibility index. Using a compendial compressibility index, the powders would be classified as 'relatively poorly flowing' according to the United States Pharmacopoeia (USP) except for SuperTab 21AN and Lactopress Anhydrous, which exhibit 'sufficient flow' and are used as direct compression excipients (United States Pharmacopoeia, 2009).

3.7. Powder compressibility

As previously discussed, in terms of flow, powder 'compressibility' is typically determined *via* a 'compressibility index', such as

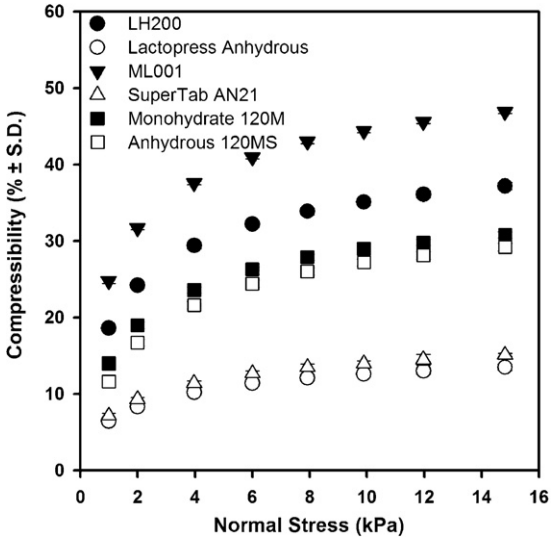

Fig. 4. The relationship between compressibility (%) and applied stress for the lactose excipients.

that given in the USP and by Carr's compressibility indices. However, modern techniques such as the rheometry can provide further information about powder flow. The compressibility of the powders was measured as a function of an applied normal stress using a FT4 Powder Rheometer. The helical blade of the rheometer was replaced with a porous piston that was pressed onto the powder bed. In this way, the change in the free volume of the powder as a function of applied normal stress was measured. The % compressibility describes the percentage increase in bulk density (*i.e.* decrease in free volume) of the powder on application of a stress, as described previously (Shur et al., 2008). Typical powder compressibilities (reported as % compressibility) of the different grades of lactose as functions of applied load are shown in Fig. 4. The behaviour of powders under compression can be used as a generic criterion for powder flow and fluidisation. Generally, less cohesive powders exhibit ordered packing and good flow and are not very compressible under consolidation. In contrast, cohesive powders pack in open structures and compress more easily, but exhibit poorer flow.

It can be seen from Fig. 4 that between applied stresses of 1–15 kPa the compressibility of the powders increases with increasing applied stress, with Lactopress Anhydrous and SuperTab 21AN increasing from *ca.* 5–12% and ML001 from *ca.* 25–40%. The relatively higher compressibility of LH200 and ML001 suggests that both materials are cohesive and therefore, would exhibit relatively poor powder flow behaviour, as suggested by their bulk and tapped densities. In contrast, the compressibility of the direct compression excipients, exhibited significantly lower ($p < 0.05$) compressibilities of *ca.* 15%. These data confirm that both Lactopress Anhydrous and SuperTab 21AN are, as expected, less cohesive than the other milled and sieved grades of lactose. Importantly, the general order of compressibility from Fig. 4 is in general agreement with the compressibility indices in Table 1. Previous studies have reported that under increasing consolidation stresses the tensile strength of a cohesive material will increase. Thus, consolidation stresses imposed on the material during processing, device filling and handling may directly affect the tensile strength of the bulk powder, which may in turn influence the fluidisation and hence the overall performance of a DPI formulation. In relation to this, these data suggest that both Lactopress Anhydrous and SuperTab 21AN grades of lactose are less likely to be influenced by such consolidation stresses.

3.8. Powder permeation

To understand the effects of the bulk powder properties on the fluidisation properties of the excipients, powder permeability tests were also conducted. For these investigations, a constant air flow rate of 2 mm s^{-1} was permeated through the powder bed under a constant stress of 1 kPa, whilst the pressure drop across the powder bed required to maintain a constant air flow velocity was determined. The average pressure drop across the powder beds of all grades of lactose as a function of the stress applied to the powder bed is shown in Fig. 5. It is evident from Fig. 5 that a range of pressure differentials was observed across each grade of lactose, however, the following rank order of the grades of lactose was LH200 ~ ML001 > SuperTab 21AN ~ Lactopress Anhydrous > Anhydrous 120MS > Monohydrate 120M. Indeed, the data in Fig. 5 suggests that, in comparison to the other grades of lactose, the pressure drop created across powder beds of Monohydrate 120M and Anhydrous 120MS are significantly lower ($p < 0.05$). These measurements suggest that these lactose grades were highly permeable and exhibited low cohesivity and tensile strength. These powders should, therefore, fluidise relatively easily which may not result in the creation of a significant pressure differential to increase the aerodynamic drag forces across the static powder bed. Such powders have previously been observed to fluidise homogenously due to their lower tensile strength. In contrast, Fig. 5 suggests that the pressure drop generated across Lactopress Anhydrous and SuperTab 21AN was significantly ($p < 0.05$) greater than for both Monohydrate 120M and Anhydrous 120MS, which suggests that the fluidisation behaviour and therefore DPI performance of formulations containing Lactopress Anhydrous and SuperTab 21AN may be different.

The pressure drop generated across LH200 and ML001 powder beds was significantly ($p < 0.05$) greater than for the other grades of milled and sieved lactose, with average pressure drop values of approximately 0.5 kPa. Such behaviour is indicative of cohesive powders, which have relatively low permeability to the flow of air through the powder bed (Castellanos et al., 2002). The situation is clearly more complex since there appears to be no simple apparent relationships between the powder densities and compressibilities, in Table 1, and the permeation data in Fig. 5. It has previously

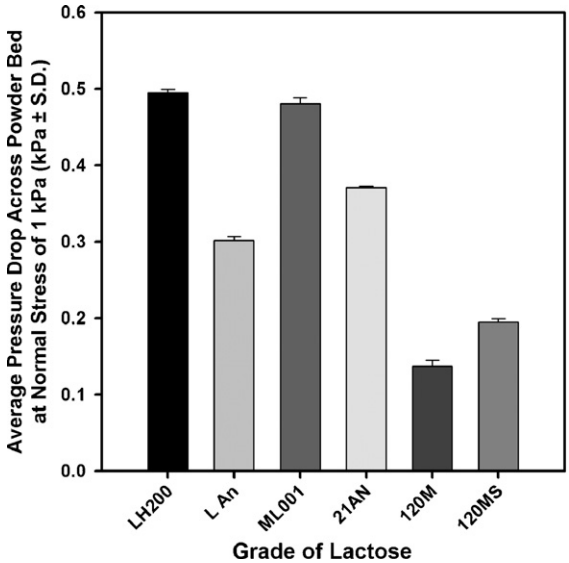

Fig. 5. The average pressure drop across powder beds of lactose excipients at a constant airflow velocity of 2 mm s^{-1} under a normal stress of 1 kPa. LH200, Lactohale LH200; L. An, Lactopress Anhydrous; ML001, Respitose ML001; 21AN, SuperTab 21AN; 120M, Monohydrate 120M; and 120MS, Anhydrous 120MS.

Table 3
Fluidisation energy of lactose excipients.

Grade of lactose	Fluidisation energy (mJ ± SD)
Lactohale LH200	19.9 (1.1)
Lactopress Anhydrous	17.2 (1.8)
Respitose ML001	24.0 (2.9)
SuperTab 21AN	21.5 (3.5)
Monohydrate 120M	10.3 (1.8)
Anhydrous 120MS	11.9 (1.4)

reported that powders of high cohesive strength within the powder bed are difficult to disturb *via* an air flow (Jackson, 2000). As a result, air is not free to uniformly permeate through the powder bed, and therefore flows through channels formed within the powder bed and results in the powder being lifted as a 'plug'. Generally, DPI capsule (and blister) based products only contain relatively small masses of materials, of the order of milligrams compared to these permeation experiments. But it should be remembered that even though the mass in such products is small, the powder has also undergone a bulk and large scale powder manufacturing process which will affect the apparent performance. However, it is conceivable that the increase in air flow resistance due to the greater cohesive strength of the powder would result in the generation of higher aerodynamic drag forces within a DPI device (Shur et al., 2008). Thus, the fluidisation and entrainment properties of the formulations produced using these different grades of lactose may be directly related to differences in their bulk powder properties and characteristics, however, clearly, such relationships may not be simple.

3.9. Powder fluidisation

The resistance of the different grades of lactose to fluidise, quantified as fluidisation energy, was also determined and are shown in Table 3. The powders show similar trends in their fluidisation energy measurements to the permeability characteristics of the powders with the following rank order ML001 > SuperTab 21AN > LH200 > Lactopress Anhydrous > Anhydrous 120MS ~ Monohydrate 120M. These data suggest that the increase in air flow resistance due to the greater cohesive strength of the powder may generate higher aerodynamic drag forces within a formulation in a DPI device that may result in increased liberation of fine drug particles. This was investigated using a budesonide formulation.

3.10. In vitro aerosol deposition of budesonide

The *in vitro* aerosolisation performance of each of the budesonide formulations, as indicated by the emitted dose, fine particle dose and fine particle fraction (<5 μm) of the loaded (nominal dose) (FPF_{LD}) are shown in Table 4 and the NGI stage distributions are shown in Fig. 6. It can be seen from Table 4 all formulations exhibited good emitted dose uniformity. However, the FPD ranged from 24 to 49 μg, which suggests, as expected, that the PSD and nature of the excipient play a crucial for DPI performance when formulations are prepared using similar protocols. Indeed it is interesting to note that the difference in performance of the direct compression anhydrous lactose excipients and the sieved Anhydrous 120MS. A previous study reported that anhydrous lactose, as a 63–90 μm sieve fraction, produced the highest aerosolisation efficiency for salbutamol sulphate compared to monohydrate grades (Larhrib et al., 1999). Such observations confirm the dependency of product performance on formulation and testing protocols.

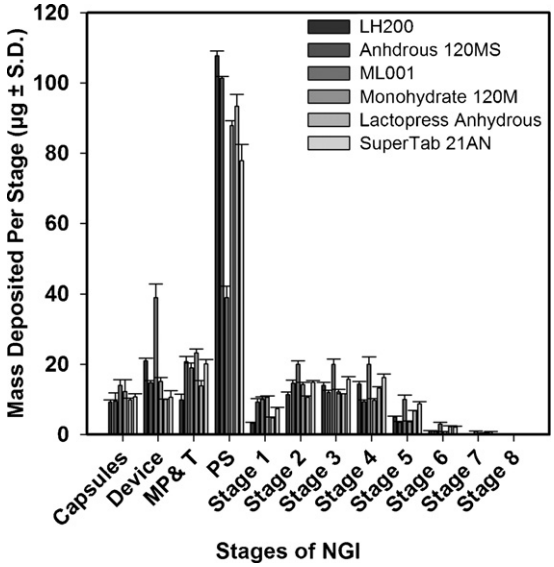

Fig. 6. Stage deposition of budesonide from formulations containing different lactose excipients. NGI at 90 L min^{-1}. MP & T, mouthpiece and throat.

3.11. Relationship between in vitro aerosolisation performance and bulk powder properties

One of the aims of this study was to further elucidate any relationships between bulk excipient properties and drug aerosolisation. As expected there are no apparent simple relationships between a PSD descriptor, powder properties, such as bulk and tapped density and FPD. Linear regression analysis of such descriptors gave R^2 values of 0.02–0.07 and suggests that there were no simple relationships between excipient characteristics, such as particle size and powder density, and *in vitro* performance. Interestingly, there appears to be no simple apparent linear relationship between fines content, as measured by d_{10}, and FPD (R^2, 0.06). Of all the bulk powder property descriptors, the only simple linear relationship found to exist was between FPD and fluidisation energy (R^2, 0.92), shown in Fig. 7, where it appears that increasing fluidisation energy of the excipient results in a higher apparent FPD. Obviously, and importantly, the fluidisation measurements were performed based on powder volume and not mass. However, when the powders are fluidised they will be at a steady state and at their aerated densities which would be independent of mass at the relatively low masses of powder used in this study, making qualitative comparisons possible.

Table 4
Budesonide aerosolisation performance from lactose formulations. $n = 3$.

Grade of lactose	Emitted dose (μg ± SD)	FPD (μg ± SD)	FPF_{LD} (% ± SD)	MMAD ± GSD
LH200	188.5 (2.6)	35.2 (1.6)	17.7 (0.6)	2.61 (1.83)
Lactopress Anhydrous	179.8 (3.2)	33.3 (0.9)	16.7 (0.8)	2.54 (2.03)
ML001	173.5 (7.9)	49.2 (4.9)	26.0 (1.7)	2.76 (2.06)
SuperTab 21AN	180.5 (4.6)	44.6 (1.1)	22.3 (0.3)	2.68 (2.06)
Monohydrate 120M	174.1 (3.5)	24.7 (1.7)	13.1 (0.9)	3.54 (2.09)
Anhydrous 120MS	185.2 (2.7)	24.0 (1.3)	12.7 (0.6)	3.47 (2.02)

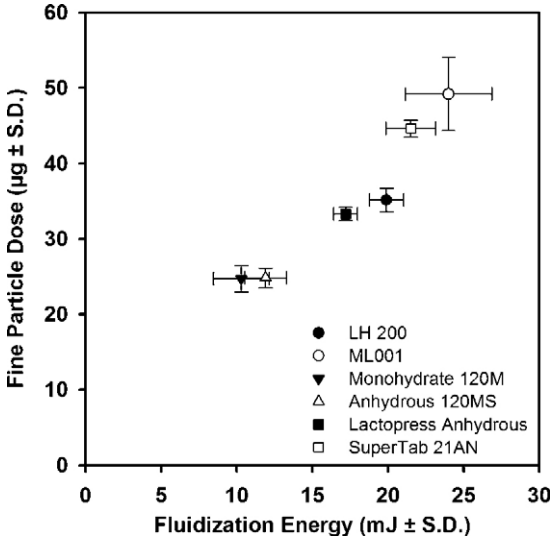

Fig. 7. The relationship between the resistance of the powder to fluidise as quantified as fluidisation energy and PFD.

It is also evident from Fig. 7 that anhydrous and monohydrate grades from the same supplier appear to exhibit similar fluidisation energies and FPDs of budesonide, with Anhydrous 120MS and Monohydrate 120M, which are supplied by Sheffield Pharma Ingredients, exhibiting the lowest fluidisation energies and FPDs. As well as suggesting that monohydrate and anhydrous grades of inhalation lactose exhibit similar fluidisation energies, there is also a suggestion that differences in the processing of lactose grades between suppliers may also result in differences in fluidisation energy making a simple equivalence-based approach for lactose inter-changeability difficult without a complete understanding of the materials functional properties.

As previously stated, the role of excipients in DPI technologies is somewhat different to those in typical pharmaceutical solid dosage forms, such as tablets, and it is widely accepted that PSD, and in particular, fines content, is important for product performance, for both manufacturing and drug aerosolisation. The results in this study suggest that there are no simple relationships between powder descriptors and FPD, when formulations are prepared in a similar manner. Indeed the level of fines in the excipient did not affect the FPD (linear, R^2, 0.06) This is in contrast a previous report describing that suggesting that excipient fines in carrier-based DPI formulations have a significant influence on the bulk characteristics of DPI formulations (*i.e.* powder density, flowability, packing properties and cohesive strength) and drug aerosolisation (Shur et al., 2008). Obviously, the aerosolisation performance may change if different formulation protocols are employed, but, it is interesting that in this study, supplier grades of anhydrous and monohydrate grades could be essentially inter-changeable. This observation would suggest that the chemical differences between alpha and beta lactose could be negated and that bulk powder properties may be more relevant to DPI performance.

4. Conclusions

Inhalation grades anhydrous lactose are readily characterisable using standard analytical methods suggesting they could be controlled in any supply chain. Initial studies suggested that the recently available inhalation grade lactose can be used to produce carrier-based DPI budesonide formulations with acceptable powder properties and DPI performance. However, using a simple equivalence approach for lactose inter-changeability, for both monohydrate and anhydrous grades, as expected, resulted in variations in aerosolisation performance and highlights that systematic optimisation would always be required when developing formulations with new carrier excipients. Interestingly, there appeared to be no simple relationships between powder descriptors and drug aerosolisation except for FPD and excipient fluidisation energy suggesting that increased shearing during the aerosolisation process may allow greater liberation of fine drug particles. Further studies are underway to further investigate the effect of powder properties, fluidisation and drug aerosolisation.

References

Carr, R.L., 1965. Evaluating the flow properties of solids—classifying flow properties of solids. Chem. Eng. 72, 163–168.
Castellanos, A., 2005. The relationship between attractive interparticle forces and bulk behaviour in dry and uncharged fine powders. Adv. Phys. 54, 263–376.
Castellanos, A., Valverde, J.M., Quintanilla, M.A.S., 2002. Fine cohesive powders in rotating drums: transition from rigid-plastic flow to gas-fluidized regime. Phys. Rev. E: Stat. Nonlin. Soft Matter Phys., 65.
Crowder, T.M., Sethuraman, V., Fields, T.B., Hickey, A.J., 1999. Signal processing and analysis applied to powder behavior in a rotating drum. Part. Part. Syst. Char. 16, 191–196.
Edge, S., Mueller, S., Price, R., Shur, J., 2008. Factors affecting defining the quality and functionality of excipients used in the manufacture of dry powder inhaler products. Drug Dev. Ind. Pharm. 34, 966–973.
Edge, S., Kibbe, A., Shur, J., 2009. Lactose monohydrate. In: Rowe, R.C., Sheskey, P.J., Owen, S.C. (Eds.), Handbook of Pharmaceutical Excipients, 6th ed. Pharmaceutical Press, London, pp. 364–369.
Freeman, R., 2007. Measuring the flow properties of consolidated, conditioned and aerated powders—a comparative study using a powder rheometer and a rotational shear cell. Powder Technol. 174, 25–33.
Hickey, A.J., Mansour, H.M., Telko, M.J., Xu, Z., Smyth, H.D.C., Mulder, T., McLean, R., Langridge, J., Papadopoulos, D., 2007a. Physical characterization of component particles included in dry powder inhalers. I. Strategy review and static characteristics. J. Pharm. Sci. 96, 1282–1301.
Hickey, A.J., Mansour, H.M., Telko, M.J., Xu, Z., Smyth, H.D.C., Mulder, T., McLean, R., Langridge, J., Papadopoulos, D., 2007b. Physical characterization of component particles included in dry powder inhalers. II. Dynamic characteristics. J. Pharm. Sci. 96, 1302–1319.
Hooton, J.C., Jones, M.D., Price, R., 2006. Predicting the behaviour of novel sugar carriers for dry powder inhaler formulations via the use of a cohesive–adhesive force balance approach. J. Pharm. Sci. 95, 1288–1297.
Jackson, R., 2000. The Dynamics of Fluidized Particles. Cambridge University Press, Cambridge.
Jones, M.D., Harris, H., Hooton, J.C., Shur, J., King, G.S., Mathoulin, C.A., Nichol, K., Smith, T.L., Dawson, M.L., Ferrie, A.R., Price, R., 2008. An investigation into the relationship between carrier-based dry powder inhalation performance and formulation cohesive–adhesive force balances. Eur. J. Pharm. Biopharm. 69, 496–507.
Jones, M.D., Price, R., 2006. The effect of fines on the performance of DPI formulations. Pharm. Res. 23, 1665–1673.
Larhrib, H., Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 1999. The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. Int. J. Pharm. 191, 1–14.
Lerk, C.F., Andreae, A.C., de Boer, A.H., de Hoog, P., Kussindrager, K., van Leverink, J., 1984. Alterations of α-lactose during differential scanning calorimetry. J. Pharm. Sci. 73, 856–857.
Lucas, P., Anderson, K., Potter, U.J., Staniforth, J.N., 1998. Enhancement of small particle size dry powder aerosol formulations using an ultra low density additive. Pharm. Res. 16, 1643–1716.
Price, R., Young, P.M., Edge, S., Staniforth, J.N., 2002. The influence of relative humidity on particulate interactions in carrier-based dry powder inhaler formulations. Int. J. Pharm. 246, 47–59.
Shah, K.R., Hussain, M.A., Hubert, M., Badawy, S.I.F., 2008. Form conversion of anhydrous lactose during wet granulation and its effect on compactibility. Int. J. Pharm. 357, 228–234.
Shur, J., Harris, H., Jones, M.D., Kaerger, J.S., Price, R., 2008. The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations. Pharm. Res. 25, 1931–1940.
Steckel, H., Bolzen, N., 2004. Alternative sugars as potential carriers for dry powder inhalations. Int. J. Pharm 270, 297–306.
Tee, S.K., Marriott, C., Zeng, X.M., Martin, G.P., 2000. The use of different sugars as fine and coarse carriers for aerosolised sulbutamol sulphate. Int. J. Pharm. 208, 111–123.
Telko, M., Hickey, A.J., 2005. Dry powder inhaler formulations. Respir. Care 50, 1209–1227.
United States Pharmacopoeia XXXII, 2009. Rockville, MD, USA. Powder flow (1174).
Valverde, J.M., Rasenack, N., Castellanos, A., Waston, P.K., 1998. The tensile strength of cohesive powders and its relationship to consolidation, free volume and cohesivity. Powder Technol. 97, 237–245.