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Research Article

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Investigation into the Degree of Variability in the Solid-State Properties of Common Pharmaceutical Excipients—Anhydrous Lactose

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Abstract. This paper reports the batch-to-batch and vendor-to-vendor variations in the solid-state characteristics of multiple batches of lactose anhydrous from each of three vendors and the subsequent impact of these differences on processability and/or functionality.

KEY WORDS: compaction; excipients; lactose; physical properties; variability.

INTRODUCTION

In the pharmaceutical industry, excipients are often defined as non-functional constituents within a dosage form. Excipients are added to pharmaceutical dosage formulations for multiple reasons, but most commonly, they are included in order to aid the processing or to enhance stability, bioavailability or patient acceptability of the final dosage form. Although they do not produce a medical effect, excipients have been proven to be essential in both biopharmaceutical and technical aspects. Due to their importance, interchangeability and uniformity of excipients is necessary in order to ensure consistent quality in the finished products, as well as to deal with the eventuality that a particular grade of excipient is unavailable for any reason (http://www.metolose.jp/e/pdf/news_20070322.pdf).

All raw materials, including excipients, should meet the expectations of Regulatory authorities (or their delegates, for instance National Pharmacopoeias). However, pharmacopoeial testing of excipients is often based primarily on the verification of identity, purity and chemical stability with only limited testing of particle and powder physical properties. As such, there are examples of excipients meeting the pharmacopaeial monograph but performing with unexpected characteristics during processing and in the final dosage form due differences in solid-state characteristics (1,2). As a result, certificate of analysis of excipients may not provide sufficient confidence of equivalency between vendors and/or batches.

Many factors can contribute to batch-to-batch variability from a single vendor or between multiple vendors, such as differences in raw material, manufacturing processes, storage conditions and transportation (3). In fact, the functionality of excipients may not only depend on their intrinsic properties but also their applications and the formulation into which they are incorporated (4). As such, it is controversial to include functionality or physical testing related to functional properties in the monograph due to the many different ways that an excipient can be used (5). Nevertheless, a better understanding of the properties of excipients and their relationships to the functionalities can help formulators to select appropriate excipients and validate manufacturing processes accordingly, thereby improving process control and moving towards more controlled products with consistent quality in line with the FDA's Quality by Design initiative.

Lactose is one of the most commonly used excipients within the pharmaceutical industry in the production of solid dosage forms. Lactose is commonly used as a diluent/binder in order to produce tablets of sufficient hardness whilst maintaining good disintegration properties.

There are four solid forms of lactose known to exist: α-lactose monohydrate, anhydrous α-lactose, anhydrous β-lactose and amorphous lactose, with each form known to exhibit different compaction properties (6,7). Some forms of pharmaceutical lactose (e.g. spray-dried lactose for direct compression) may contain multiple forms. Anhydrous β-lactose has been shown to demonstrate better compaction behaviour than α-lactose monohydrate due to the presence of more spherical particles, rougher surfaces and a higher degree of fragmentation (8). Commercially available β-lactose tends to consist of approximately 85% β-lactose with the remaining 15% consisting of α-lactose monohydrate or anhydrous α-lactose (9). As such, the compaction properties of the material are a consolidation of both the α-lactose monohydrate and the β-lactose components (10).

The popularity of lactose as an excipient can be attributed to its cost, availability, bland taste, low hygroscopicity, good compatibility with other ingredients, excellent stability and water solubility (11).

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Anhydrous lactose is generally produced by roller drying a lactose solution, which is then milled and sieved to a desired size range. It is widely used in direct compression tableting processes as well as a capsule or tablet filler/binder, especially with moisture-sensitive compounds where low moisture content is desirable (12).

One known limitation of lactose, a reducing sugar itself, is the propensity of the material to react with primary and secondary amine drugs via a Maillard reaction to produce a multitude of coloured products (13,14). Lactose may contain reactive impurities such as glucose, formaldehyde, furfuraldehyde, formic acid and other aldehydes. The level of the reactive impurities may vary among vendors and lots. Formaldehyde is known to react with primary amine drugs to form *N*-formyl products and further to form dimers. The presence of these reactive impurities, even though at trace levels, could be detrimental to the stability, efficacy and safety of the final drug product.

In this paper, batch-to-batch and vendor-to-vendor variations in the solid-state characteristics in multiple batches of anhydrous lactose from each of three vendors and the subsequent impact of these differences on processability and/or functionality are reported.

MATERIALS

The lactose anhydrous batches investigated in this study were SuperTab 21AN (DMV-Fonterra Excipients GmbH & Co., Goch, Germany), Lactopress 250 (Friesland Foods Domo, Zwolle, Netherlands) and Lactose anhydrous NF DT (Kerry Bioscience, Norwich, NY, USA).

METHODS

Specific Surface Area

Samples were analysed using a Gemini 2390A surface area analyser (Micromeritics, Norcross, USA). Samples were out-gassed for 12 h at 100°C under nitrogen gas prior to analysis. Samples were then evacuated at a rate of 500 mmHg/min for 5 min and equilibrated for 5 min. Multipoint measurements (5 points) over the range of 0.06–0.2p_o were performed. All samples were analysed in triplicate.

Image-Based Particle Size

Particle size analysis was determined using a Morphologi G3 particle characterisation system (Malvern Instruments Limited, Malvern, UK). Samples were dry-dispersed using the systems automated dispersion system onto a glass plate. Particle imaging was conducted using a combination of ×10 magnification lens (3.5–210 μm resolution range) and ×5 magnification (6.5–420 μm resolution range). Morphological filtering was applied to remove any residual aggregates or overlapping particles from the final analysis.

Inverse Gas Chromatography

The dispersive surface energy of samples was determined by inverse gas chromatography using an inverse gas chromatography-surface measurement system (Alperton, Middlesex, UK). Samples were packed into 30-cm (3 cm inside diameter) silonised glass columns, plugged at either end by silonised glass wool. They were conditioned at 30°C (303 K), 0% RH, 10 sccm for 3 h prior to analysis. The dispersive surface energy analysis was conducted by injecting a range of hydrocarbon probes; decane, nonane, octane, heptane and hexane at 0.04 p/p_o. The polar-free energy of absorption analysis was determined using a range of polar probes: acetone, acetonitrile, ethyl acetate and ethanol at 0.04 p/p_o. The column dead time was determined using an inert probe (methane at 0.2 p/p_o). All samples were analysed in triplicate.

True Density

True density was determined with an Accupyc 1330 helium pycnometer (Micromeritics, Norcross, USA). Samples were dried at 50°C for 12 h prior to analysis.

Determination of Formaldehyde

A reverse-phase HPLC method with pre-column derivatisation using dinitrophenylhydrazine was developed to determine trace levels of formaldehyde. Kinetic studies were conducted to determine the minimum amount of dinitrophenylhydrazine and the necessary time for the derivatisation reaction. Samples were prepared by suspending the excipients

Table I. Specific Surface Area and Particle Size Results for Lactose Anhydrous Samples

Vendor	Batch reference	Specific surface area [m^2/g] (Std. Dev.)	Geometric particle size [μm] (Std. Dev.)			Arithmetic particle size [μm] (Std. Dev.)		
			D_{10}	D_{50}	D_{90}	D_{10}	D_{50}	D_{90}
DMV-Fontera	10421277	0.40 (0.00)	23.0 (2.5)	116.8 (14.8)	282.3 (14.0)	1.4 (0.1)	4.4 (0.4)	11.8 (0.6)
	10428173	0.39 (0.01)	34.0 (8.5)	130.4 (16.8)	265.7 (15.6)	1.3 (0.0)	3.6 (0.1)	9.8 (1.0)
	10444667	0.41 (0.01)	33.5 (7.1)	158.7 (2.0)	309.5 (23.7)	1.5 (0.1)	4.2 (0.6)	10.6 (1.0)
Borculo Domo	632751	0.48 (0.00)	28.8 (4.5)	114.3 (5.5)	248.4 (52.8)	1.4 (0.0)	4.1 (0.3)	11.8 (1.3)
	633379	0.48 (0.01)	26.5 (1.6)	103.2 (16.4)	260.8 (86.2)	1.6 (0.1)	5.0 (0.1)	14.0 (0.5)
	631678	0.48 (0.01)	25.7 (1.5)	110.8 (10.4)	255.3 (34.6)	1.3 (0.1)	3.8 (1.0)	12.4 (1.1)
Kerry Bioscience	1320010016	0.50 (0.00)	26.5 (2.9)	164.0 (25.1)	394.5 (59.3)	1.4 (0.2)	4.2 (1.1)	12.8 (1.1)
	1320010017	0.50 (0.01)	29.5 (3.9)	185.9 (11.0)	356.8 (47.6)	1.3 (0.1)	5.5 (0.3)	15.6 (0.3)
	1320010021	0.54 (0.00)	31.3 (2.7)	154.5 (18.6)	327.5 (3.7)	1.3 (0.0)	4.2 (1.1)	16.1 (1.3)
	1320019937	0.55 (0.01)	26.8 (0.8)	118.8 (17.6)	285.3 (14.4)	1.5 (0.0)	4.4 (0.6)	19.5 (0.7)

in 50:50 acetonitrile/water at room temperature. The suspensions were then filtered through 0.45-μm filter prior to analysis.

Angle of Repose

Samples were tested on the Geldart Mark4 Angle of Repose tester (Powder Research Ltd., UK). One hundred grams of each sample was poured slowly into the upper part of the chute. A motor was employed to generate a minimum degree of vibration in order to aid sample flow in the upper chute. The angle of repose value was calculated using Eq. 1.

$$\mathrm{AOR} = \tan^{-1}\left(\frac{h}{r}\right) \tag{1}$$

Where h = height of the semi-cone (mm), r = average radius of the base (mm). All samples were analysed in triplicate.

Powder Compaction

Samples were compacted using a Stylcam 100R compaction simulator (MedelPharm, Bourg-en-Bresse, France). Round, flat-faced compacts of 11.28 mm (equivalent to 1 cm^2 of compaction area) diameter were compressed to a target solid fraction of 0.85, which is a representative solid fraction commonly used in comparing materials. Before filling the die, the punches were manually lubricated using a 2% *w*/*v* magnesium stearate in acetone slurry to reduce tablet die ejection forces. Six compacts were produced for each sample, and once ejected, the accurate weight and thickness of each tablet was measured. Yield pressure (P_y) values were determined using the Heckel analysis, using the Analis analysis package (Medelpharm, Bourg-en-Bresse, France), and the tensile strength was calculated using Eq. 2.

$$T = \left(\frac{2P}{\pi Dt}\right) \tag{2}$$

Where T = tensile strength (MPa), P = hardness (N), t = compact thickness (mm) and D = diameter of compact (mm).

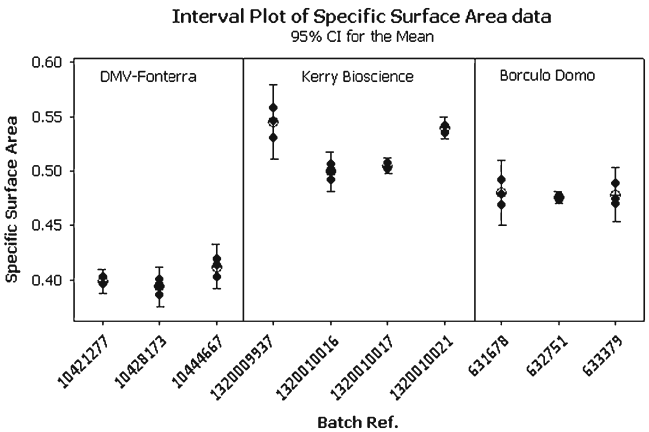

Fig. 1. Interval plot for specific surface area results for lactose anhydrous samples

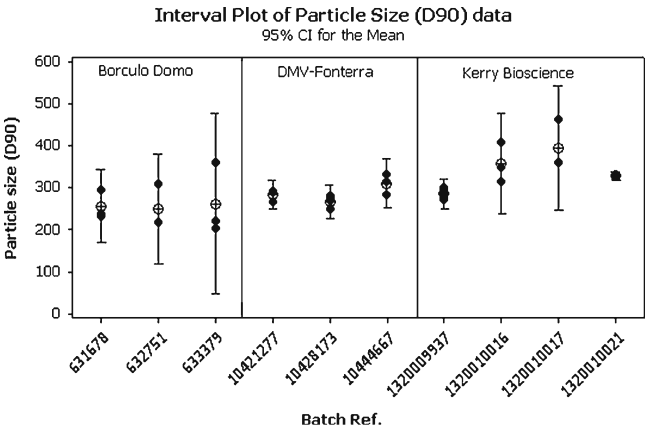

Fig. 2. Interval plot particle size results for lactose anhydrous samples

Compact Hardness

Compact hardness was measured using a Schleuniger tablet tester (Dr. Schleuniger Pharmatron, Manchester, NH, USA). Six samples were tested at each condition.

Data Analysis

Data analysis was performed using Minitab 15 (Minitab, State College, PA, USA).

RESULTS AND DISCUSSION

Specific Surface Area

The specific surface area results (Table I) indicated statistically significant differences between the three vendors, with the highest surface areas measured for the Kerry Bioscience batches (0.50–0.55 m^2/g) and the lowest for DMV-Fonterra batches (0.39–0.41 m^2/g). Intra-vendor batch-to-batch variability for both DMV-Fonterra and Borculo Domo materials was observed to be low in comparison to the Kerry Bioscience batches. One-way ANOVA, combined with Fisher's pair-wise analysis, was employed to analyse the statistical significance of the variation in surface area (Fig. 1). The results demonstrate that the materials from each of the three vendors are distinctly separated from each other. However, both DMV-Fonterra and Borculo Domo batches are relatively more self-consistent while Kerry Bioscience batches are more variable (differences between batches significant at the $p<0.05$ level).

Particle Size

All samples contained a wide distribution of particle sizes, with a portion of the distribution (below 3.5 μm) below the resolution range of the image-based particle sizing method used. The results (Table I) show that the batches all have similar particle size distributions, although the variation in some materials is quite significant (Fig. 2). When the results are viewed in conjunction with the previously discussed specific surface area data, the data indicate that the materials from each of the three vendors

Table II. Dispersive Surface Energy Results for Lactose Anhydrous Samples

Vendor	Batch reference	Dispersive surface energy [mJ/m^2] (S.D.)	Free energy of absorption (J/mol)			
			Acetone	Acetonitrile	Ethanol	Ethyl acetate
DMV-Fonterra	10421277	46.02 (0.22)	8,970.0	11,924.1	13,266.2	11,638.5
	10428173	45.66 (1.35)	8,537.3	11,918.0	13,386.7	11,635.5
	10444667	45.66 (0.56)	8,624.9	11,875.0	13,262.7	11,683.4
Borculo Domo	632751	43.19 (0.54)	8,245.0	11,227.6	12,385.5	10,950.8
	633379	43.31 (0.54)	8,340.3	11,275.0	12,492.4	11,123.4
	631678	43.11 (0.68)	8,231.6	11,338.5	12,483.6	11,060.6
Kerry Bioscience	1320010016	39.81 (0.44)	8,616.1	11,426.3	12,945.4	10,973.1
	1320010017	39.68 (1.78)	9,005.6	11,907.2	13,896.2	11,901.8
	1320010021	44.02 (0.81)	9,173.1	12,537.3	14,375.5	12,441.3
	1320019937	42.51 (0.83)	9,308.7	12,024.2	14,045.9	11,994.5

contain varied levels of both coarse and fine particle populations, although the batches from DMV-Fonterra appear to be very consistent.

Inverse Gas Chromatography

The dispersive surface energy results (Table II) indicated that the materials from each of the three vendors was variable enough to separate the three classes, with similar trends to the specific surface area and particle size data again observed. The three DMV-Fonterra batches were observed to have higher dispersive surface energies (~45.8 mJ/m^2) than the Borculo Domo batches (~43.2 mJ/m^2), whilst the lowest dispersive surface energies were generally observed for Kerry Bioscience batches (~41.5 mJ/m^2). Batch-to-batch variability for DMV-Fonterra and Borculo Domo materials was observed to be low, but the Kerry batches were again found to be more variable (Fig. 3). The source of the differences in dispersive surface energy for the materials was not fully investigated; however, it could be explained by slight differences in mechanically induced amorphous content on the surface of the samples (15,16).

Slight variations in the polar free energy of absorption results between materials from each of the three vendors were also observed (Fig. 2). The variations for DMV-Fonterra and Borculo Domo batches were found to have a relationship with the measured specific surface area, probably through variations in the availability of crystalline faces for probe interaction due to the degree of milling. This relationship was not observed for the Kerry Bioscience batches, which again showed the greatest inter-batch variability.

Angle of Repose

Despite the difference in the particle size and surface energetics observed, the materials demonstrated very similar angles of repose in all batches tested (Table III). The results indicate that the differences in particle size and surface energy measured are not significant enough to afford a change in the bulk powder flow properties.

Compressibility and Compactability

Batch-to-batch variability was observed to be low for all vendors in terms of both compressibility and compactability (Table III); however, statistically significant differences between the suppliers were still observed. The compressibility (yield pressure) data (Fig. 4) indicated that the DMV-Fonterra

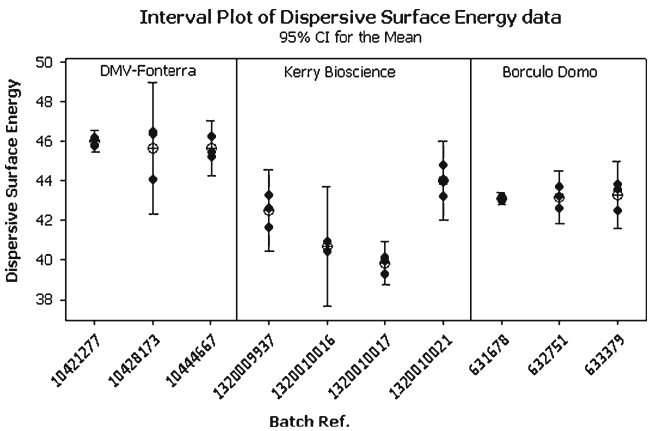

Fig. 3. Interval plot for dispersive surface energy results for lactose anhydrous samples

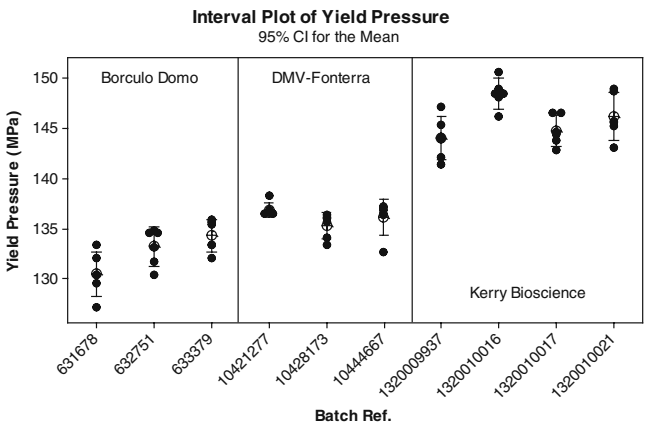

Fig. 4. Interval plot for yield pressure at 0.85 solid fraction results for lactose anhydrous samples

Table III. Compression/Compaction Data

Vendor	Batch reference	Angle of repose (°)	Yield pressure (MPa)	Tensile strength (MPa)
DMV-Fonterra	10421277	39±2	136.9±0.7	1.7±0.1
	10428173	39±1	135.2±1.2	1.8±0.0
	10444667	38±1	136.1±1.7	1.9±0.1
Borculo Domo	632751	39±1	133.2±1.9	1.6±0.1
	633379	41±2	134.3±1.6	1.8±0.1
	631678	40±1	130.4±2.1	1.4±0.1
Kerry Bioscience	1320010016	40±2	148.4±1.4	2.4±0.2
	1320010017	39±1	144.7±1.5	2.4±0.2
	1320010021	40±1	146.2±2.3	2.5±0.1
	1320019937	40±2	144.0±2.1	2.5±0.2

and Borculo Domo batches possessed similar particle deformability characteristics consistent with previously published results (17), whilst the four Kerry Bioscience batches required distinctly higher stresses to initiate deformation. This could result from the increased fines content, suggested by the specific surface area data, filling up inter-particulate voids. This may lead to a reduction in particle rearrangement during compression; therefore, a greater pressure would be required to instigate particle deformation. Moreover, it is generally concluded that lactose deforms predominantly by brittle fracture with some plastic deformation at the contact points. Therefore, a reduction in particle size may also contribute to the increased yield pressure (P_y) by reducing the amount of fragmentation (18,19).

In terms of compactability, Kerry Bioscience batches produced tablets with greater tensile strengths than the DMV-Fonterra and Borculo Domo batches. As the tensile strength increases with increasing bonding capacity of the powder, the presence of increased levels of fine particles could lead to the greater interparticulate contact areas and, hence, higher compacted strengths within the tablets (20).

Determination of Formaldehyde

The measured formaldehyde levels (Table IV) showed similar traits to previous data with the batch-to-batch variability in both DMV-Fonterra and Borculo Domo batches found to be low. Once again, the Kerry Bioscience batches were observed to demonstrate increased variability, with these batches having both the highest and lowest formaldehyde levels. As a very small and reactive chemical compound, formaldehyde could cause drug product instability even at trace levels. Assuming the formulation product has a 2% drug load and a weight of 0.5 g, 1 ppm formaldehyde corresponds to ~1% of API (molar to molar ratio). The higher levels of formaldehyde in some of the Kerry Bioscience batches, in conjunction with the previously discussed higher specific surface areas, could lead to an increased risk of drug degradation in formulations containing these batches (21).

Table IV. Formaldehyde Data

Vendor	Batch reference	Formaldehyde content (ppm)
DMV-Fonterra	10421277	0.50
	10428173	0.49
	10444667	0.47
Borculo Domo	632751	0.55
	633379	0.64
	631678	0.57
Kerry Bioscience	1320010016	0.54
	1320010017	0.31
	1320010021	0.81
	1320019937	0.28

CONCLUSIONS

The study was able to demonstrate differences in the solid-state properties of batches of anhydrous lactose from each of the three vendors included in this study. The intra-vendor variability was generally low, although some batch-to-batch variation was observed.

Despite these measured inter- and intra-vendor variations in powder properties, none of the differences were observed to have any significant impact on the compression/compaction characteristics, although the greater level of fines present in the Kerry Bioscience batches did lead to slightly stronger compacts.

The results from this study do, however, indicate that some sources of excipients can have lower levels of variability which may be of interest for the purpose of reducing sources of variation in processes. It would be questionable as to whether the differences would have any significant impact on the performance of a typical final dosage form, although this would be affected by the level of the material used within a formulation as well as the characteristics of each of the other constituents.

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