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Research Article

Elucidating Raw Material Variability—Importance of Surface Properties and Functionality in Pharmaceutical Powders

Sai P. Chamarthy,[1,2] Rodolfo Pinal,[1] and M. Teresa Carvajal[1,3]

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Abstract. The purpose of this study is to illustrate, with a controlled example, the influence of raw material variability on the excipient's functionality during processing. Soluble starch was used as model raw material to investigate the effect of variability on its compaction properties. Soluble starch used in pharmaceutical applications has undergone a purification procedure including washing steps. In this study, a lot of commercially available starch was divided into two parts. One was left intact and the other was subjected to an extra washing step. The two resulting lots were subjected to a series of physical characterization tests typical of those used to qualify raw materials. The two resulting lots gave virtually identical results from the tests. From the physical testing point of view, the two lots can be considered as two equivalent lots of the same excipient. However, when tested for their functionality when subjected to a compaction process, the two lots were found to be completely different. The compaction properties of the two lots were distinctly different under all environmental and processing conditions tested. From the functionality point of view, the two lots are two very different materials. The similar physical testing results but different functionality can be reconciled by considering the surface properties of the powders. It was found that the washing step significantly altered the surface energetic properties of the excipient. The washed lot consistently produced stronger compacts. These results are attributable to the measurably higher surface energy of induced by the additional washing step.

KEY WORDS: excipient variability; functionality of excipients; pharmaceutical sameness; powder functionality; raw material variability.

INTRODUCTION

Variability in the functionality of powdered raw materials is an important quality issue for pharmaceutical dosage forms. Even though it is widely recognized that different physical characterization techniques provide complementary information, a robust definition of *sameness with respect to functionality* in pharmaceutical materials remains something of a challenge. Solid dosage forms can be broadly considered as consisting of the active pharmaceutical ingredient (API) and excipients or "inactive" ingredients. It is widely accepted that, although therapeutically inactive, excipients are by no means inert constituents of a formulation. Excipients are active in a physical sense; they embody, so to speak, the functionality of the dosage form. This fact was first recognized in the 1960s when an outbreak of phenytoin toxicity was found to be caused by changes in the excipient used in the capsule formulation (1,2). It is now well recognized that the performance of a dosage form is inextricably linked to the physical and chemical properties of all ingredients in the formulation, of which a majority is often constituted by excipients. In fact, excipients often constitute up to 90% by weight of the formulation and hence critically influence the drug product performance. It follows that the performance of a dosage form cannot be separated from the functionality of the excipients that constitute it.

Any given excipient can be available from a number of different manufacturers, and supply chain considerations make it desirable for a pharmaceutical product to have more than one source for each of its raw materials. Consequently, one critical aspect of the use of pharmaceutical excipients is *sameness*; the certainty that the same types of excipient from different sources are indeed interchangeable in a formulation. The exact same concern extends to different batches of an excipient coming from a single source. A good number of pharmaceutical excipients are derived from natural products, making them susceptible to seasonal as well as natural and man-made environmental changes that affect the end characteristics of the excipient (3–9). Furthermore, excipients are manufactured using batch processes, which lead to the possibility of batch-to-batch variation in the excipient obtained from the same manufacturer (10,11). The production of pharmaceutical excipients uses a series of processing steps aimed at eliminating the natural variability of such materials. Despite such efforts, however, excipient variability is not uncommon; there are frequent reports of excipient variability in the pharmaceutical literature (12–18). In order

[1] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana 47907, USA.
[2] Oral and respiratory Product Development, Schering-Plough Research Institute, 556 Morris Avenue, Summit, New Jersey 07901, USA.
[3] To whom correspondence should be addressed. (e-mail: carvajal@pharmacy.purdue.edu)

to assure interchangeability between the different sources (manufacturers) of the same excipient or between different batches from the same source, the common practice in the industry is to perform a series of analytical tests, based on strict specifications for the particular raw material. If two lots of the same type of excipient, either lots from a different source or different batches from the same manufacturer, give test results within the same specifications, they are deemed as being the *same*, hence interchangeable.

In this report, we examine the effectiveness of typical characterization tests for assuring *sameness* between two lots of the same excipient. This is a controlled study where the two lots under study are identical in all respects (truly the same), except for an additional processing step purposely introduced as part of the study. We use soluble starch (a compression aid) as a model excipient. Soluble starch is also known as amylodextrin or amylogen (19) and is derived from starch by hydrolysis with dilute hydrochloric acid (19,20). The treatment with dilute hydrochloric acid results in the breaking of glucosidic bonds in starch (20). The production process involves multiple processing steps, including a series of washing steps (20–22).

MATERIALS AND METHODS

We simulated a hypothetical situation where two manufacturers use the exact same natural source and follow identical manufacturing processes with one exception: one manufacturer chooses to do an extra washing step on the raw material. A commercially available lot of soluble starch was split into two portions. One portion was used as received and is designated here as lot A. The remaining portion, designated as lot B, was subjected to an extra washing step with the purpose of creating a situation where the origin of any differences between the two lots is unambiguously established. Accordingly, the two lots used in this study can be viewed as batches of the same type of excipient coming from two different manufacturers. The two lots of soluble starch were subjected to a series of routine characterization tests in order to establish if they could be deemed as equivalent. The two lots were subsequently compared for equivalence in terms of their functionality, i.e., when used in a compression process.

Soluble Starch

ACS grade soluble starch was obtained from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA). The commercial lot was split into two portions. One half was subjected to an extra washing step with acetone. The washed half was dried under vacuum in an oven at 25°C for a period of 72 h. The unwashed and washed portions are referred to as lot A and lot B, respectively.

True Density

True density (ρ_{true}) of the two lots was determined using a helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corp., Norcross, GA, USA). Accuracy of the instrument was checked using AccuPyc 1330 calibration standard (AccuPyc 1330, Micromeritics) of known volume of 6.3723 cc. Before measurements, the powder samples were stored under 0% RH conditions (over phosphorus pentoxide) in a desiccator for a 2-week period to remove any surface moisture. During measurements, powder samples were purged with dry helium and vacuumed ten times in the instrument test chamber. This was done to effectively remove any residual surface moisture prior to final data collection. The reported results are averages of ten consecutive measurements.

Specific Surface Area

The specific surface area of the two lots was determined using multipoint BET adsorption isotherm analysis with a Tristar 3000 gas adsorption analyzer (Micromeritics). Nitrogen was used as the adsorbate, with a maximum manifold pressure of 1,050 mmHg. Carbon black (reference material no. 004-16833-00, Micromeritics) was used as a specific surface area reference material to calibrate the instrument. All analyses were performed in 3/8-in. sample tubes with a volume of 4.8608 cm^3, using filler rods and isothermal jackets. The powder samples were stored over phosphorus pentoxide in desiccators for 2 weeks prior to the measurement. The samples were further degassed in the instrument at 25°C for 24 h before the measurement. Vapor adsorption data for Nitrogen at 77 K were obtained for relative vapor pressures (p/p^o) in the range of 0.001 up to 0.30, split equally in 25 points. The equilibration time was set at 10 s. For the estimation of surface area, a cross-sectional area of 16.2 $Å^2$ for nitrogen was used.

Particle Size Distribution

The particle size distributions of soluble starch were determined by image analysis using an optical Nikon Labphot-2 microscope equipped with a Javelin CCD camera. Image capture and Image analysis were done using Image-pro plus software. The particle size calibrations were performed using NIST traceable particle size standards 19.9± 1.8 μm and 497±10 μm (Duke Scientific, Palo Alto, CA, USA). The calibration was further checked using particle size standards of average particle size 98.7±4.9 μm and 200±4 μm. For each lot greater than 1,000, individual particles were counted and the frequency and cumulative mass percentage were obtained. The mass distribution was calculated for spheres of equivalent diameter and the same absolute density.

Fourier Transform Infrared (FTIR)

Infrared spectra were obtained on a Bio-Rad FTS-6000 FTIR spectrophotometer (Bio-Rad, Cambridge, MA, USA). The measurements were performed on a total attenuated reflectance (ATR) sample stage (Specac Incorporated, Woodstock, GA, USA). Spectra in the range of 4,000 cm^{-1} to 500 cm^{-1} were obtained as the average of 128 scans at a resolution of 4 cm^{-1}. The spectrometer was purged with conditioned air preventing spectral interference from water vapor and CO2. The spectra were collected using Win-IR Pro v3.3 software (Digilab, Randolph, MA, USA). The spectra were analyzed using GRAMS/AI V.7.02 software (Thermo Fisher Scientific, Waltham, MA, USA).

Table I. Particle Size and Surface Area of the Two Lots of Soluble Starch

Parameter	Lot B	Lot A
Particle size (μm)		
d_{10}	28.4	34.8
d_{50}	52.4	66.7
d_{90}	72.1	103.1
Number mean	30.7	32.24
BET specific surface area (m^2/g)	0.98±0.1	1.01±0.1
True density (cm^3/g)	1.449 (±0.04)	1.472 (±0.03)

Moisture Equilibration

The two lots of soluble starch were initially stored under 0% RH for 2 weeks. Each lot was subsequently split into smaller portions. Different portions were then stored for a period of 2 weeks under different RH conditions, using desiccators containing different saturated salt solutions according to the ASTM method (23). The powder subsamples equilibrated under different RH conditions were then subjected to analytical testing and compaction studies.

Equilibrium Moisture Uptake

The moisture sorption isotherms of the two lots of soluble starch at 25°C were determined on a symmetrical gravimetric analyzer (Model SGA-100, VTI Corporation, Hialeah, FL, USA) from 10% to 95% RH. Prior to water sorption experiments, the powder was stored over phosphorus pentoxide for 2 weeks. The samples were then dried on the instrument at 25°C using the same equilibrium criteria as that used for the moisture sorption experiment. Sodium chloride and PVP were used as calibration standards to ensure the proper functioning of the instrument.

X-Ray Powder Diffraction

Powder X-ray diffraction analysis was done with Shimadzu X-6000 X-ray powder diffractometer. The Cu Kα radiation was utilized (λ=1.54 Å). The instrument is equipped with a long fine-focus X-ray tube. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 0.5° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A θ–2θ continuous scan at 3°/min (0.4 s/0.03° step) from 10 to 40° 2θ was used. A silicon standard was used to check the instrument alignment. Data were collected and analyzed using XRD-6000 v. 4.1. Samples were prepared directly in an aluminum holder for analysis. Care was taken to minimize the time each sample spent outside the relative humidity (RH) chambers during the course of the measurement.

Performance as a Compaction Aid

The compression properties of soluble starch were tested as a function of storage relative humidity. A weight of 500 mg of the pre-equilibrated soluble starch samples was compacted using a 13 mm flat-faced round punch and die set (Natoli Engineering Co., Charles, MO, USA) in an automated single station carver press (Carver, Inc., Wabash, IN, USA). The compression force used varied from 700 to 12,000 lb. The dwell time was maintained at 30 s. During the process of compaction, care was taken to minimize the time the powders spent outside controlled RH conditions. After compaction, the tablets were replaced back in their respective storage RH chambers for a period of 48 h for re-equilibration. The dimensions of the compact were used to calculate the volume. The apparent density of the compact was obtained from the measured volume and measured weight of the compact. The weight of the tablets was corrected for the water content obtained from the water sorption measurements. The solid fraction was calculated by dividing the apparent density of the tablet by the true density of the powder (measured by helium pycnometry).

The diametrical crushing strength (CS) of the compacts was measured using a tablet hardness tester (Vankel Industries, Cary, NC, USA). From the crushing strength values, the tensile strength (σ) of the compacts was calculated according to (24,25)

$$\sigma = \frac{2\,CS}{\pi\, d\, t} \tag{1}$$

where d and t are the diameter and the thickness of the compact, respectively.

The interrelationships between compaction pressure, solid fraction, and tensile strength, the three critical factors in a compaction process, were further analyzed. Tabletability (tensile strength *vs.* compaction pressure)(26–28), compactibility (tensile strength *vs.* solid fraction or porosity)(26–28), and compressibility (solid fraction or porosity *vs.* compression pressure) (26–28) of the two sources of soluble starch as a function of storage relative humidity were analyzed.

The compressibility data (porosity *vs.* compression pressure) was analyzed using the equation proposed by Heckel (29,30):

$$Log\frac{1}{\varepsilon} = K_y P + K_r \tag{2}$$

where P is the compaction pressure, ε is the porosity, K_y is a material dependent constant, inversely proportional to the yield strength S (K_y=1/3S) (29) and K_r is related to the initial repacking stage.

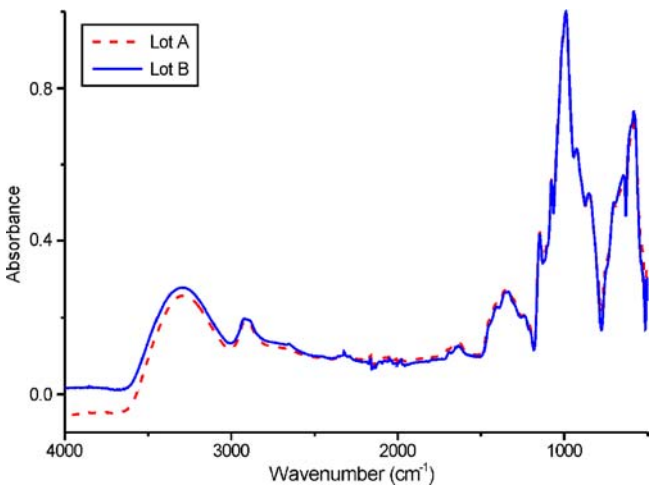

Fig. 1. FTIR absorption spectra of the two lots soluble starch

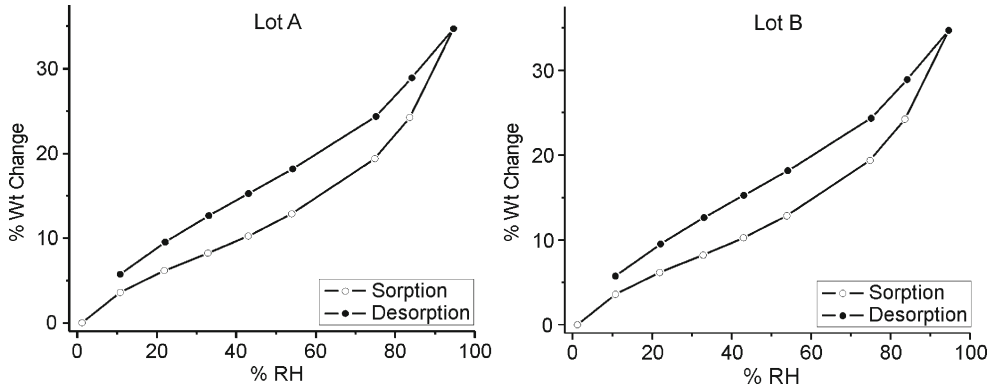

Fig. 2. Moisture sorption isotherms of the two lots of soluble starch

Compactibility data was used to estimate tensile strength at zero porosity (σ_0), at different storage relative humidity conditions by extrapolating the tensile strength (σ) at a known porosity (ε) using the expression proposed by Ryshkewitch (31) and Newton *et al.* (32):

$$\sigma = \sigma_0 \exp(-b\,\varepsilon) \tag{3}$$

where b is a constant.

Surface Energy

Inverse gas chromatography (IGC) was used to measure the surface energy of the powder samples. The IGC experiments were conducted using a commercial IGC system (*i*GC, Surface Measurements Systems Ltd., UK). Approximately 800 mg of the powder was weighed and packed in a silanized glass column (340 mm length and 4 mm internal diameter). Before measurements, samples were equilibrated with dry helium (10 ml/min) at 303 K for 48 h in the instrument. Helium was used as carrier gas. Methane (0.03 p/p^o) was used to determine the dead volume (V_o) of the column. The vapor probes used include a linear hydrocarbon series (C_6, C_7, C_8, C_9, and C_{10}), methanol, acetonitrile, and ethylacetate. The probes at infinite dilution (0.03 p/p^o) were injected as a pulse at 303 K and peaks were measured using a flame ionization detector (FID) and thermal conductivity detector (TCD).

Calculation of the dispersive surface energy as well as the specific free energy was made according to the method proposed by Schultz *et al.* (33). From the specific free energies of methanol, ethylacetate, and acetonitrile, the base number (BN) and acid number (AN), as defined in the Gutman electron donor acceptor model, were calculated according to the method proposed by Mukhopadhyay *et al.* (34).

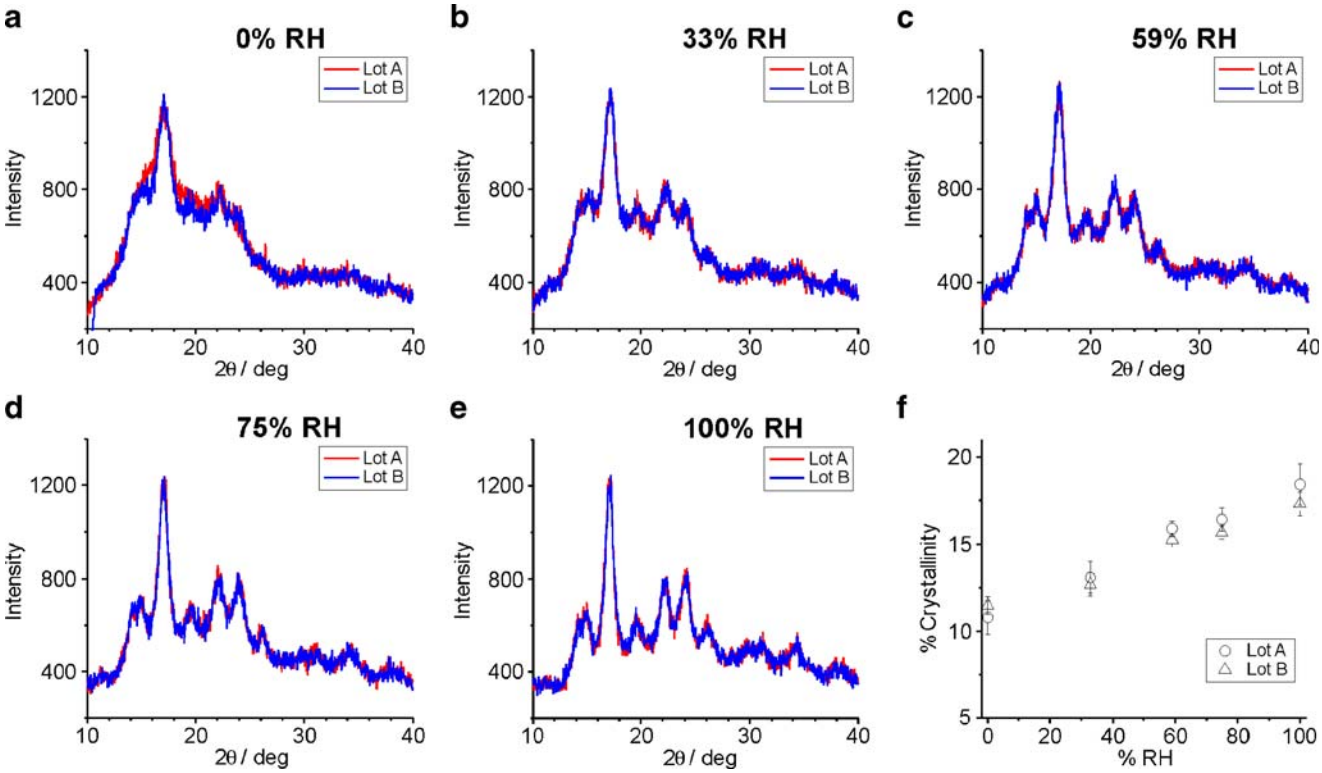

Fig. 3. **a**–**e** X-ray diffraction patterns for the two lots of soluble starch as a function of storage relative humidity. **f** Apparent crystallinity of the two lots of soluble starch determined using (X-ray) diffraction as a function of storage relative humidity

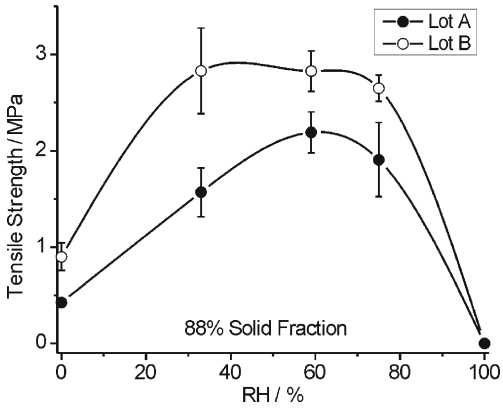

Fig. 4. Tensile strength of compacts at a constant solid fraction of 0.88 prepared from the two sources A and B of soluble starch as a function of storage relative humidity

RESULTS AND DISCUSSION

The data on particle size, specific surface area, and true density for the two lots of soluble starch are summarized in Table I.

The extra washing performed on lot B resulted in a slight reduction of the particle size. Such a reduction, however, was not significant enough to manifest itself as a change in the specific area of the powders or as a significant change in the number mean particle size. The infrared absorption spectra for the two lots are presented in Fig. 1. The spectra of the two lots are essentially over imposable. The peak positions as well as the intensities of the two lots are very similar. The two lots can be deemed equivalent from an FTIR standpoint. Figure 2 shows the moisture sorption isotherms for lots A and B, both of which give isotherms with a typical type II shape. The isotherms themselves are very similar for the two lots.

Results from the X-ray diffraction analysis are shown in Fig. 3. The effect of relative humidity conditions on the obtained X-ray patterns is shown in Fig. 3a–e. Changing RH from 0% to 100% has a marked effect on the X-ray patterns of soluble starch. Figure 3e shows the peak positions and respective *d* spacing for soluble starch 100% RH. The natural source for the soluble starch used in this study is potato starch, which is a type B native starch. The peaks and *d* spacing shown in the figure are consistent with the diffraction peaks for type B native starch (21). The X-ray patterns show an increase in diffraction peaks with increasing moisture content, indicating change in the degree of crystallinity of the excipient. Estimates of the apparent crystallinity as a function of relative humidity are shown in Fig. 3f for the two lots. The method used, proposed by Cheetham *et al.* (35), is based on the two-phase assumption, where the area of the peaks is attributed to regions of crystalline order and the area of the underlying halo is attributed to the non-crystalline regions in the matrix. Crystallinity values obtained from this empirical method are approximations since it does not take into account the effects of the size of crystallites in the polymer or the effect of crystal defects (36). Thus, in using this method, it is important that no assumptions regarding the true nature of the non-crystalline phase of the material are made. The method employed is still informative, since the purpose is to compare relative changes in crystallinity in the samples when the two are exposed to the same change in environmental or processing conditions. From the results of the X-ray analysis, it is clear that, under every RH condition investigated, the two lots of soluble starch give virtually identical X-ray patterns. Consequently, the two lots show very similar increase in crystallinity as a function of moisture content.

The results presented above correspond to tests that are traditionally part of a certificate of analysis (CA) testing of pharmaceutical raw materials, necessary for their acceptability for the manufacture of dosage forms. Lots A and B exhibit similar properties but, most importantly, also exhibit virtually identical behavior when exposed to changes in relative humidity. Based on these results, the two lots of soluble starch could be considered as similar enough on a CA basis, i.e., equivalent in the sense that one lot could be used as a substitute for the other in a pharmaceutical formulation. This situation brings us to an important point regarding variability in pharmaceutical situations. If two lots of the same material have similar properties and exhibit similar behavior under testing conditions, they are expected to exhibit similar functionality when used in pharmaceutical processing. We investigate the latter point by comparing the compaction properties of lots A and B of soluble starch in the following section.

Figure 4 shows the mechanical strength, as a function of relative humidity, of compacts made with lots A and B of soluble starch. In order to make an objective comparison, every compact represented in Fig. 4 has the same solid fraction value (0.88). It is clear that even though lots A and B give similar results when tested as bulk powders, they exhibit distinctly different functionality as compression aids. The

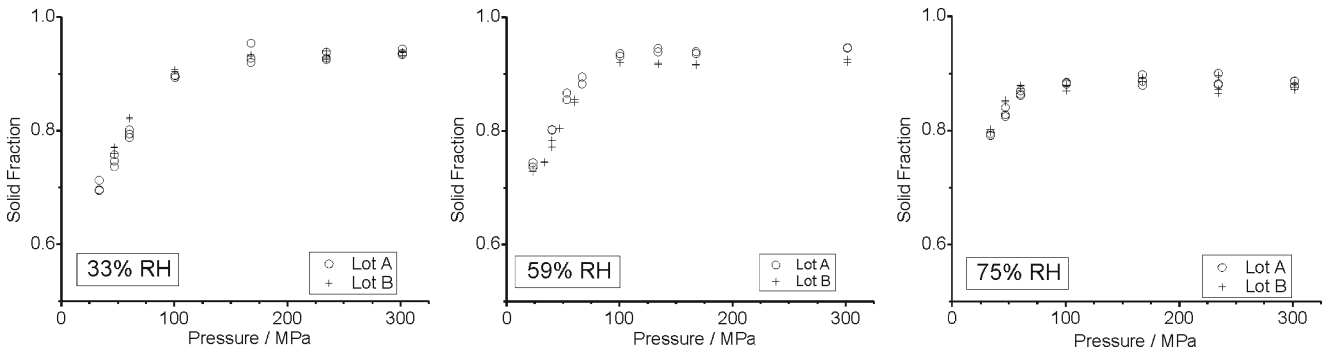

Fig. 5. Compressibility profiles (solid fraction *vs.* compaction pressure) of the two lots of soluble starch under different relative humidity (*RH*)

Table II. Heckel Analysis of the Two Lots of Soluble Starch

	Lot B		Lot A	
Relative humidity	K_y ×1,000	K_r ×100	K_y ×1,000	K_r ×100
33%	1.8	2.27	2	2.16
59%	0.3	2.47	0.8	2.67
75%	2	2.06	2.3	2.08

Compression data are shown in Fig. 5

washed lot, B, consistently produces stronger compacts. The two lots never perform the same, until the system is saturated with water. The difference in performance is striking, considering that the change in particle size produced by washing is insufficient to explain the results from compression experiments. The strength of a compact is one of the most critical characteristics of pharmaceutical tablets. The main cause for concern here is that such a significant difference in performance between the two lots could not be anticipated based on any results from the detailed characterization tests presented above. The results from the functionality test of the excipient raise the question as to whether the difference in performance between lots A and B is maintained when the compacts are produced under different compression pressures and/or with different solid fractions.

Before proceeding further, it is pertinent to establish the terminology used in this report. The clarification is important because the same set of terms is often used with different connotations.

Compressibility. Refers to the ability of a powdered material to yield volume as the result of an applied pressure. Quantitatively, compressibility relates the applied pressure to the resulting solid fraction (or porosity) of the material (26–28). Compressibility of a powder is often described by the Heckel equation (30).

Compactibility. Refers to the ability of a powdered material to form a cohesive body of defined mechanical strength, i.e., a compact such as a tablet, upon *compression* (densification). Quantitatively, compactibility relates the tensile strength and the porosity (or solid fraction) of the compact obtained by compressing the powder. Compactibility profiles of pharmaceutical powders are generally described by the Ryshkewitch model (26,37).

Tabletability. Refers to the capacity of a powder to transform into a compact of specified strength under the effect of a given compaction pressure. Quantitatively, tabletability relates the mechanical strength of the compact to the compression pressure. Tabletability demonstrates the effectiveness in the applied compression pressure to increase the tensile strength of a tablet.

Tabletability is the relationship most commonly used in practice, since it relates an operating parameter with a property of the final compact. The first two terms, however, are conceptually important since they bear information regarding powder functionality. For this reason, our analysis focuses on the first two aspects of compact formation defined above.

The compressibility profiles of the two lots of soluble starch under different RH conditions are shown on the top part of Fig. 5. Heckel analysis (Eq. 2) has been extensively used to deduce valuable information on the deformation mechanisms of the material and also as a tool to estimate yield stress (26,38–44). The results from Heckel analysis on the data in Fig. 5 are summarized in Table II. The K_y values are comparable for the two lots of soluble starch. The low magnitude of K_y indicates that the material is hard and brittle, undergoing little plastic deformation during compaction (45).

The equivalence in compressibility behavior between the two lots leads to a very important consideration: if two lots of the same excipient are to meet the criteria for *sameness* in the pharmaceutical sense, they must exhibit the same compactibility if they have the same compressibility. The compactibility results for the two lots are shown in Fig. 6, where the six lines represent the fit to the Ryshkewitch equation (Eq. 3). An important use of the Ryshkewitch analysis is that it estimates the tensile strength of a hypothetical compact of the material having zero porosity; such a parameter reflects the inherent cohesiveness of a powder. The values of tensile strength at zero porosity are shown in Fig. 7 as a function of relative humidity. In more practical terms, the difference in functionality between the two lots is unmistakable in Fig. 8, where the tabetability (tablet strength *vs.* compression pressure) is shown at different relative humidities. From the data in Figs. 5 through 8, it is evident that the two lots of the excipient do not meet the criteria for pharmaceutical sameness and that the difference between lots persists under different relative humidity conditions. Lot B consistently produces stronger compacts under all processing and environmental conditions investigated.

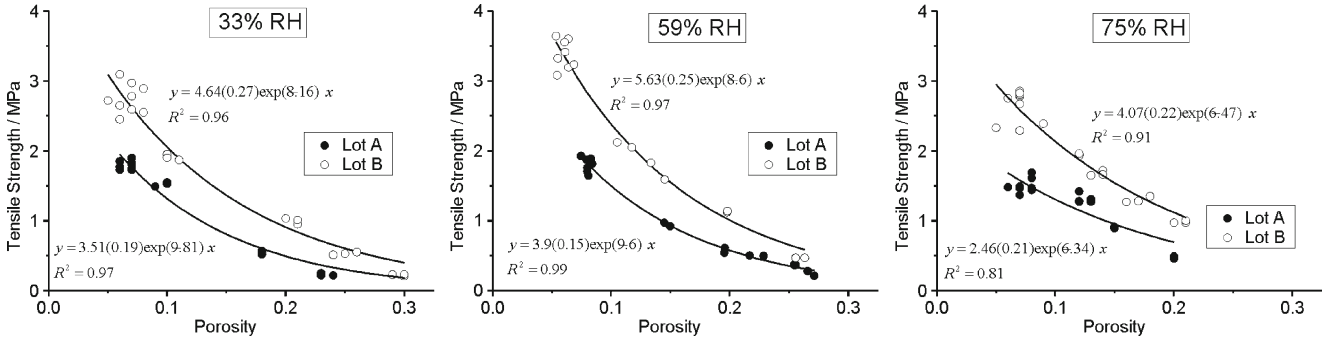

Fig. 6. Compactibility profiles (tensile strength *vs.* porosity) of the two grades of soluble starch at a storage relative humidity (*RH*) of 33%, 59%, and 75%. The best fit lines for Ryshkewitch equation are plotted on the graph

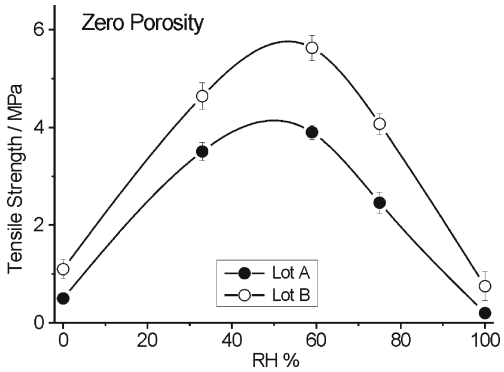

Fig. 7. Estimated tensile strength at zero porosity (σ_0) for the two lots of soluble starch as a function of storage relative humidity (*RH*). The *error bars* represent the 95% confidence intervals obtained for the fit

There are a number of bonding mechanisms between powder particles to form compacts (46,47). Solid bridges, mechanical interlocking, and van der Waals adhesion forces are among them. However, independently of the bonding mechanisms at play, a common feature of compact formation is that the powder particles interact at the surface level. In the example presented here, we have two lots of soluble starch with very similar particle size distributions and the same specific surface area. The two powders also exhibit similar compressibility. The Heckel analysis shows that two lots also exhibit similar yield strength. From these considerations, it is reasonable to infer that the two lots of soluble starch present similar number of particle-to-particle contacts in their bulk. This means that the surface area of contact between particles can be expected to be very similar for compacts of the two lots made under identical conditions. It follows that the marked differences in strength of the compacts produced from the two lots of the excipient originate from differences in intermolecular interaction forces at their surfaces. The interactive properties of powder surfaces can be quantitatively assessed through surface energy measurements, as discussed below.

Inverse gas chromatography (IGC) was used to study the surface energetics of the two lots of the excipient. Among the different methods available for studying the surface energy of solids, IGC is suitable for materials with undefined geometry such as powders (48). IGC is also a bulk testing technique in the sense that the measurements are done on the undisturbed powder, where large surfaces are being exposed (about 1 m^2 of powder surface is being probed at a time in the present study). Surface energy measurements based on IGC yield a dispersive surface energy, assessed through the interactions of the powder with non-polar vapor probes. Based on the interactions with polar probes, the free energy of specific interactions (i.e., involving functional groups), corrected for the dispersive component, can be obtained. The acid–base characteristics of the surface can be estimated from the free energy of specific interactions using the Gutman acid base model (34), which results in an acid number and base number for the powder sample. Acid number reflects the electron-accepting nature of the surface and the base number reflects the electron-donating nature of the surface. The ratio between the acid number and the base number is taken as a reflection of the polarity of the surface.

Table III. Surface Energy Values of the Two Lots of Soluble Starch Determined Using Inverse Gas Chromatography

Description	Lot B	Lot A
Dispersive surface energy(mJ/m^2)	41.7 (±1.2)	34.0 (±0.74)
ΔG acetonitrile (kJ/mol)	12.7 (±0.44)	10.53 (±0.23)
ΔG methanol (kJ/mol)	18.67 (±0.64)	15.3 (±0.37)
ΔG ethyl acetate (kJ/mol)	9.57 (±0.27)	7.61 (±0.16)
KB	0.236	0.21
KA	0.11	0.09
KA/KB	0.47	0.43

The results for the surface characterization of the two lots are presented in Table III. The data show that soluble starch from lot B has a higher surface energy than that of lot A. The dispersive surface energy as well as the specific free energy of interaction with acetonitrile, methanol, and ethylacetate for soluble starch from lot B is significantly higher than that of lot A. Considering that the particle size and surface area of the two lots of soluble starch are similar, the IGC results indicate that interparticulate interactions among particles in lot B are stronger even if they are the same in number than in lot A. Based on these results, it can be expected that, at constant solid fraction, compacts from lot B will have higher strength than compacts from lot A. The differences in performance of the two lots can be rationalized, even anticipated, based on the surface energy results. Powdered particles in a compact interact with each other using their surfaces, and hence it is logical to anticipate that particles with higher surface energy will result in stronger compacts.

This study illustrates that simple changes in the manufacturing of excipients, such as an additional washing step in

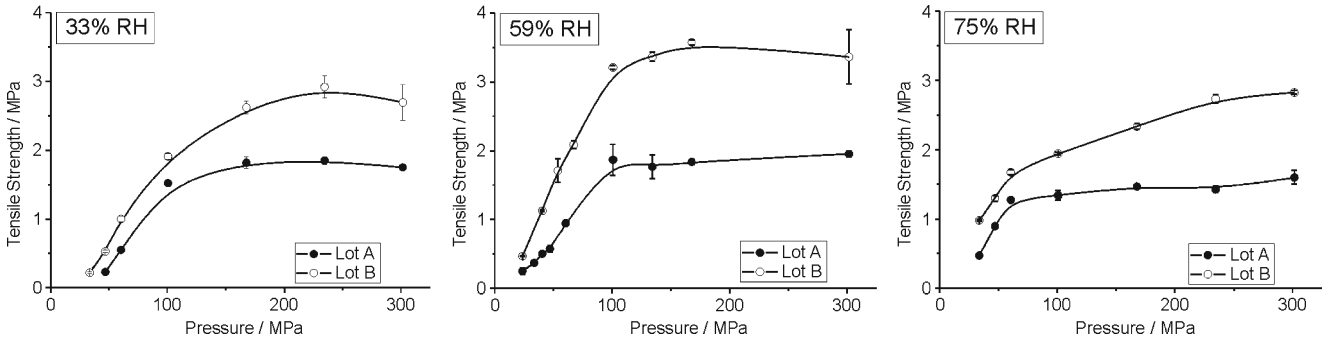

Fig. 8. Tabletability of the two lots of soluble starch as a function of storage relative humidity (*RH*)

this case, can result in a type of variability that, while being virtually undetectable by routine tests used for the qualification of raw materials, (an additional washing step), can result in significant changes in the surface properties, which can in turn lead to significant differences in the desired performance characteristics of the material. Given the importance of surface interactions on the performance powders, the study stresses the relevance of surface characterization for assessing functional sameness between lots pharmaceutical raw materials.

CONCLUSIONS

Characterization of the surface properties of powdered excipients presents a critical factor in assessing variability. Specifically, in terms of powder functionality, it is now possible to have a greater understanding of batch-to-batch variation from the same manufacturer or from source-to-source variation of the performance of an excipient. The controlled example presented here clearly illustrates this type of situation. The two lots of soluble starch in this study were indistinguishable by a variety of routine characterization tests (particle size, specific surface area, apparent crystallinity, moisture sorption, and FTIR). Despite showing similar results with different testing methods, the two lots were nonetheless very different with regard to their performance as a compaction aid under all conditions of compression pressure and storage relative humidity studied. Surface characterization results provided the valuable pieces of information for reconciling the observed results. The lot with higher surface energy resulted in compacts with higher strength. Surface characterization results not only help us in understanding the difference in performance but also would help in anticipating the difference in performance. It is expected that the improved characterization of the surface will not only help to better control excipient variability but will also help us in better understanding other properties of powders of pharmaceutical importance where surface energetics play a critical role, such as segregation, flowability, blending, and compaction. While this particular study makes a good case for characterizing the surface of pharmaceutical powders such as starch, a more general line of thought is that pharmaceutical *sameness* (or variability) is best defined in terms of properties (and tests) that reflect the interactions of the excipient in the context of its intended function.

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