Understanding Flow Properties of Mannitol Powder at a Range of Temperature and Humidity

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Abstract:

Inadequate flowability of powders in industries during handling can cause many problems. For example, lack of flow from hoppers, poor tablet weight consistency, and low production rate in tableting. Many factors are known to commonly affect flow properties of powders, such as temperature, humidity and conditioning duration. In this paper, flow properties of a mannitol powder, which was conditioned between 24-72 hours at various high relative humidities and temperature, were measured using a shear tester. A statistical model was developed to investigate the relative importance of these variables on the mannitol flow properties. The developed model showed all independent variables are significant in estimating bulk cohesion. Two separate approaches were used to evaluate inter-particle forces in the bulk, and how these changed with environmental conditions. First, inter-particle forces were inferred from the measured bulk properties using the Rumpf model approach. Secondly, inter-particle forces were predicted based on a model of moisture present on the particle surface using a combination of Kelvin model with the Laplace-Young (KLY) equation. The second approach also involved a new method to measure surface energy of mannitol powder based on measurements using Finite Dilution Inverse Gas Chromatography (FD-IGC). The surface energies of the mannitol powder were measured at high temperature (35 °C) and at different range of relative humidities. In spite of the fundamentally different approaches to the two ways of inferring inter-particles forces, these forces came out within less than 1.5:1 in magnitude. The Rumpf approach from bulk behaviour data obviously reflected the measured change in behaviour with humidity in particular, but this was not predicted from the KLY approach, however the likely reasons for this are postulated and recommendations for improvement are made.

Key words: flow properties, interparticle forces, continuous mechanical modelling, statistical modelling, shear tester.

1. Introduction

Flow behaviour of powders is difficult to predict due to different variables that can change their flowability. It is self-evident that flow properties of powders depend mainly on the interaction forces between their particles. It is also well known that extrinsic factors, such as temperature (Chirone et al., 2016) and humidity of the environment surrounding the particles (Landi et al., 2011) or intrinsic factors, such as particle size distribution (Lu et al., 2015), shape, moisture content (Sun, 2016) and surface tension (Shah et al., 2017) each can play a part in powder flowability through the effect they have on the inter-particle forces. The influence of these interactions on powder flow properties in application, can only be evaluated in a meaningful way by conducting flow property measurements with the powder conditioned to the realistic storage conditions (Tomasetta, 2013).

Generally, increasing humidity of the storage environment will decrease powder flowability (Hirschberg et al., 2019; Landi et al., 2012; Lu et al., 2018, 2017; Omar et al., 2016); however there is a very wide range of response, some powders being severely affected whereas others are little affected. Particularly, liquid bridges can be formed between particles as a result of adsorbed water to the particle surfaces. A liquid bridge causes an increase in the interparticle capillary forces, due to both the particle surface energy (surface tension) as well as bridge surface curvature between the two neighbouring particles (Landi et al., 2012). Cohesion and tensile strength of powder increases as a result of higher capillary forces, therefore the flowability of powder decreases (Salehi et al., 2020).

Whilst such influence on inter-particle forces and the resulting change of flow properties are well known in qualitative terms, obtaining useful quantitative relationships between the inter-particle effects and the bulk effects remains elusive. The driving force for this work was to try to develop useful linkage between the change in inter-particle forces and the change in bulk behaviour, through an approach of inferring the interparticle forces from bulk flow property measurement, and then comparing against inter-particle forces predicted by established contact law theories and surface characterisation measurements.

The material chosen for the study was mannitol ($C_6H_{14}O_6$), frequently used as an excipient in pharmaceutical industries (Krok et al., 2017; Paul et al., 2019). The mannitol powder has 4 polymorphic forms, namely: α, β (most stable polymorph), γ, and δ. The interest in using mannitol has been increasing in recent years (Paul et al., 2018). In comparison with other widely used excipient, i.e. lactose and microcrystalline cellulose (MCC), mannitol is less hygroscopic, more water soluble, more chemically inert (e.g. less susceptible to Maillard reaction in processing than lactose (Wirth et al., 1998)), produces more robust tablets, inert towards patient’s body and the API, good taste and mouth feeling, good flow properties and high compactibility (mainly useful for direct compression) (Ohrem et al., 2014), suitable for people with lactose intolerance (Paul et al., 2018) and low hygroscopicity.

In comparison with other commercial excipients, mannitol has attracted less attention in scientific literature. This is probably because in spite of its advantages it is relatively much less used compare to lactose and MCC, so there has not been commercial drive to undertake such studies. Furthermore systematic understanding of important properties of mannitol at high temperature and humidity is lacking (Paul et al., 2018). It is self-evident that the flow behaviour of a powder is regulated by the forces between the particles so it would be appear to be logical to attempt to study the variation in inter-particle forces caused by changing environmental conditions. However, this is no easy task. Few experimental and theoretical studies are considering the effect of capillary condensation on interparticle forces between particles and powder flow behaviour (Karde et al., 2017; Landi et al., 2011). Application of direct techniques for measuring interparticle forces, such as atomic force microscopy, show very scattered results due to the complex effect of particle surface tension, particle size and shape, surface roughness as well as particle surface chemical composition (Drelich and Mittal, 2005). The polydispersity of these factors in real powders means that the link between inter-particle actions and bulk powder behaviour must be considered to be stochastic, so the only means available to us to explore links between inter-particle forces and powder flow is to use simplified models of powder structure (shapes, sizes, packing etc.) and calibrate these from measurements from powder behaviour (e.g. Rumpf approach (Rumpf, 1970)). In principle, it may be possible to join this up with models that link inter-particle forces directly to environmental conditions, in order to obtain a theory that links powder flow to environmental conditions. The theoretical approach based on the Laplace–Young model as well as Kelvin equation is widely used as a method to predict the interparticle forces (Landi et al., 2011). However, this approach needs the correct measurements of particle surface energy and roughness. For instance, two studies (Butt and Kappl, 2009; Rabinovich et al., 2002) highlighted the effect of particle surface roughness on the interparticle capillary forces. Rumpf microscale approach (Rumpf, 1970) modified by Molerus (Molerus, 1975) was applied by Chirone et al., (Chirone et al., 2016) to study flow properties of ceramic powders at elevated temperature (up to 500 °C) and by Lu et al. (Lu et al., 2018) to investigate the effect of added water on the flow properties of pulverised coal. In their work, flow properties of different powders were used in combination with the

Laplace-Young model to infer inter-particle forces between the coal particles with different moisture contents, but no validation was made against inter-particle forces measured or inferred from other means.

It is essential to evaluate the bulk material flow properties at realistic conditions, similar to the range of real industrial storage and production conditions, for instance at high humidity up to typically 90% (Gröger et al., 2003; Landi et al., 2012; Teunou and Fitzpatrick, 1999), at a range of consolidation stresses from low e.g. a few tens or hundreds of Pascals (Bruni et al., 2007; Salehi et al., 2018, 2017b; Stavrou et al., 2020) to moderately high e.g. to about a few tens of kPa (Salehi et al., 2019) and at elevated temperature typically up to 65 °C in transport but several hundred Celsius in processing (Chirone et al., 2016; Ripp and Ripperger, 2010; Salehi et al., 2020; Smith et al., 1997; Tomasetta et al., 2013; Zimmerlin et al., 2008). In this paper, the effects of air relative humidity, temperature and storage time (over ranges commonly experienced in pharmaceutical processes) on the flow properties of a sieved highly functional spray-dried commercial pharmaceutical grade mannitol powder (D-mannitol), were evaluated. With regards to consolidation stresses a range of 0.5 to 5 kPa was used, humidities up to 90% and temperatures up to 35 °C were used because these ranges are similar to those encountered commonly in pharmaceutical powder handling. Other factors that are known to affect powder flowability, e.g. particle size distribution, shape were kept constant. The inter-particle forces of the powder at different moisture contents (resulting from changing temperature and humidity) were inferred by using the Rumpf approach applied to powder flow measurements from the Brookfield Powder Flow Tester (PFT), and also using the combination of the Kelvin and the Laplace–Young equations based on moisture level and measured surface energy (Loreti and Wu, 2018), and the results compared. Furthermore, a statistical analysis was conducted to determine experimentally the most influential conditioning variables on the flow properties of the mannitol powder.

2. Materials and methods

Mannitol powder was provided by Roquette Company. The mannitol powder was sieved (at the University of Greenwich) with a mechanical sieve in order to get a narrow particle size distribution between 75 and 180 µm. The instantaneous Flow Function of the mannitol was evaluated with the Brookfield Powder Flow Tester (PFT). The PFT is a direct shear tester employing an annular shear cell, using the well-known Jenike (Jenike, 1964) approach for determination of the Flow Function of a powder (Berry et al., 2014). The PFT operates by applying a vertical compression through the lid onto the powder sample contained in the annular trough whilst simultaneously applying shear and measuring the torsion to determine shear stress. An internal automated procedure controlled by the 'Powder Flow Pro' software is used to operate the cell to reproduce the sequences of normal stresses and the shear movement necessary to define the yield loci (Berry et al., 2014). Flow properties of mannitol powder measured at laboratory conditions (temperature of 18 °C ± 2 °C and humidity range between 30 % to 40 %) are reported in Table 1. Namely, cohesion, c, bulk density, ρ_b, particle density, ρ_p, friction angle, φ_i, and effective angle of internal friction, φ_e.

The unconfined failure strength, f_c, is the derivation from the Mohr circle that passes through the interaction of τ-σ diagram and tangent to the yield locus line. Therefore, unconfined failure strength is a combined function of friction angle, φ_i, and the powder cohesion, c (Sun and Sun, 2019). The major principal stress, σ_1, is the derivation from the Mohr circle that passes through the preshear point in the τ-σ diagram and is tangent to the yield locus line. The graph that relates f_c to σ_1 is known as the "Powder Flow Function" which is the most important parameter involved in powder flow, since its interpretation is the way that powder flowability is classified and reported, and also used for engineering calculations for equipment design. The detail of the procedure to derive the flow properties of powder from the shear tester is reported in details by Jenike (Jenike, 1964). The fully detailed representation of the powder flowability is the curve that fits through these points (powder Flow Function curve as indicated in Figure 1), however it is often desirable to have a single value for the powder flowability to make a quick and easy comparison between powders; this is frequently achieved by putting the best fit line through the origin and through the Flow Function data. The Jenike flowability classification, Flow Function value, $ff_c = \sigma_1/f_c$, is a commonly used method for reporting powder flowability, however in practice it is more intuitive to consider $1/ff_c$, i.e. the slope of the best fit straight line on the graph of f_c versus σ_1. The classes generally considered are the free flowing ($ff_c \geq 10$ or $1/ff_c < 0.1$), easy flowing ($4 < ff_c \leq 10$ or $0.1 < 1/ff_c < 0.25$), cohesive ($2 < ff_c \leq 4$ or $0.25 < 1/ff_c < 0.5$), very cohesive ($1 < ff_c \leq 2$ or $0.5 < 1/ff_c < 1$) and non-flowing ($ff_c \leq 1$ or $1/ff_c > 1$). Figure 1 shows an example of a Flow Function curve measured from the mannitol powder in one of the experiments, and also shows the commonly used conventional grouping of powder flow properties across the range from free flowing to non-flowing.

Particle density was measured with Helium pycnometry (AccuPyc II 1340, Micromeritics Instrument Corp.) with the assumption that particles have no porosity at their surface. The Helium pycnometer consists of two controlled temperature chambers of accurately known volume. A known mass of powder is placed in one of the chambers and its temperature kept constant. A known mass of Helium gas is added to the other chamber, then a communicating valve is opened between the chambers, and the equilibrated gas pressure indicates the volume of the particles in the powder sample. The particle density of the powder is determined by using equilibrium pressures with the ideal gas law and Archimedes principle; value is reported in Table 1.

Particle size distribution of the mannitol powder measured with a laser diffraction particle size analyzer (Malvern, Mastersizer Sirocco 2000) with Sirocco dry powder feeder and using dry air as the dispersion medium. The dispersive air pressure used was 1 bar, this was chosen because the Mannitol powder as supplied was very free flowing so did not require any effort to disperse it. The data derived from the Mastersizer is presented in Table 1. Namely, Sauter mean diameter (d_{sv}), D_{10} (µm), D_{50} (µm), and D_{90} (µm) based on spheres of equivalent volume to the particles. D_{50} is the volume median of the particle size distribution, which is taken as the mass median based on the assumption that all particles are of the same density. D_{10} is the particle size below which 10% of the sample mass falls and D_{90} is the size below which 90% of the sample mass falls, based on the same assumptions as for D_{50}.

2.1. Sample preparation

In this study sieved mannitol powder was placed in an open sided drum rotating at approximately 2 revolutions per minute, which was placed in the environmental chamber to optimize the exchange of humidity between powders and surrounding air. The container is similar to the tester to measure the dynamic angle of repose (Ye et al., 2019). This system was preferred by the authors over the alternative of conditioning in a static tray for the following reasons. We noticed in static conditioning of mannitol powder, a crust layer is formed at the top surface of the powder which hinders the humidity exchange of the controlled atmosphere with powder in the lower part of the bed. This also caused the physical heterogeneity inside the bulk material which adversely affect the powder flow properties. The use of the conditioning drum overcome these problems.

The variables in this study were temperature, T, (ranging from 25 °C to 35 °C), relative humidity, RH, (ranging from 65% to 90%) and conditioning durations, h, (ranging from 24 to 72 hours). Consideration of previous experience working in pharmaceutical plants led to the view that temperatures from 25 °C to 35 °C and relative humidities between 40 to 90% should be considered. Initial experiments showed no change in flow properties of mannitol powder below 60% relative humidity and temperature of 25 ˚C compared to the untreated mannitol, therefore the main study covered humdities between 60 to 90%.

2.2. Surface energy analysis

The surface energy of the D-Mannitol powder was determined using Finite Dilution Inverse Gas Chromatography (FD-IGC) Surface Energy Analyser (Surface Measurement Systems, London, UK). About 1.2 g of powder dried sample was packed into a silanized glass column (300 mm length and 4 mm I.D.) and plugged with silanized glass wool (Sigma-Aldrich, UK) on both the ends. The sample was further packed properly in the column with the help of jolting voltameter (Surface Measurement Systems, London, UK) which provides mechanical tapping to remove the voids in the packed sample bed. The packed sample column was mounted into the column oven with the required column fittings. A series of n-alkane probes (nonane, octane, heptane and hexane) and polar probes (ethyl acetate and dichloromethane) were injected (in dry Helium) to obtain the retention behavior of the probes and the subsequent dispersive (γ^{d}) and acid-base (γ^{ab}) surface energies were calculated using the Schultz approach. Helium was used as a carrier gas at a flow rate of 10 ml/min and methane was used as a reference gas to calculate the dead volume. The surface energies of the mannitol powder were measured at different relative humidities of 0 % (at both 20 °C and 35 °C), 60 %, 70 %, 80 % and 90 % (at 35 °C).

2.3. Experimental design

Experimental design and statistical analysis of the results were conducted with MODDE 12.0 software package (Umetrics, Umeå, Sweden). A Central Composite Face experimental design was selected. This design is composed of an imbedded fractional factorial design with centre points that is augmented with a group of 'star points' which placed on the faces of the sides of the controlled parameter domain in order to allow estimation of curvature. The variables were temperature, *T*, relative humidity, *RH*, and conditioning duration, *h*. The experimental design gave 15 experimental conditions with one centre point. The experimental conditions of the centre point was repeated twice. All other experimental conditions did not have any replicates. Previous study (Salehi et al., 2017a) showed that the standard deviation of the unconfined failure strength derived from the PFT shear tester is very low (0.01 kPa with mean 5 kPa). All experimental conditions were reported in Table 2.

3. Results

The cohesion, c, friction angle, φ_i, and $1/ff_c$, were reported in Table 2. In general, as it was, the cohesion and friction angle increased when mannitol powder were stored for longer time at higher relative humidity and temperature. The Flow Function, ff_c, σ_1/f_c, is inversely related to flow properties of powder. Therefore, for the sake of simplifying usually the powder flow properties are reported as $1/ ff_c$ to give values that increase as the powder gets more difficult to handle.

A polynomial regression model with degree 2 (square law) has been developed to estimate cohesion (c), friction angle (φ_i) and Flow Function (ff_c) by temperature (T), relative humidity (RH) and conditioning duration (h). The systematic part of the model is:

$$\log\left(\hat{Y}\right)=\sum_{j=1}^{3}\left(\alpha'_j x_j+\beta'_j x_j^2\right)+\left(\chi_1 x_1 x_2+\chi_2 x_1 x_3+\chi_3 x_2 x_3\right) \qquad \text{Equation 1}$$

where $\hat{Y}$ is the estimated response variables (c and φ_i, ff_c), x_j is the explanatory variable from $\left[T \quad Rh \quad h\right]$, α' is the coefficient for the main effects of explanatory variables, β' is the coefficient for the square of variables and χ is the corresponding coefficient for interaction between variables. The outcome variables of this model are cohesion, friction angle and Flow Function, which are all non-negative values. The logarithm link function makes sure that the estimated values (predicted values) from the model are always positive. The errors of this model are mutually independent with a log-normal distribution. The parameters of the model are calculated by maximum likelihood (ML) estimation. The likelihood function is defined based on the parameters of the model. The desired estimators are the parameters that maximize the likelihood function. The log-likelihood function, L, of the presented model is calculated as:

$$\mathrm{L}=\frac{-n}{2}\log\left(2\pi\sigma_l{}^2\right)-\sum_{i=1}^{n}\log\left(y_i\right)-\frac{1}{2\sigma_l{}^2}\sum_{i=1}^{n}\left(\log\left(y_i\right)-\hat{Y}_i\right)^2 \qquad \text{Equation 2}$$

where n is the number of observations, $\sigma_l{}^2$ is the variance of the log-linear distribution, y_i is the observed response variable and $\hat{Y}$ is the estimated values for the response variable from Equation 1.

The goodness of fit for the presented model is defined by R^2 value. The R^2 is a proportion value between 0 and 1, that shows how much of the total variation of the response variable is captured by the fitted model. Values near 0 indicate that the model failed to explain the variations in the response variable, on the other hand, values near 1 show that almost all the variations are captured by the fitted model. The R^2 is calculated from equation 3 where $\bar{y}$ is the average of the response variable:

$$R^2=1-\frac{\sum_{i=1}^{n}\left(y_i-\hat{Y}_i\right)^2}{\sum_{i=1}^{n}\left(y_i-\hat{Y}_i\right)^2+\sum_{i=1}^{n}\left(\bar{y}_i-\hat{Y}_i\right)^2} \qquad \text{Equation 3}$$

The predictive ability of the model is described by the *Coefficient of multiple determination*, (Q^2) and calculated from Equation 4. Q^2 is a number between 0 and 1 that shows how much of the variance of the response variable can be predicted by the model. The definition of Q^2 is very close to R^2, but in the *Coefficient of multiple determination,* the errors are calculated based on the difference of experimental results (y) and the predicted values ($\hat{P}$). In fact, in this criteria, we are interested to know how much the predicted values are different from the observations. Same as R^2, higher values show the better predictive ability of the developed model. The $R^2$and Q^2 values of the developed model are reported in Table 3.

$$Q^2 = 1 - \frac{\sum_{i=1}^{n}\left(y_i - \hat{P}_i\right)^2}{\sum_{i=1}^{n}\left(y_i - \hat{P}_i\right)^2 + \sum_{i=1}^{n}\left(\bar{y} - \hat{P}_i\right)^2} \qquad \text{Equation 4}$$

Figure 2 illustrates the observed response values against predicted response values (cohesion and friction angle) from the model. The reference red line shows the case that the model predicts the observed values without any error. In this figure, the scatters are located close to the reference line, which means the errors in predicting values are low (negligible).

In order to examine the predictive ability of the model, the flow properties of the mannitol powder conditioned for 4 days at the temperature of 40 °C and relative humidity of 90 % were evaluated by the PFT. It should be noted that, this sample is not considered in the statistical modelling development. After conditioning, the PFT reported the cohesion value of 0.36 kPa and friction angle of 35 °.The results from the statistical model gave the cohesion value of 0.347 kPa and friction angle of 35.6 °. The squared errors of these values (difference between the predicted values ($\hat{P}$) and experimental results (y)) is calculated from: $\sqrt{\left(y - \hat{P}\right)^2}$, and the percentage of this error is: 2.8 % and 1.7 % for the cohesion and friction angle, respectively. These negligible percentages show the ability of the model in predicting flow properties of mannitol stored at different environmental conditions.

The developed model regression coefficients and the p-values are summarized in Table 4 for all response variables. The presented coefficients are fitted by log likelihood maximization and explain the effects of each explanatory variable on the response variable. If the coefficient of one variable is equal to zero, means there is no evidence to show the relationship of that variable with the response variable. For instance, investigating Table 4 shows that the effect of relative humidity of conditioning unit on the bulk cohesion (coefficient value of 0.0011) is less effective than the effect on friction angle (coefficient value of 0.0472).

Generally, the coefficients are statistically significant if their p-values is less than 0.05. For cohesion, all the main variables are significant. Only temperature and conditioning duration are significant variables for internal friction angle. The coefficients of square of temperature, relative humidity and conditioning duration as well as interaction between the main variables are not significant in the fitted models. This means that by removing those from the model, the goodness of fits (0.89 for cohesion and 0.84 for friction angle) were unchanged. However, omitting these variables from the model makes it simpler which may be desirable.

The outcome of the developed model could be demonstrated by using surface response contour plots. These graphs were used to investigate the interactions between two independent variables (temperature and relative humidity in this case) at the fixed third independent variable (in this case conditioning duration) on the one of the response model (in this case $1/ff_c$). The surface response plots for $1/ff_c$ as a function of temperature and relative humidity are depicted in Figure 3. Particularly, Figure 3a is after 24 hours conditioning, Figure 3b after 48 hours conditioning and Figure 3c after 72 hours conditioning.

Such plots are particularly useful for a quality controller to help ensure that the product maintains the desired flow properties, by showing the environmental conditions that should be avoided. An increase in the lowest $1/ff_c$ number is observed by comparing Figure 3a to Figure 3c. Particularly, the lowest $1/ff_c$ number increased from 0.23 to 0.27 when conditioning duration increased from 24 hours to 72 hours. It is useful to consider the practical significance of this change; although a user would not notice a very large difference in handleability in this change of $1/ ff_c$ (because the material remains around the upper end of the “easy flowing” range), as a 20% increase in the strength of the material it is sufficient to indicate a measurable change in the powder. This is also an indication that the critical storage temperature to maintain a good level of flowability (low value of $1/ff_c$) reduced continuously as a results of increased conditioning duration.

4. Analysis

The key influence on powder flowability in the model, that the authors set out to explore, was the effect of adsorbed moisture, so for this reason the experimental work focused upon varying the humidity across a range that was known to affect the powder flow behaviour. Therefore, for the sake of reducing experimental work, the conditioning condition were set to temperature of 35 ˚C and duration time of 72 hours while the level of relative humidity was from 60% to 90%.

Flow properties of particulate material can be correlated to inter-particle forces between particles at different environmental conditions, i.e. temperature and relative humidity, by using Rumpf (Rumpf, 1970) and by Molerus (Molerus, 1975) microscale approach. In this model, the van der Waals inter-particle forces can account alternatively for either plastic or elastic contact deformation. In this research project, plastic contact deformation was assumed because of the results presented by Tomasseta et al., (Tomasetta, 2013) and Chirone et al., (Chirone et al., 2016). These two studies showed that the plastic contact deformation assumption could predict the tensile strength value of the powder stored at elevated temperature and/or relative humidity with correct order of magnitude. However, this approach is based on several assumptions:

1. Particles, only spherical and monodisperse, are randomly packed.

2. The contact area between particles are small enough compare to the particle surface, hence, contact areas can be considered as contact points.

3. The contact points between particles are uniformly distributed over particles surfaces.

4. The packing structure and the state of stress are isotropic and isostatic respectively.

5. The model assumed that $k\varepsilon \approx 3.1 \approx \pi$, where k and ε are the coordination number and bed porosity respectively.

6. The particle Sauter mean diameter (d_{sv}) is considered in equation 5. Sauter mean diameter has been widely used in Rumpf approach since it relates stress with average interparticle force values.

Rumpf proposed equation 5 which relates cohesive force (F_c) and tensile strength (σ_t) of powder by considering the above assumptions.

$$F_c = \frac{d_{sv}^2 \sigma_t \varepsilon}{(1-\varepsilon)} \qquad \text{Equation 5}$$

Where ε is the bed porosity which can be calculated from

$$\varepsilon = 1 - \left(\frac{\rho_b}{\rho_p}\right)\left(1 - \frac{M}{100}\right) \qquad \text{Equation 6}$$

where ρ_b is the powder bulk density measured by the PFT. ρ_p is particle density measured with pycnometer method. M is the fractional moisture content of the powder stored at different relative humidity, temperature and duration, calculated on a wet basis (mass of water divided by total mass of water + dry solid).

The tensile strength (σ_t) of the mannitol powder at different moisture content was calculated from the Mohr–Coulomb approach considering the linear yield locus line derived from PFT shear tester.

$$\sigma_t = \frac{c}{\tan \varphi_i} \qquad \text{Equation 7}$$

Cohesive force (F_c), equation 5, was calculated by substituting equations 6 and 7 into it.

The alternative approach used to predict the interparticle forces for comparison, was a theoretical method to predict interparticle capillary forces by combining the Kelvin equation with the Laplace-Young equation. In this model, the capillary force (Equation 8) can be predicted by considering the effect of both particle surface tension and pressure differences. The detailed description of the combination of the Kelvin and the Laplace–Young equations which was applied in this study in order to estimate the interparticle forces are described in detail by Landi et al., (Landi et al., 2012). They applied this approach to estimate the interparticle forces between glass beads particles when exposed to humid air, although they did not validate against measured interparticle forces.

$$F_c = 2\pi r_2 \sigma_s + \pi r_2^2 \sigma_s \left(\frac{1}{r_1} - \frac{1}{r_2} \right) \qquad \text{Equation 8}$$

Where σ_s is particle surface energy, r_1 and r_2 are the principal radii of the meniscus and could be calculated from equation 9 and 10 with some geometrical consideration:

$$r_1 = r_a \left[\left(1 + \frac{a}{2r_a} \right) \sec\beta - 1 \right] \qquad \text{Equation 9}$$

$$r_2 = r_a \left[\left(1 + \frac{a}{2r_a} \right) \tan\beta - \left(1 + \frac{a}{2r_a} \right) \sec\beta + 1 \right] \qquad \text{Equation 10}$$

where r_a is the particle asperity radius, α is the bridge gap and β is the half filling bridge angle (which depends on the powder moisture content, the values are provided elsewhere (Medhe and Pitchumani, 2006)). All depicted in Figure 4. Asperity radius, r_a, is considered to be 0.01 times smaller than d_{50} of the sieved particles as reported by Landi et al., (Landi et al., 2012). Hence the value of 1.25 µm was selected.

We have assumed σ_s, in Equation 8, as the solid surface energy which was calculated from the IGC method. The surface energies of the powder were measured in 0 %, 60 %, 70 % and 90 % relative humidities. The dispersive (γ^d), acid-base (γ^{ab}) and the total (γ^t) surface energies determined for mannitol at different relative humidities are provided in Figure 5 and also in Table S1, S2 and S3 in appendix. Figure 5 shows a range of surface energies of mannitol as a function of fractional surface coverage. For the sample conditioned at 0 % relative humidity and 20 °C, the γ^d varied from 42.4 mJ/m^2 to 46.6 mJ/m^2, γ^{ab} from 3.3 mJ/m^2 to 4.8 mJ/m^2 and γ^t from 45.7 mJ/m^2 to 51.4 mJ/m^2 indicating the heterogeneity of the mannitol sample. The dispersive (γ^d) surface energy of the mannitol powder increased slightly (about 10% or so) when relative humidity increased from 0 to 90 %, however the trend changed a little with the surface coverage. At high surface coverage (8 % and above) the trend was linear, but at lower surface coverages the increase happened across the range from 0% to 70% above which it tended to plateau. In contrast, the acid-base (γ^{ab}) surface energy had a different trend. The γ^{ab} of the powder changed only slightly from 0 to 60% RH then increased drastically (a factor between 2 and 3 times) between 60 and 70% above which it was fairly static but tended to drop a little at 90%. For the force calculations, the total surface energy (γ^t) of mannitol at 0.01 coverage was selected as a representative value of surface energy (at all tested relative humidities). The particular surface coverage and the surface energy value was considered for the calculation, keeping in mind that at very low coverages the surface energy data can be skewed towards predominantly the higher energy sites present on the solid surface. On the other hand, at very high coverages the contribution from the active sites to the interparticle cohesion could get diluted. The detailed description of the surface energy heterogeneity of the mannitol powder is reported by Karde et al., (Karde et al., 2020). Furthermore, one could argue that the area between particles are filled with water and hence instead of particle surface energy the water surface energy (72.8 mJ/m^2) should be considered.

The interparticle forces estimated by equation 8 is mainly a function of particle cohesive forces which in turn is a function of particle asperity radius, r_a, as well as bridge gap, α. Fairbrother and Simons (Fairbrother and Simons, 1998) reported that the larger the bridge gap volume, the lower interparticle cohesion. Landi et al., (Landi et al., 2011) did sensitivity studies to investigate the effect of bridge gap value on the cohesive forces of glass beads powder. They reported that α values larger than 0.01 μm, leads to cohesive forces of almost zero for the tested glass beads powder at relative humidity between 15% till 80%. Hence the value of α was selected 0.01 μm here.

5. Discussion

The results of the cohesive force (F_c) inferred by the Rumpf model by considering the data derived from shear tester are presented in Figure 6. Furthermore, the interparticle force predicted from the combination of Kelvin equation with the Laplace-Young equation considering particle total surface energy at different conditioning relative humidities and water surface energy are presented in Figure 6. As already discussed, both Rumpf method and the combination of the Kelvin and the Laplace–Young equations (KLY) were used to detect and predict interparticle forces. The interparticle force results calculated from the both methods are plotted in Figure 6. The interparticle force values derived from Rumpf approach are lower than the ones derived from the Laplace–Young method except for at the relative humidity of 90%. At this storage relative humidity, interparticle force predicted by Rumpf stays between the two results derived from the KLY method. The F_c values derived by Rumpf method were substantially constant between relative humidity of 60 and 70%. However, in contrast, the Rumpf F_c values increased quite significantly once the relative humidity exceeded 70%, this increase continuing up to maximum relative humidity measured of 90%. Using the KLY model with the surface energy measured at different humidties predicted an increase in interparticle force with increased humidities but not following the same pattern as detected experimentally. The change in IGC measurements and hence predicted particle forces all happened between 60 and 70% RH (around 30 % increasing force) with no change above this whereas the interparticle forces detected experimentally increased most substantially between 70% and 90% RH (about 100% increase in force). From this we can conclude clearly that the mechanisms causing increase in surface energy measurement by the IGC are not the same as the mechanisms that cause the increase in the actual measure of particle forces. Considering the mechanisms that control actual interparticle forces, it is widely understood that both the mechanical surface energy at the point of contact and surface area of contact multiply together to control this (Edmans and Sinka, 2020a, 2020b). During the measurement of flow function, stress is applied to bulk solids which deform the particles at the points of contact. By contrast, in the FD-IGC measurement there is not likely to be any particle deformation that changes the area that our measurements work on. Therefore, one possibility that should be examined is whether the increased intreparticle force measured experimentally arose due to softening of particles at high humidity leading to increased contact area rather than any change in surface energy. Other possibility for the diversion could be speculated upon, however it is clear that further investigations are required.

Many studies demonstrated that adsorbed moisture to the particle surface can lead to the development of liquid bridges which give rise to capillary forces between particles (Fitzpatrick et al., 2010; Juarez-Enriquez et al., 2017; Landi et al., 2011; Lu et al., 2018; Scoville and Peleg, 1981; Teunou and Fitzpatrick, 1999). The presence of liquid bridges can be a highly dominant factor affecting the magnitude of interparticle forces especially with fine particles (Scoville and Peleg, 1981). The used sieved mannitol powder has fine particles, hence it is considered that the interparticle forces of the powder would be mainly affected by the presence of any moisture in the area between the particles. The two different trends in the Rumpf interparticle force prediction suggest that the moisture hardly adsorbed to the particle surface at conditioning relative humidity below 80%, since the interparticle forces only increased at relative humidity above 70%. This is one of the characteristics of non-hygroscopic powder. A hygroscopicity classification of powders was proposed by Murikipudi et al. (Juarez-Enriquez et al., 2017), based on the quantity and velocity of adsorbed water by particles from storage environment at the fixed relative humidity and temperature. According to this classification, powders with high hygroscopicity can adsorb water to their particle surfaces when the relative humidity of storage condition is just 50% or even lower, such as amorphous lactose. On the other hand, non-hygroscopic powders do not adsorb water to the particle surface in storage conditions below 80%. When the moisture level is highly enough at the storage unit, water is either adsorbed onto the surface of the particles or absorbed/bounded into the surface of particles' pores.

Inspecting Figure 6 shows that the values derived from the KLY model fall reasonably close to the values inferred from the Rumpf approach based on measured flow properties, being mostly within a range of 1.5:1. This is a remarkable result bearing in mind the many simplifications used in both models, compared to the complexity of the real powder system.

The KLY approach tends to provide higher interparticle force compared to the Rumpf model. However, the most significant shortfall of the KLY model is that even though it is based on the increased moisture being adsorbed to the particle surfaces, it does not show anything like enough increase in interparticle force with increasing humidity. If the increase in particle forces indicated by the increase in powder strength ($1/ff_c$) is indeed caused by capillary forces due to increased surface moisture at higher humidity, then the KLY approach is under-estimating the capillary forces severely.

The quantitative difference between the particle forces inferred by the two different approaches should be considered. It must be understood that there are many assumptions in both models which may contribute to the quantitative difference between the results. Both KLY and Rumpf models are based upon a physical model of particle structure and contact that is very highly simplified compared to the real system. In particular, they rely on smooth spherical particles all of the same size in a structured packing, whereas the real system has particles with sizes ranging across at least 2:1, every particle a different shape, all angular, and packed together in an almost infinite variety of juxtapositions. Furthermore, the value of comparing the models is based upon a speculation that surface energy measured using the FD-IGC may have a meaningful relationship to the mechanical forces that particles experience between one and another, which has not to date been evidenced clearly. Furthermore, some KLY equations parameters are taken from literature and needs to be further investigated and confirmed.

6. Conclusion

Flow properties of mannitol powder was measured at different environmental conditions of temperature, humidity and conditioning period, similar to industrial or transport conditions, using a shear tester. No change in flow properties of mannitol was observed at relative humidity below 60% and temperature below 25 °C, but above these values the results showed adverse effects on the flow properties. A polynomial regression model has been developed to estimate the effect of different independent variables, namely temperature, relative humidity and conditioning duration on cohesion (c), internal friction angle (φ_{i}) and Flow Function (ff_{c}). The developed model showed that all independent variables significantly affecting bulk cohesion. Friction angle is mostly affected by conditioning duration and temperature, respectively. The contour plots were developed to study the effect of two independent variables (relative humidity and temperature) at the different conditioning durations on the flow properties of the mannitol powder. These graphs could potentially be used in quality control for pharmaceutical companies to avoid mannitol handling problems.

Two fundamentally different approaches were used to infer or predict the interparticle forces, and the values compared. First, these were inferred by measuring the flow properties and using the well-known Rumpf model that links interparticle forces to bulk strength based on certain simplifications regarding the structure of the powder bed. Secondly, the interparticle forces were predicted from a knowledge of particle size, surface anergy (measured using FD-IGC analysis) and moisture content, using a combination of the Kelvin and the Laplace–Young equations (KLY). The interparticle forces inferred from the bulk measurements, and those predicted from the KLY theory were compared. Both the dispersive (γ^d) and acid-base (γ^{ab}), and also the total (γ^t), surface energies were determined from the FD-IGC analysis for mannitol powder conditioning at a range of relative humidities (60 to 90 %) and fixed temperature of 35 °C. For the calculation of the interparticle forces, the total (γ^t) surface energy data was used in KLY equations and comparing it with those inferred from the Rumpf model gave an overall better agreement.

The interparticle force values derived from the two disparate approaches gave results that were remarkably close given the large number of simplifications that are inherent in the various models used, typically being within a range of about 1.5:1. Both approaches showed increase in interparticle force with humidity, however the trend were significantly different. This gives some support to the hope that it may be possible in future to construct a model that links bulk behaviour to particle surface properties, powder granulometry and environmental effects via interparticle forces, in a way that may be meaningful for formulation purposes, with suitable refinement and improvement of the models that have been employed in this study.

Generally the Rumpf approach gave lower interparticle forces compared to the results from the KLY equation. Such a deviation is not unexpected given the simplifications in the models, it is particularly interesting to note that the prediction of interparticle forces from KLY approach using surface energy of water did not show anything like enough effect of relative humidity whereas using surface energy from IGC showed some effects however still not nearly enough to predict the increase detected from the experimental measurement of powder behaviour.

There are several reasons that the authors postulate for this;

(a) The increased humidity may affect the plasticity of the particle surface and therefore the contact area between particles, which would not show up in surface energy measurements.

(b) The increased plasticity of the particles may allow a change in the packing structure, whereas the models featured constant packing structure.

The KLY approach included the assumption that all of the increased moisture due to humidity exposure is located on the surface and involved in capillary structures between particles. The fact that in spite of this assumption it still underpredicted the increase in interparticle strength, even when the surface energy was measured across the range of humidities, appears to be a clear indicator that the major influence on strength growth is much more likely to be due to the above effects than to capillary action, so a focus on particle plasticity (including how it may affect packing) as well as change in surface energy with humidity exposure is the most likely line of enquiry to yield improvement.

Readers are cautioned against using the interparticle force values presented here for any other purposes (such as for calibration of contact laws for DEM etc.) or comparison against directly measured interparticle forces (e.g. from AFM). The interparticle forces in this study being calculated from models that embody many simplifications, they should be regarded as aggregated stochastic values based specifically on the models of packing and granulometry (shape and size) used, and are intended as a link between the two modelling approaches, and not in any way representative of the real interparticle forces that occurred in the bulk.

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Nomenclature

c	cohesion, Pa
D_{10}	particle size below which 10% of the sample mass/volume falls, m
D_{50}	volume/mass median of the particle size distribution, m
D_{90}	particle size below which 90% of the sample mass/volume falls, m
d_{sv}	particle Sauter mean diameter, m
f_{c}	unconfined failure strength, Pa
F_{c}	cohesive force, N
ff_{c}	Flow Function value, -
h	conditioning durations, hr
k	coordination number, -
L	log-likelihood of the statistical model
M	fractional moisture content of samples, kg
n	number of observations
$\hat{P}$	predicted values
Q^2	coefficient of multiple determination
R^2	goodness of the fit of the statistical model
r_1 & r_2	principal radii of the meniscus, m
r_{a}	particle asperity radius, m
RH	air relative humidity, $\mathrm{kg}_{\mathrm{water}}/\mathrm{kg}_{\mathrm{air}}$

χ	coefficient for interaction between variables
x_j	explanatory variable
y	Experimental results
$\overline{y}$	average of the response variable
$\hat{Y}$	estimated response variables
y_i	observed response variable

Greek symbols

α	bridge gap, m
β	water filling angle in the bridge, deg
α'	coefficient for the main effects of explanatory variables
β'	coefficient for the square of variables
γ^d	dispersive surface energy, J m^{-2}
γ^{ab}	acid-base surface energy, J m^{-2}
γ^t	total surface energy, J m^{-2}
ε	bed porosity, -
ρ_b	bulk density, kg m^{-3}
ρ_p	particle density, kg m^{-3}
σ	normal stress, Pa
σ_1	major principal stress, Pa

σ_l^2	variance of the log-linear distribution
σ_t	tensile strength, Pa
σ_s	solid surface energy (surface tension), J m^{-2}
τ	shear stress, Pa
φ_i	friction angle, deg
φ_e	effective angle of internal friction, deg

Figure 1 Instantaneous Flow Function of the mannitol powder at room temperature and humidity.

Figure 2. Observed response Vs. predicted response values for cohesion and friction angle.

Figure 3. Surface response contour plots for $1/ff_c$ as a function of relative humidity Vs. temperature at 3 different conditioning durations, namely a) 24 hours, b) 48 hours and c) 72 hours.

Figure 4. Schematic demonstration of a capillary bridge formed between two same size particles.

Figure 5. Surface energy of mannitol powder as a function of surface coverage measured with IGC. A) Dispersive Surface Energy; B) Acid-Base Surface Energy; C) Total Surface Energy at different relative humidities and fixed temperature of 35 °C.

Figure 6. The interparticle forces calculated from both Rumpf approach (●, —); combination of Kelvin and the Laplace–Young equations by considering fixed particle total surface energy of 50.7 mj/m^{-2} measured at 20° C and Rh of 0% (▲,–); combination of Kelvin and the Laplace–Young equations by considering different total surface energy measured at different Relative humidity and fixed temperature of 35 ° C (■, —); combination of Kelvin and the Laplace–Young equations by considering water surface energy (♦, —).

Table 1. Flow properties of mannitol powder measured at laboratory conditions (temperature of 18 °C ± 2 °C and humidity range between 30% to 40%).

Table 2. Experimental conditions and results derived from the PFT shear tester.

Table 3. Coefficient of determination and Coefficient of multiple determination of the response variables.

Table 4. Effects for the scaled and cantered factors in the response model coefficients.

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