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Vapour Sorption Techniques for Particle Engineering

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BACKGROUND

Drug substances intended for drug delivery to the lungs typically require particle size reduction. High energy processes are typically utilized to produce particles smaller than 10 µm but these processes are also known to influence crystallinity, which can lead to a reduction in physical and sometimes even chemical stability. Therefore, these materials may be conditioned following micronization before further processing. Such a "deamorphization" step typically involves the treatment of the materials with an appropriate solvent that plasticizes the material and induces crystallization. While the selection of the solvent is critical, the degree of control over the deamorphization process is also very important. A treatment time that is too short may lead to incomplete crystallization of the material, while overtreatment may cause partial dissolution and agglomeration. In order to estimate the appropriate treatment time, knowledge of the crystallization kinetics may be predicted from Dynamic Vapour Sorption (DVS) studies. Changes in surface chemistry; from a heterogeneous surface property to a homogeneous and low wettability surface property would affect the variability in powder flow behavior and agglomeration which may be monitored using Inverse Gas Chromatography Surface Energy Analyser (IGC-SEA).

MATERIALS AND METHODS

A. Samples and Solvents

Salbutamol Sulphate (SS) was purchased from SigmaAldrich. Salbutamol Sulphate was chosen as a model hydrophilic drug substance. Amorphous regions were created by milling the samples using a mortar and pestle or by ball-milling.

D-mannitol was used as received (M4125 ≥98%; Sigma Aldrich). D-mannitol is a crystalline pharmaceutical excipient, commonly used in formulations for oral and chewable tablets, powder granules and moisture sensitive API's. Surface modified mannitol was prepared via a silanisation process.

B. Dynamic Vapour Sorption Experiments

Dynamic Vapour Sorption (DVS) isotherm experiments were performed on the milled drug substances to ensure amorphous regions were present. A vapour-induced crystallization can be observed in a DVS isotherm experiment by an initial increase in mass followed by a sharp decrease in mass. The decrease in mass is due to the crystalline phase having a lower vapour sorption capacity than the amorphous phase. This mass loss behaviour in an amorphous to crystalline transformation was monitored at different temperatures to determine the crystallization kinetics. Water vapor was used for the crystallization kinetics of SS.

C. Kinetic Modelling

Crystallization data was modelled using Netzsch Thermokinetics® software, (Netzsch, Selb, Germany). This software allows for visual/manual manipulation of fit parameters and then performs the least squares optimization to generate the best fit parameters.

D. Surface Energy Anaylsis

Surface energy analysis was carried out using the iGC Surface Energy Analyzer. For all experiments, about 2g of samples were packed into individual silanised glass columns. Helium was used as carrier gas and experiments were conducted at 30°C.

E. Powder Flow Test

Flow tests were conducted using FT4 Powder Rheometer (Freeman Technology, Tewkesbury, UK). All samples were first sieved at 500µm to remove any soft agglomerates. Each sample was then held in a glass jar in which it was tumbled prior to testing to put it into a homogeneous state with respect to segregation. All flow tests, including determination of dynamic, bulk and shear properties were carried out with a 23.5mm blade and a 25mm diameter vessel.

RESULTS AND DISCUSSIONS

Crystallization Kinetics by DVS

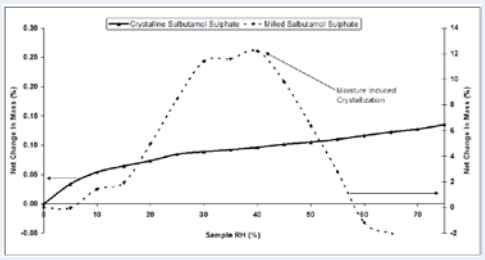
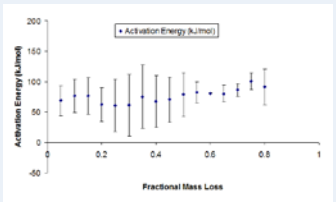


Fig. 1: Water vapor isotherms for crystalline (solid) and milled (dashed) SS at 25 ° C

Representative water vapor sorption isotherms for crystalline and milled salbutamol sulphate samples at 25 ° C are displayed in Figure 1. The crystalline sample (solid line) shows very little water uptake across the entire humidity range studied, indicating water vapor uptake is dominated by surface adsorption. Below 40% RH, the milled sample (dashed line) sorbs significantly more water vapor; high water uptake is typically indicative of bulk water absorption. Above the 40% RH step the sample begins to lose mass. The net mass loss observed in Figure 1 for the milled sample is attributed to moisture induced crystallization.



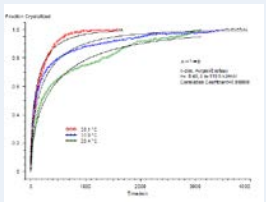


Fig. 2: (a) Friedmann analysis shows a single-step reaction mechanism. (b) Fractional crystallization of amorphous salbutamol sulphate over a range of temperatures

To model the crystallization kinetics, experiments on the milled salbutamol sulphate material were performed at three temperatures between 29 and 38 ° C at 42% RH. These conditions fell within the kinetically controlled crystallization regime between the glass transition and complete crystallization. Figure 2a illustrates the Friedmann analysis for salbutamol sulphate. The activation energy (within error margins) was found to be relatively constant, indicating that a single-step reaction is taking place which can be described by an appropriate kinetic model. The fraction of amorphous salbutamol sulphate crystallized and the resulting best-fit mechanism are displayed in Figure 2b. The best fit model (R=0.99999) was an nth order (0.5) Avrami-Erofeev mechanism with an activation energy of 119.5 kJ/mol. The Avrami-Erofeev mechanism is based on a random nucleation model. This suggests that amorphous salbutamol sulphate crystallizes with no preferential growth direction on the surface followed by growth of the nuclei.

Dispersive Surface Energy by iGC-SEA

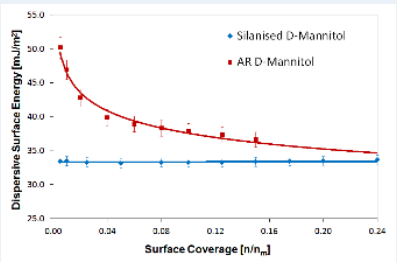


Fig. 3: Dispersive surface energy profiles

Dispersive surface energy profiles show that As Received (AR) mannitol and silanised mannitol have different values across surface coverages measured. Additionally, the AR-Mannitol exhibits a higher degree of energetic heterogeneity. There is some degree of heterogeneity, even for the crystalline sample, which could be due to different crystal facets having different surface energies [1-3]. The silanised mannitol is more energetically homogeneous.

Work of Cohesion

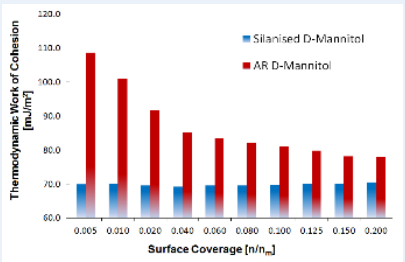


Fig. 4: Thermodynamic work of cohesion of powders

Surface Energy is directly related to the thermodynamic work of adhesion between two materials. When irreversible chemical interactions are neglected and only physical interctions are present, the total work of cohesion can be determined according to geometric mean method.

$$W_{Cohesion}^{total} = 2[(\gamma_s^D \cdot \gamma_s^D)^{1/2} + (\gamma_s^+ \cdot \gamma_s^-)^{1/2} + (\gamma_s^- \cdot \gamma_s^+)^{1/2}]$$

Figure 4 shows a higher work of cohesion for the AR D-mannitol, which is consistent with the flowability data. This is most likely due to its more active surface sites and heterogeneous surface property.

Powder Flow

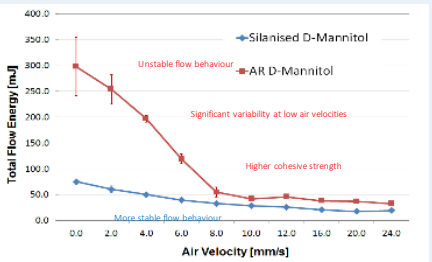


Fig. 5: Flowability energy as a function of aeration

Powder flow results indicate clear rheological differences between AR D-mannitol and silanised D-mannitol. AR D-mannitol exhibited unstable flow behavior, in particular in the aeration test, showing dramatic variability at low air velocities, as presented in Figure 4. Flowability energy of AR D-mannitol was observed here reducing from 333.0 to 50.0 mJ, before fully aerates and stabilizes at 32.4 mJ. Silanised D-mannitol however has a much lower flowability energy and aerated energy, implying a less cohesive (more free-flowing) powder property.

CONCLUSIONS

Water vapor has been shown to induce crystallization for milled salbutamol sulphate, with one-step mechanism. DVS can be used to investigate moisture-induced crystallization kinetics, over a wide range of temperature and humidity conditions.

Silanisation process has clearly improved the flow properties of D-mannitol in a low-stress environment. iGC-SEA is a fast and accurate way to predict agglomeration and powder flow behavior, using surface energy heterogeneity and work of cohesion as the parameters.

REFERENCES

[1] J.Y.Y. Heng, A. Bismark, and D.R. Williams, *AAPS PharmSciTech* **7**, Article 84 (2006).
[2] R. Ho, S.J. Hinder, J.F. Watts, S.E. Dilworth, D.R. Williams, and J.Y.Y. Heng, *Int. J. Pharm.* **387,** 79-86 (2010).
[3] R. Ho, J.Y.Y. Heng, S.E. Dilworth, and D.R. Williams, *J. Adhesion* **84**, 483-501 (2008).
[4] J.F. Gamble, M. Leane. D. Olusanmi, E. Supuk, J. Khoo and Naderi, M. International Journal of Pharmaceutics 422 238– 244 (2012).
[5] F. Thielmann, DJ Burnett and J.Y.Y Heng, *Drug Dev. Ind. Pharm*. **33**, 1240-1253 (2007).
[6] P.P. Yla-Maihaniemi, J.Y.Y. Heng, F. Thielmann and D.R. Williams, *Langmuir* **24**, 9551-9557 (2008).