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Merits and Limitations of Dynamic Vapor Sorption Studies on the Morphology and Physicochemical State of Freeze-Dried Products

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ABSTRACT

The goal of the present study was to assess the applicability of dynamic vapor sorption analysis of freeze-dried products. Water vapor sorption profiles of intact and ground cakes were recorded to determine the relevance of powder handling. Grinding prior to measurements appeared to be related with a more rapid uptake of water vapor and crystallization. Crystallization may be prevented when analyzing intact cakes. More hygroscopic materials appeared to require a longer time to achieve a constant mass. The specific surface area of different freeze-dried products was calculated from the sorption isotherms using water, organic solvents, and krypton. The specific surface areas calculated for mannitol with water and ethanol was in good agreement with krypton data. False high values were obtained from water vapor sorption of the investigated amorphous materials. The results were slightly improved by the application of vacuum. For trehalose and sucrose, no sorption and thus faulty results were detected with the studied organic solvents. The degree of crystallinity of mannitol within a binary formulation could not be determined by dynamic vapor sorption. Differences in sorption and crystallization tendencies of mannitol and sucrose that were freeze-dried separately and in a binary mixture were considered as the root cause.

Introduction

In the pharmaceutical field, dynamic vapor sorption (DVS) has been used for a variety of applications, such as screening early drug and excipient candidates, defining processing parameters, and identifying packaging and storage requirements.[1] Owing to the typically slow establishment of an equilibrium, DVS experiments are rather time-consuming.[2]

Morphologic and physicochemical properties of a freeze-dried cake relate to process and product quality attributes.[3,4] Determination of the specific surface area (SSA), as well as the degree of crystallinity, has an integral role during process development and scale-up.[3,5-7] These characteristics may greatly differ depending on excipient concentration, other components, process, and storage conditions.[8] For example, crystallization of mannitol may be reduced in case the weight ratio of mannitol relative to other amorphous solutes, such as a stabilizer or a protein, is low.[8]

Depending on the geometrical and physicochemical properties of a sample, behavior toward water vapor differs between materials.[9] Crystalline solids either adsorb vapors in small quantities (adhesion of vapor molecules to the surface) or take up larger stoichiometric quantities to form solvates.[9] The water molecules may be evenly adsorbed in a few layers at the surface of the crystalline material without causing physicochemical changes.[10] On the other hand, amorphous materials can adsorb and absorb (vapor molecules enter some bulk phase) solvent vapors in relatively large amounts.[9] Because of the slow vapor diffusion into the bulk of the solid, the absorption process is more time-consuming than surface adsorption.[1] An amorphous phase may convert to the crystalline state when sufficient molecular mobility exists (i.e., by an increase in heat or moisture).[11] Furthermore, water may be adsorbed in several layers to the surfaces of both crystalline and amorphous materials, which may lead to liquefaction.[10] Depending on the morphology (e.g., pores) and dissolution characteristics, liquefaction can occur by 2 mechanisms: capillary condensation and deliquescence.[1] By liquefaction, water-soluble ingredients may be dissolved below 100% relative humidity (RH), thereby changing the surface of a material during measurement.[12]

It is recognized that water vapor sorption behavior of an amorphous material may vary in the presence of an additive. The rate and extent of water uptake, as well as the crystallization tendency, depend on the type, proportion, and interaction of the

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constituents of a mixture of a multicomponent formulation.[13] Two mechanisms have already been described in the literature by which additives may affect the crystallization tendency of a material. First, an additive with a higher T_g increases the overall T_g of a mixture by reducing the molecular mobility in the matrix.[13] Second, increased interactions (e.g., hydrogen bonds) between the components of a multicomponent formulation restrict the availability of water-binding sites, thus resulting in decreased water vapor uptake.[14] It has been found that the crystallization tendency of sucrose was reduced in the mixture, relative to sucrose alone.[14-16] Sorption isotherms of polyvinylpyrrolidone (PVP)/sucrose co-lyophilized mixtures perfectly overlapped with the sum of the isotherms of the individual materials in the absence of sucrose crystallization.[15]

The degree of crystallinity of several active ingredients or excipients has been investigated by DVS analysis.[17,18] There are several publications on the comparison of DVS with other common techniques for the analysis of the degree of crystallinity, such as differential scanning calorimetry, X-ray powder diffraction (XRPD), and inverse gas chromatography.[2,10,19,20] A higher sensitivity to small crystallinity changes has been reported for results obtained from DVS analyses.[10,11,21] Water uptake by raffinose and freeze-dried sucrose at a certain RH was found to linearly increase with increasing amorphous content.[2,21,22] It was found to deliver very precise results for several compounds (e.g., lactose, salbutamol) by plotting the relative mass difference at a specific RH before and after water vapor–induced crystallization against the amorphous content (difference in water uptake at a defined RH).[2,17,18,23-25]

The Brunauer, Emmett, Teller (BET) multilayer adsorption model allows one to estimate the amount of adsorbate in a monolayer, V_m. With the knowledge of V_m, the SSA can be calculated according to Equations 1 and 2:[26]

$$\frac{p}{(p_0 - p)\cdot V} = \frac{1}{C\cdot V_m} + \frac{C-1}{C\cdot V_m}\cdot\frac{p}{p_0} \tag{1}$$

$$SSA = N_A\cdot\sigma\cdot V_m \tag{2}$$

where p corresponds to the absolute pressure (Pa); p_0 to the saturation pressure (Pa); V to the total amount of adsorbate (mol/g); C to the BET constant, which is related to the heat of sorption; V_m to the amount of adsorbate that forms a monolayer (mol/g); SSA to the SSA (cm^2/g); N_A to the Avogadro constant ($6.022\cdot10^{-23}$ mol^{-1}); and σ to the area of the adsorbate molecule (cm^2).[26,27] In addition to its use for gas-adsorption data, it has already been proposed to apply the equation to water vapor sorption isotherms.[28] As previously described, absorbed water can, in many cases, freely diffuse into the bulk or rearrange the surface by means of liquefaction.[29] Results based on BET analysis of water sorption isotherms have thus been shown to overestimate SSAs compared to gas-adsorption values.[27,30] The use of water may be suboptimal because it has a very low T_g (i.e., −137.15°C) and may strongly plasticize solids.[21,31,32] Other polar organic solvents may similarly lower the T_g of amorphous materials (e.g., ethanol, with a reported T_g of −175.95°C).[33,34] In contrast, nonpolar probes, such as octane or cyclohexane, do not cause plasticization and morphologic changes to some materials.[29,35,36]

In earlier studies, SSA was determined for both ground lyophilisates and raw materials.[27,28] However, relevance of the sorption behavior of intact lyophilisates has not been considered so far. Moreover, comparative data on the use of different solvents for freeze-dried cakes are not available. Previous studies on the degree of crystallinity, outlined previously, only assessed individual ingredients or excipients. The premise of determining the degree of crystallinity of a bulking agent within a multicomponent freeze-dried product by DVS has not been evaluated to date.

In the present work, applicability of DVS for the characterization of the SSA and crystallinity for lyophilisates has been evaluated. Factors affecting water vapor sorption profiles of lyophilisates were studied, such as (1) sample processing, (2) choice of the solvent, (3) the presence of other compounds, and (4) equilibration time.

Materials and Methods

Materials

Mannitol, polyvinylpyrrolidone (40,000 MW), trehalose, and sucrose were purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Ethanol, octane, and cyclohexane were a gift from Surface Measurement Systems Ltd. (London, UK). All chemicals were of analytical grade and used as supplied. Deionized water was filtered through a 0.2-μm filter and used for the preparation of all solutions. Glass vials (20R, 6R, and 2R) were purchased from Schott AG (Mainz, Germany) and Westar® RS igloo stoppers were a gift from West Pharmaceuticals (Eschweiler, Germany).

Methods

Preparation of Freeze-Dried Samples

Excipients were dissolved in water in a concentration range of 5%-10% w/v. The sample solution was filled into vials, and the vials were semistoppered and placed on the shelves in a close hexagonal packing profile. Table 1 shows the composition of the samples, vial size, and fill volume. A stainless steel tray with a stainless steel frame was used to transfer the vials into the freeze dryer. The bottom of the tray was removed prior to freeze-drying. One row of empty dummy vials surrounded the product vials and acted as a thermal barrier. Product temperature was monitored in 4 center-positioned vials per freeze-drying cycle using thin wire thermocouples (36 gauge; Omega Engineering, Newport, CT). The vials were loaded into the freeze dryer, and aluminum foil was placed on the interior side of the front door as radiation shielding.[37] The samples were freeze-dried using a VirTis AdVantage Plus (SP Scientific, Gardiner, NY). Freezing was performed as a multistep process to ensure a more homogeneous temperature distribution. The ramp rate applied during the freezing step was 1°C/min unless stated otherwise (compare, Table 1). First, the shelf inlet temperature (T_s) was lowered to 5°C and held for 30 min. Then, the shelf was cooled to −5°C and equilibrated for another 30 min. For freezing, T_s was reduced to −40°C and maintained for 2 h. Subsequently, the system was evacuated, and the shelf temperature was increased to the respective primary drying temperature at 0.5°C/min. A shelf temperature was set as stated in Table 1. A high shelf temperature of 7°C was selected for 50 mg/mL sucrose (w/v) to induce cake collapse in a subsequent freeze-drying run. For secondary drying, the shelf temperature was increased at 0.2°C/min to 40°C and held for 6 h. After completion of the cycle, the vials were stoppered under vacuum.

Dynamic Vapor Sorption

The water vapor sorption profiles were recorded using a DVS Intrinsic (Surface Measurement Systems Ltd., London, UK). A DVS Advantage 1 (Surface Measurement Systems Ltd.) was used to determine the SSA of the 4 included excipients by application of organic solvents (i.e., ethanol, octane, and cyclohexane). A DVS Vacuum (Surface Measurement Systems Ltd.) was used to