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Spray-dried amorphous isomalt and melibiose, two potential protein-stabilizing excipients

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ABSTRACT

The possibility of producing amorphous isomalt and melibiose by spray drying was studied. The impact of process parameters on yield and solid-state stability was compared to sucrose and trehalose. All powders remained amorphous during 2–3 weeks. Processing was challenging due to powder stickiness. Low-temperature and low-humidity drying processes generally performed best. Most isomalt and sucrose powder was retrieved when using 60 °C inlet temperature, 800 L/h atomizing rate, 1.4 ml/min feed rate, 15% concentration and 100% aspirator rate, giving 42–43 °C outlet temperature. Isomalt was the most problematic, because it had the lowest T_g and became sticky very easily, therefore process parameters needed to be precisely balanced. There was more freedom in designing processes for melibiose but best yields were obtained with low-temperature (50 °C inlet temperature, 800 L/h atomizing rate, 4.9 ml/min feed rate, 10% concentration and 100% aspirator, 39 °C outlet temperature). Trehalose was different in that higher temperatures resulted in better yields. Yet, trehalose generally contained the highest moisture contents. The possibility to produce amorphous isomalt and melibiose at low-temperature process conditions makes them promising considering spray drying applications for heat-sensitive proteins. Melibiose is a better candidate than isomalt because of easier processability and superior solid-state stability.

1. Introduction

Spray drying is a unit operation drying process for fast transformation of liquids to powders with controllable particle properties such as size, shape and surface composition (Paudel et al., 2013; Singh and Van den Mooter, 2016; Vehring, 2008). Particles produced by spray drying are often amorphous because of the millisecond time scale of droplet-to-particle transition, not giving molecules enough time to arrange and crystallize (Singh and Van den Mooter, 2016). The amorphous form is thermodynamically unstable and it is energetically driven towards a more stable crystalline state. Crystallization tendency is enhanced if molecular mobility in the amorphous system increases, e.g. as a result of elevated temperature or presence of plasticizers such as water (Heljo et al., 2012). Glass transition temperature (T_g) is a threshold point, above which the molecules gain highly increased mobility compared to the high-viscosity glassy state where they are below the T_g (Simperler et al., 2006). T_g is a non-equilibrium kinetic event, not a material-specific exact temperature, but it still is related to material properties and reduced by plasticizers. When amorphous materials are kept above T_g, crystallization is a likely outcome.

Disaccharides and other carbohydrates are efficient protein-stabilizing excipients in the dried state (Prestrelski et al., 1993). For optimal stability the excipient must remain in the same amorphous phase as the protein where interactions, such as hydrogen bonding between protein water-binding sites and excipient, and decreased molecular mobility in the glassy matrix can provide stabilization (Arakawa et al., 2001; Chang et al., 2005; Ohtake et al., 2011; Wang et al., 2009). Lyophilization is the most common technique for production of dried pharmaceutical protein formulations, but spray drying can be a convenient alternative especially when powders for inhalation or nasal delivery are desired (Bürki et al., 2011; Chan et al., 1997; Chen et al., 2013; Schüle et al., 2008; Sou et al., 2016; Trows and Scherließ, 2016). Spray drying has also been used in the production of other types of dosage forms, such as injection formulation (suspension) for sustained release of human growth hormone or for protein-loaded polymer implants where spray-dried particles maintain protein

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stability during hot-melt extrusion process (Kim and Kim, 2016; Rajagopal et al., 2013). There are at least two FDA- or EMA-approved spray-dried protein products on the market: Raplixa, which is a powder containing thrombin, fibrinogen and trehalose, used to control bleeding (EMA, 2015; FDA, 2015) and Afrezza, an insulin powder for inhalation (FDA, 2014). In formulation development of dried proteins, a choice for the amorphous component is commonly made between sucrose and trehalose. It is of interest to evaluate if the selection of such excipients could be broadened by new excipients that may have improved qualities such as processability or physical stability. In this work, we are investigating the value of isomalt and melibiose for spray-dried formulations.

Isomalt, also known as hydrogenated isomaltulose, is a sugar alcohol, produced from sucrose. It is a mixture of two diastereomers: gluco-mannitol (GPM) and gluco-sorbitol (GPS) (Sentko and Willibald-Ettle, 2012). Isomalt is used in food and pharmaceutical industries, in sugar-free confectionary products and coated tablets, for example. It has similar physicochemical characteristics as sucrose (Sentko and Willibald-Ettle, 2012). The characteristics depend on isomalt composition (the ratio between GPM and GPS). No Maillard reaction occurs with isomalt, making it attractive for protein formulations. There is little literature describing the spray drying of isomalt. A process where spray drying is combined with a secondary crystallization step produces crystalline isomalt agglomerates (Bayerköhler et al., 2005). Because of its non-hygroscopic nature, isomalt was used as a component in a spray-dried, high-dose L-arginine formulation with 2:2:1 (w/w) arginine:isomalt:leucine ratio (outlet temperature 70 °C) (Lakio et al., 2015). An attempt has also been made to co-spray dry isomalt with acetaminophen (1:1 w/w, inlet temperature 140 °C, outlet temperature 60 °C), but the process was not feasible using these parameters since the material was reported to accumulate in the piping and cyclone causing their complete blockage (Gonnissen et al., 2007).

Melibiose is a disaccharide with the same molecular weight as trehalose and sucrose. It has been previously shown to protect lyophilized proteins against process and storage-induced stresses (Heljo et al., 2011). A disadvantage of melibiose is that it is a reducing sugar. However, when the stability of a lyophilized monoclonal antibody formulation containing melibiose was studied, no indication of significant amounts of Maillard reaction end-products was found during three months of storage (Heljo et al., 2013). We are not aware of previous attempts to produce spray-dried amorphous melibiose.

The aim of this work was to study the possibility of spray drying two potential protein-stabilizing excipients: isomalt and melibiose. There is little published information on spray drying these two compounds and the observations of our studies can help in designing processes for them. We evaluated the impact of process parameters on the recovery of amorphous spray-dried isomalt and melibiose powders, in comparison to the process behaviour of sucrose and trehalose, two well-known protein-stabilizers. It is important that excipients intended for protein stabilization in the dry state do not crystallize during storage. Spray-dried formulations have been reported to have a higher propensity for phase separation and crystallization compared to freeze-dried formulations (Suihko et al., 2005). Thus, we also studied the solid-state stability of these powders.

2. Materials and methods

Isomalt (GalenIQ 720, BENEO-Palatinit, GPM-GPS ratio 1:1), sucrose (84097, Sigma-Aldrich), melibiose (M5500, Sigma-Aldrich) and trehalose (T9531, Sigma-Aldrich) were dissolved in purified water. Some physicochemical properties of these carbohydrates are shown in Table 1. The solutions (100 ml) were spray dried using a Büchi Mini Spray Dryer B-191 (Büchi Labortechnik, Switzerland) with standard cyclone. Feed liquids were atomized by a two-fluid spray nozzle (0.7 mm) that had a jacket for cooling water circulation. Dry nitrogen was used as the atomizing gas. The feed solutions were pumped into the nozzle through a silicone feed tube (4 × 2 mm) by a peristaltic pump. The volumetric flow rate of drying air was controlled by aspirator motor output and the flow

Table 1
Physicochemical properties of the carbohydrates.

Name	Isomalt	Sucrose	Melibiose	Trehalose
Type	Polyol A mixture of two stereoisomers gluco-sorbitol (GPS) and gluco-mannitol (GPM)	Disaccharide	Disaccharide	Disaccharide
Molecular weight (anhydrous)	344.3	342.3	342.3	342.3
Melting point	142 °C (Isomalt 1:1 GPM-GPS) 166 °C (GPS) 168 °C (GPM)f	160–186 (with decomposition)[a]	85 °C (dihydrate) 179–181 °C monohydrate[b]	97–101 (dihydrate converts to anhydrate)[a,c,d] 203–215 C (anhydrous)[a,c,d] 175[e]
Glass transition temperature	59 °C (isomalt) 55 °C (GPS) 66 °C (GPM)[f] 51–57 °C[g]	74[e] 60[h]	100[e]	119[c,e] 107[h]
Solubility in water at 20 °C	25% (w/w)[i]	1 in 0.5[a] 1 M (34% w/v)[j] 66% (w/w)[k]	50 mg/ml (5% w/v)[j] 2500 g/l (250% w/v)[l]	50 mg/ml (5% w/v)[j] 46.6% (w/w)[k]

[a] Handbook of Pharmaceutical Excipients (2009).
[b] Fletcher and Diehl (1952).
[c] Taylor and York (1998).
[d] Sussich and Cesàro (2000).
[e] Heljo et al. (2012).
[f] Cammenga and Zielasko (1996).
[g] Koskinenet al. (2016).
[h] Simperler et al. (2006).
[i] BENEO-Palatinit GmbH. Technical literature: Isomalt, galenIQ, 2007.
[j] Sigma, Product Specification Sheet.
[k] Lammertet al. (1998).
[l] Lakio et al. (2013).