Co-spray-dried mannitol with polyethylene glycol for dry powder inhalation: Factors affecting the polymorphism and stability

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Summary

We investigated the effect of process parameters and a co-spray-dried excipient on the polymorphism and stability of spray-dried mannitol. It is known that mannitol has different crystal forms. On the other hand, the spray-drying process can possibly induce change in the crystal forms. The dispersibility of dry powder inhalers (DPI) is affected by various powder properties. Recent studies have shown that different spray-dried-mannitol polymorphisms have different dispersibility. Therefore, it is valuable to investigate the effect of the process and formulation on the polymorphism of spray-dried mannitol. Co-spray drying of mannitol and polyethylene glycol (PEG) in water produced mainly α-form in contrast to spray drying of mannitol alone, which resulted in mainly β-form. Polymorphism of co-spray-dried mannitol with PEG was affected by both process parameters related to drying efficiency and formulation. Less β-form was observed with faster drying, a higher PEG to mannitol ratio and a smaller molecular weight of PEG. The polymorphic stability also depended on the PEG ratio. At 40°C/75%RH, the transformation from α-form to β-form was faster than recrystallized α-form when co-spray drying was conducted at a low PEG ratio (1%≤) while no transformation was observed with a high PEG ratio (10%). Considering the hygroscopicity of PEG, PEG could have two opposite effects, accelerating transformation and stabilizing crystal form, on the polymorphic state of co-spray-dried mannitol. Consequently, polymorphism of co-spray-dried mannitol with PEG was suggested to be controllable by process and formulation. The polymorphic stability was also regulated by the PEG ratio added to the spray-drying system.

Introduction

The aim of this study is to investigate the effect of the process parameters and the excipient which was co-spray dried with mannitol on the polymorphic state and stability of spray-dried mannitol. The polyethylene glycol (PEG) family of various molecular weights is widely used as a group of approved excipients. One of the compounds in this family, PEG 4000, was reported to change the majority of the crystal form of mannitol from β-form to α-form when it was co-spray dried with mannitol. [1] Controlling the crystal form and polymorphic stability by process and/or formulation of solution for co-spray drying is considered important as it can improve the quality control of dry powder inhalers (DPI). This will also contribute to widening the applicability of DPI to various treatments through enabling a stricter and more stable deposition through the respiratory tract. In this study, we investigated the effect of two process parameters related to drying efficiency, inlet temperature and feeding rate, on polymorphism of spray-dried mannitol. The effect of following factors in the formulation was also studied; PEG to mannitol ratio, solid content concentration of solution for spray drying and molecular weight of PEG. The stability of resultant co-spray-dried powder of different ratios of PEG to mannitol was evaluated.

Exploring the applicability of mannitol can be deemed as valuable in the pharmaceutical industry. Mannitol is one of the excipients widely used in the industry and approved for pulmonary administration.[2] It is also used as an active pharmaceutical ingredient of diagnostic medicine for asthma and is marketed in many countries.[3] Previous studies reported that mannitol had high potential as a useful excipient of DPI formulation.[4, 5] Besides its regulatory applicability which is comparable to lactose, mannitol has different features compared to lactose; it is a non-reducing sugar and has no risk of Maillard reaction with proteins or peptides, it is free from the risk of the transmissible spongiform encephalopathy and not likely to become unstable amorphous. [6] These features can provide formulators with good reasons to choose mannitol instead of lactose for their inhalation products.

Spray drying is widely used in the industry to produce powdered materials. The process has an advantage in achieving narrow particle size distributions and homogeneous morphologies. These tendencies allow the process to be suitable for powder manufacturing of DPI. Spray drying has strength in not only controlling the powder properties but also producing mixed powder particles through co-spraying of multiple compounds. It provides higher homogeneity compared to conventional physical mixing. This is attractive in the case of administration of multiple drugs to the same region, such as the currently wide-spread combination therapy of inhaled corticosteroids (ICS), long-acting muscarinic receptor antagonists (LAMA) and long-acting beta agonists (LABA). The applicability of spray drying to produce one particle containing ICS and LABA with mannitol as material for the matrix was reported. [7] Co-spray drying is also applicable to produce carrier particles of multiple compounds with different features from particles solely spray dried.

While spray drying of mannitol seems to be of practical use for the pharmaceutical industry, the process has to be developed focusing on polymorphism when polymorphic change can occur. The spray-drying process displays a high possibility of changing the crystal forms of drying materials as the materials are generally dissolved once in solvent and then solidified through drying with heat in a very short period of time. However, mannitol is widely known to have polymorphism [8] and has been reported to contain different crystal forms after spray drying with other components in the solution for drying. [1, 7, 9, and 10]

Study of co-spray drying to produce mannitol powder of different polymorphisms is considered valuable. Effects of the crystal form of mannitol on the dispersibility are not widely studied; however, this would be beneficial for wider applications of the excipient. Recent studies showed that a different aerodynamic particle size distribution was observed with the change of crystal forms[11], and particles of different aerodynamic diameters had different ratios of the α-form and β-form.[10] These findings have revealed the possible importance of crystal forms of mannitol on the performance of the DPI containing it. Spray-drying with controllability of polymorphism can be used as a tool to overcome the technical hurdle in changing only the crystal forms of powder particles while keeping other properties the same, while inhalation properties, especially dispersibility, are known to be a multidisciplinary phenomenon.

Materials and Methods

Mannitol (β-form) was purchased from Merck Co., Ltd. Ethylene glycol was purchased from Wako Pure Chemicals Industries, Ltd. PEG of different molecular weights, 200, 400 and 4000 was purchased from Wako Pure Chemicals Industries, Ltd. PEG of 20000 Da was purchased from NOF Corporation. Intact mannitol was used as the reference β-form. The reference α-form was prepared by dissolving mannitol into 70% ethanol until a clear solution was obtained. The solution was slowly cooled down to room temperature and then further cooled in the refrigerator for approximately 12 h. The received crystals were filtered and dried under a vacuum condition. Solutions for spray drying were prepared by dissolving mannitol into distilled water containing different amounts of PEG (0, 0.5, 1, 2, 5 and 10% of mannitol weight). The mannitol concentration in the solution for spray drying was 5 or 15% (w/w). All spray-drying processes were performed by using a spray dryer, GS-31 (Yamato Scientific Co., Ltd.). An X-ray powder diffraction pattern was obtained by a powder X-ray diffractometer Empyrean system (Spectris Co., Ltd., Panalytical B.V.) over the range of 5–40° of 2-θ with a CuK_α X-ray source at 45 kV and 40 mA. The moisture adsorption-desorption behaviour was observed using a VTI-SA symmetric vapor sorption instrument VTI-SA (SGA-CX) (TA instruments). Solid-state NMR spectra were acquired using AVANCE400 (Bruker Biospin) operating at 100 MHz for ^{13}C. Spectra were acquired using amplitude cross polarization (CP), magic-angle spinning (MAS) with total sideband suppression (TOSS), and high-power proton decoupling with two-pulse phase modulation (TPPM). Contact times of 1 ms were used to acquire all spectra. The MAS frequency was 5 kHz. Saturation recovery experiments were used to measure the ^1H spin-lattice relaxation time (T_1). Electron-micrographs of spray dried powder were obtained using scanning electron microscopy VE-7800 (Keyence Corporation). The specimens were mounted on a metal stub with double-sided adhesive tape and coated with gold under a vacuum prior to observation. The samples for the stability study were stored in chambers of different humidity (with silica gel for dry condition, 75% and 94%RH) at 40°C.

Results and Discussions

All the mannitol-PEG co-spray drying resulted in mainly α-form of mannitol with a difference in β-form and δ-form ratios depending on the variables both in the process parameters and formulation of the aqueous solution. However, spray drying of aqueous solution containing only mannitol produced mainly β-form with a small amount of α-form. [12, 13]

Changing the spray drying process parameters toward faster drying, i.e. a higher temperature and a slower feeding rate of solution, showed a decrease of both β-forms (Fig. 1). This conforms to previous reports on increase of the α-form with higher temperature [14] and smaller particle size. [11]

The PEG to mannitol ratio, solid content concentration of solution for spray drying and molecular weight of PEG also affected mannitol polymorphism. First, increasing the PEG to mannitol ratio decreased the β-form and increased the δ form (Fig. 2 left). With the PEG to mannitol ratio at more than 2%, β-form peaks were not detected on the PXRD pattern in all molecular weights of PEG studied. On the other hand, spray drying of mannitol with ethylene glycol produced mainly the β-form even though the ratio of ethylene glycol to mannitol was 10%. The ^1H T_1 relaxation time of the mannitol with 10% PEG4000 is longer than that of the mannitol without PEG4000; the T_1 values were 20-40 sec and 4-8 sec, respectively. These results suggested that the mannitol had lower mobility when it was spray dried with PEG. Therefore, high viscous circumstance with PEG would hinder polymorphic transformation toward the most

stable β-form during spray drying. Secondly, more β-form was produced with higher solid content concentration (Fig. 2 right). Faster solidification of the surface of the sprayed droplets with higher solid content concentration would decrease the drying rate and enhance transformation of the α-form to β-form. Lastly, co-spray drying of mannitol with PEG of smaller molecular weights (200 and 400 Da) showed less β-form compared to larger molecular weights (4,000 and 20,000 Da). Considering the PEG of larger molecular weights has higher viscosity, suppression of transformation by less molecular mobility caused by viscosity cannot thoroughly explain the mechanism. Crystallization and transformation of mannitol in water are reported to be complex [15, 16] and it is possible that PEG also affected these processes in different ways from molecular mobility suppression through viscosity.

The stability study showed that the rate of transformation from α-form to β-form was affected by the PEG to mannitol ratio. The transformation from α-form to β-form was faster than the recrystallized α-form with co-spray-dried mannitol containing a low ratio of PEG (not more than 1%), while no transformation was observed with co-spray-dried mannitol containing a high ratio of PEG (10%). At a low PEG to mannitol ratio, the rate of transformation highly depended on the humidity of the storage condition, showing high stability in a dry condition and faster transformation at higher humidity. This confirms the previous reports that transformation from α-form to β-form is a water-mediated process. [15] Higher uptake of water was observed with samples of a higher PEG ratio and hygroscopicity of PEG would enhance water adsorption by co-spray-dried powder. When the β-form was physically mixed with recrystallized α-form, acceleration of polymorphic transformation of α-form to β-form was observed. Substituting the recrystallized α-form to co-spray-dried α-form containing 10% PEG resulted in no acceleration of transformation and showed high stability of the α-form. Based on these findings of water adsorption properties and stability dependency on the PEG ratio, PEG could be expected to have two opposite effects on stability of the α-form, i.e. acceleration through water-adsorption and suppression of polymorphic transformation. The balance of these two effects could depend on the ratio of PEG.

Conclusions

Polymorphism of co-spray-dried mannitol with PEG was suggested to be controllable by process parameters related to drying efficiency and formulation. The polymorphic stability of the co-spray-dried powder depended on the PEG to mannitol ratio. Considering that co-spray drying of mannitol with PEG is a unique technique to produce mainly the α-form by a water-based system, these findings could widen the applicability of spray-dried mannitol as an excipient for DPIs.

Figures

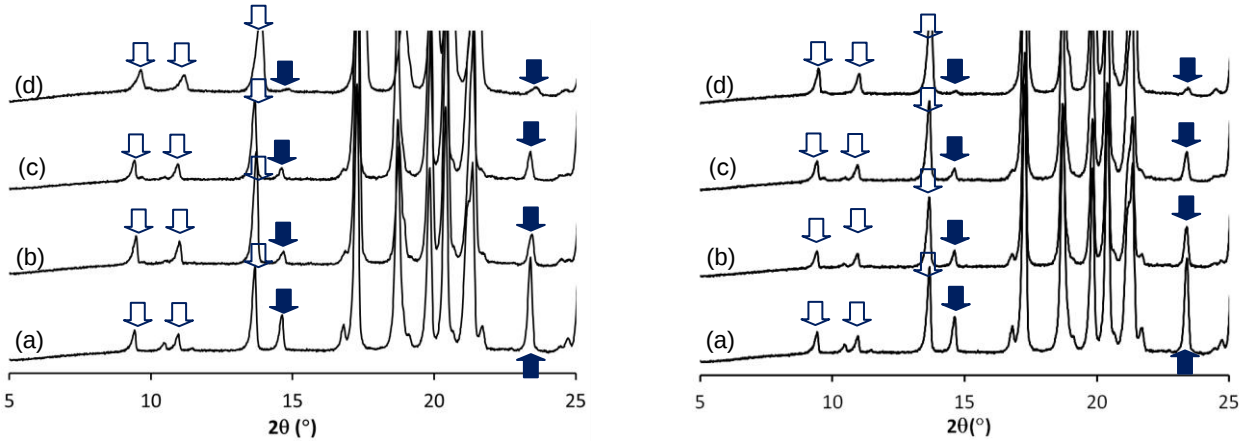

Figure 1 - Effect of process parameters of spray drying observed in X-ray powder diffraction patterns
Open arrows shows specific peaks of the α-form and closed arrows shows specific peaks of the β-form.
Left: Effect of inlet temperature on spray drying of 15% mannitol aqueous solution fed at 3 g/min; (a) contained 0.5% PEG4000 dried at 130°C, (b) contained 0.5% PEG4000 dried at 150°C, (c) contained 1.0% PEG4000 dried at 130°C and (d) contained 1.0% PEG4000 dried at 150°C
Right: Effect of feeding rate on spray drying of 15% mannitol aqueous solution dried at 130°C ; (a) contained 0.5% PEG4000 fed at 3 g/min, (b) contained 0.5% PEG4000 fed at 1.5 g/min, (c) contained 1.0% PEG4000 fed at 3 g/min and (d) contained 1.0% PEG4000 fed at 1.5 g/min

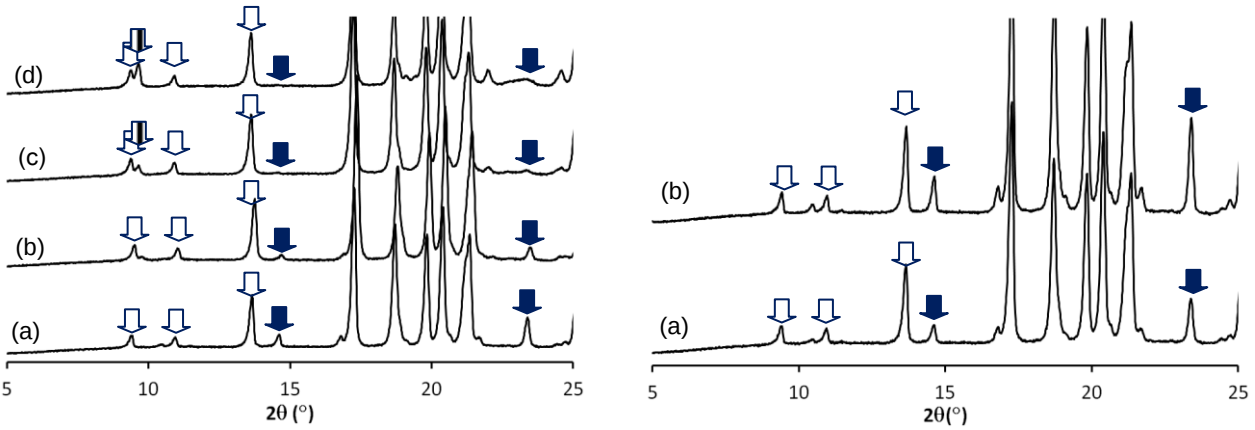

Figure 2 - Effect of formulation of aqueous solution for spray drying observed in X-ray powder diffraction patterns
Open arrows shows specific peaks of the α-form, closed arrows shows specific peaks of the β-form and striped arrows shows a specific peak for the δ-form.
Left: The effect of PEG to mannitol ratio on spray drying of 5% mannitol aqueous solution containing PEG4000 dried at 130°C and fed at 3 g/min. The PEG4000 to mannitol ratio was (a) 0.5%, (b) 1.0%, (c) 2.0% and (d) 5.0%.
Right: Effect of mannitol concentration on spray drying of mannitol aqueous solution containing PEG40000 at the ratio of 0.5% to mannitol dried at 130°C and fed at 3 g/min. Mannitol concentration was (a) 5% and (b) 15%.

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