The surface energy effect of co-spray-dried mannitol with polyethylene glycol on the aerosolization performance in a dry powder inhalation formulation

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Summary

The objective of this study is to clearly assess the surface energy effect of co-spray-dried mannitol (co-SDM) particles with polyethylene glycol (PEG) on the aerosolization performance in a dry powder inhalation (DPI) formulation. From the results of in vitro deposition studies in the model DPI formulation containing salbutamol sulphate (SS), the effect of PEG molecular weight (MW) and formulated amount of PEG in the co-SDM on the aerosolization performance was evaluated. The fine particle fraction (FPF) of SS in the formulation containing co-SDM with PEG 20000 was superior to that in the formulation containing spray-dried mannitol (SDM) without PEG. On the other hand, the FFPS of SS were found to be influenced by the PEG ratio and MW of PEG used in the formulation of co-SDM with PEG. The surface energies of co-SDMs with PEG were measured by an IGC technique. It was considered that the lower dispersive component of the surface energy of co-SDM may contribute to a higher FPF of SS when using PEG with a high MW. Moreover, the elevation of the basic (electron donor) energy might result in the decrease of FPF of SS when using PEG with low MWs. The elevation of the basic (electron donor) energy of a co-SDM would relate to both/either the difference in the adhesion force to the SS and/or the difference in the hygroscopicity of each PEG.

Introduction

In our previous research, a manufacturing method of producing novel mannitol carrier particles by co-spray drying with polyethylene glycol (PEG) was developed [1]. For evaluation of the properties of resultant co-spray-dried mannitol with PEG (co-SDM) particles as carrier particles, model dry powder inhalation (DPI) formulations were prepared. Salbutamol sulphate (SS) was used as the model drug substance, because SS is widely used as a model compound for DPI formulations [2]. The aerosolization performance of SS in the model formulations was evaluated by using an Andersen cascade impactor (ACI). From the results of in vitro deposition studies, the formulation using co-SDM with 2.5% PEG 4000 and co-SDM with 5% PEG 20000 showed a superior aerosolization performance of SS when compared to a commercial mannitol and its corresponding spray-dried mannitol without PEG (SDM) as carrier particles [3]. Therefore, employing co-SDM seemed to be more preferable for the DPI carrier particle than using the commercial mannitol alone or SDM. However, significant differences were found in the aerosolization performance of SS dependent on the molecular weight (MW) and the formulated amount of PEG in the co-SDMs.

The quality of DPI formulation, such as aerosolization performance, depends on the physical properties of not only the drug substance but also the carrier particles. For a preferable aerosolization performance of a drug, the characteristics of carrier particles must be well controlled in terms of size, shape, surface roughness, surface energy, etc [4]. In this study, we focused upon the surface adhesion force between the carrier particles and drug particles. Because there are numbers of studies focused on the surface adhesion force between the carrier particles and drug substances in DPI formulation [5, 6].

For the evaluation of the surface adhesion force, the surface energies of carrier particles were evaluated by using an inverse gas chromatography (IGC) technique. The surface energy was known to be one of the important factors in managing the adhesion forces on the particle surface [5, 6]. IGC can selectively detect the dispersive components and the specific (non-dispersive) components of the surface energies of solid materials [5, 7]. These two components are well known to indicate the polarity of the surface of measured materials. The specific interactions can be also classified as either electron donor or electron acceptor type interactions based on the acid/base approach using different polar probe gases [5-7]. In fact, IGC is widely used to evaluate the effect of the surface energy of carrier particles on the aerosolization performance of drug substances in DPI formulations [5-7]. Therefore, IGC is considered preferable for evaluating the adhesion force between carrier particles and drug substances.

The objective of this study is to clearly assess the effects of the formulation parameters (PEG molecular weight and formulated amount in the co-SDM) on the aerosolization performance. The surface energy of each carrier particle, including co-SDMs and SDMs, was evaluated. From the viewpoint of the surface energy, the relationship between the surface adhesion force and the aerosolization performance in each of the formulations was evaluated.
**Materials and Methods**

Mannitol (β-mannitol) was purchased from Merck Co., Ltd. PEG 400 and PEG 4000 were purchased from Wako Pure Chemical Industries, Ltd. PEG 20000 was purchased from NOF Corporation. Salbutamol sulphate (SS), which was used as the model drug for the *in vitro* deposition studies, was purchased from Tokyo Chemical Industry Co., Ltd. Hypromellose (HPMC) capsules (size 3) were purchased from Qualcaps Co., Ltd.

Two SDMs (SDM-1 and SDM-2) were manufactured by spray drying the mannitol aqueous solution using a spray dryer CL-8i (Ohkawara Kakohki Co., Ltd.) equipped with a rotation disk. Co-SDMs were manufactured by spray drying the mannitol aqueous solution with several amounts of each PEG (2.5, 5 and 10% to mannitol weight) using a spray dryer GS-31 (Yamato Scientific Co., Ltd.) equipped with a two-fluid nozzle.

The particle size of the mannitol carrier particles was measured with a laser diffraction particle size analyzer HELOS/RODOS system (Sympatec GmbH). In this research, the volume mean diameter (VMD) was used as the representative particle size for each sample. The shapes of carrier particles were observed by using a scanning electron microscope VE-7800 (Keyence Corporation).

The model formulations for deposition studies were prepared as follows. SS was milled by a Turbo Counter Jet Mill TJ 60 (Turbo Kogyo Co., Ltd.) for reduction of the particle size. The VMD of micronized SS was confirmed as 2.23 μm. SDMs and Co-SDMs were also sieved by 100 mesh screen to reduce the particle size difference of each carrier particle. Either sieved SDM or co-SDM and milled SS were blended at a constant ratio of mannitol to SS, 67.5:1 (w/w) by a Turbula mixer T2F (Willy A. Bachofen AG Maschinenfabrik). After blending, each formulation was manually filled into HPMC capsules with 34.25 mg ± 1.50 mg of the formulation powder.

The deposition profiles of model formulations aerosolized with a Handihaler (Boehringer Ingelheim GmbH) were assessed by an Andersen Cascade Impactor (Copley Scientific Ltd.). Ten capsules were continuously tested under a 28.3 L/min air flow condition. Fine particle dose (FPD) was defined as the sum of either SS or mannitol mass collected below stage 2, with a 50% cut-off diameter of aerodynamic particle size of 4.7 μm. The emitted dose (ED) was defined as the total mass of drug or mannitol emitted from the capsules. Fine particle fraction (FPF) was calculated as the percentage of FPD compared to ED.

Surface energy analyses were conducted using an inverse gas chromatography system (Surface Measurement Systems Ltd.) equipped with a flame ionization detector. The experiment was carried out at 303 K and 0% RH. The gas flow rate was 10 mL/min and helium gas was used as the carrier gas. Methane was used for the inert reference; n-decane, n-nonane, n-octane and n-heptane were used to determine the alkane line, and chloroform and ethyl acetate were employed as polar probes. The dispersive component of the surface energy (γ<sub>d</sub>) was calculated based on the retention volume of a series of injected n-alkanes [5, 7, 8]. The acidic (electron acceptor) energy (γ<sub>a</sub>) and the basic (electron donor) energy (γ<sub>b</sub>) were calculated based on the retention volumes of ethyl acetate and chloroform, respectively [5, 8]. The specific component of surface energy (γ<sub<s</sub>) was calculated using the acidic energy (γ<sub>a</sub>) and the basic energy (γ<sub>b</sub>) [5, 8].

**Results and Discussion**

The SDM particle sizes were 24.4 μm (SDM-1) and 47.9 μm (SDM-2). Particle sizes of all co-SDMs were ranged between 27.9 μm and 47.3 μm. As shown in Figure 1, the FPFs of SS when SDM-1 and SDM-2 were used were 13.5% and 14.1%, respectively. From the statistical evaluation, there was no significant difference in FPFs of SS between the model formulations prepared with both SDMs (p > 0.05), so that the particle size of carrier particles had little effect on the aerosolization performance of drug substance within the range of 24.4 μm to 47.9 μm in this system. The particle shape of SDMs showed smooth, spherical forms, whereas the appearances of all of the co-SDMs were irregular forms with corrugated surfaces. From a morphological approach, no significant difference was found by changing the PEG molecular weight and formulated amount.

It was found that the FPF of SS in the model formulation depended on the MW of PEG when co-SDMs were used as carrier particles (Figure 1). The FPF of SS when co-SDM with PEG 20000 was used was higher compared to that of the two cases of SDM, regardless of the PEG ratio. In contrast, the FPF of SS decreased along with the formulated amount of PEG when co-SDM with PEG 400 or with PEG 4000 was used. When co-SDM with 2.5% PEG 400 or co-SDM with 2.5% PEG 4000 was used as a carrier particle, the FPF of SS was higher compared to that when SDM was used. However, the FPF of SS displayed an extreme decrease in correlation with the increasing PEG ratio. It was found that the PEG property was important for the aerosolization performance of the model formulation.

The aerosolization performance of each carrier particle itself was also measured by ACI. On the induction port and preseparator, 85% to 95% of the loaded weights of mannitol carrier particles were detected. The FPF of mannitol was less than 1%. The deposition profiles of each carrier particle were almost exactly the same. This result showed that most of each mannitol carrier particle was captured before the preseparator. Hence, SS was indicated to separate from mannitol carrier particles when aerosolized and the SS separated from the mannitol carrier particles existed below the lower stage.
It was considered that the difference of the surface adhesion force between carrier particle and drug substance was related to the variety of the FPF of SS when co-SDM was used as a carrier particle. Therefore, the surface energy of mannitol carrier particles was measured as an influencing property affecting the adhesion by IGC. The dispersive component (γ_d) and the specific component (γ_s) of surface energy were assessed among mannitol carrier particles. It was reported that a linear inverse relationship between the dispersive component of the surface energy of carrier particles and the FPFs of the drug substance was found by using the IGC technique [9]. The γ_d of co-SDMs had a lower energy than that of SDM (Figure 2A). It was considered that the lower γ_d of a co-SDM with PEG 20000 may contribute to the higher FPF of SS (Figure 2A). But only this result of γ_d cannot explain well enough the decreasing FPF of SS when co-SDM with PEG 400 or with PEG 4000 was used. Although the γ_d of co-SDM with PEG 400 or PEG 4000 had a lower energy compared to that of SDM, the FPF of SS when the PEG ratio was 5% or 10% was lower than that when SDM was used as a carrier particle (Figure 2A). Figure 2B shows the relationship between the FPF of SS and the γ_s of each carrier particle. The γ_s of co-SDM with PEG 20000 was lower than that of SDM. In contrast, the γ_s of co-SDM with PEG 400 and with 10% PEG 4000 was higher than that of SDM. Moreover, the γ_s of co-SDM with PEG increased dependent on the increasing PEG ratio. The FPF of SS tended to decrease along with the increase of the γ_s of co-SDMs and SDMs. From these results, it was suspected that not only the γ_d of each carrier particle, but also its γ_s affected to the aerosolization performance of the DPI formulation.

Figure 1 - FPF of salbutamol sulfate in carrier-based formulations using mannitol carrier particles. (Mean ± SD, n = 3)

Figure 2 – The relationship between FPF of SS and dispersive component, γ_d (A) and specific component, γ_s (B) of surface energy of mannitol carrier particles. Data labels show PEG ratio.

The acidic (electron acceptor) energy (γ_a) and the basic (electron donor) energy (γ_b) were compared among mannitol carrier particles in order to evaluate the differences of specific energy in detail (Figure 3). The γ_a was higher than γ_b in each co-SDM with PEG 20000. In contrast, the γ_b was higher than γ_a in each co-SDM with PEG 400. Additionally, the γ_b of co-SDMs increased with increasing PEG ratio and the ratio of the γ_b compared to the γ_a (γ_b/γ_a) also increased with increasing the PEG ratio in co-SDMs with PEG 400. As shown in Figure 4, the FPF of SS decreased with the increase of γ_b in co-SDM for each PEG system. Hence, it was implied that the electron donor function affected the adhesion between the mannitol carrier particle and SS. This elevation of γ_b with increasing PEG ratio could be attributed to the hydroxyl group on the terminal of the carbon chain of PEG due to the higher hydroxyl value of PEG with lower MW [9].

There seemed to be two possible mechanisms that could explain the increased adhesion between mannitol carrier particles and SS when the γ_b increases. SS has a secondary amino group that behaves as a cation and several hydroxyl groups. These functional groups can work as electron acceptors. Consequently, it was considered that the surface regions of the carrier particles with high electron donor energy attached to the functional groups of SS that work as electron acceptors. Adhesion of water is also considered to be an important issue because PEG has high viscosity and high hygroscopicity [9]. Increasing viscosity on the carrier particle surface may occur due to the hygroscopicity of PEG. From the water absorption profile, hygroscopicity was found to be increased due to the ratio of PEG in the co-SDM [10]. The elevation of the basic (electron donor) energy with the increasing PEG ratio may also imply an increasing hygroscopicity. It is anticipated that the altering of the surface adhesion force of carrier particles induced based on these expected mechanisms will result in a variety of
FPFs for the drug substance. The details of this mechanism that alters the aerosolization performance of SS will be clarified in our future work.

Conclusion

The FPF of SS in the formulation containing co-SDM with PEG 20000 was superior to that in the formulation containing SDM. It was considered that the lower dispersive component of the surface energy of co-SDM may contribute to the higher FPF of SS when using PEG with a high MW. On the other hand, the FPFs of SS were found to be influenced by the formulation of the co-SDM, such as the ratio and molecular weight. It was considered that the elevation of the basic (electron donor) energy resulted in the decrease of FPF of SS when using PEG with low MWs. The elevation of the basic (electron donor) energy of a co-SDM would relate to both/either the difference in the adhesion force to the SS and/or the difference in the hygroscopicity of each PEG.

References