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# Feasibility of highly branched cyclic dextrin as an excipient matrix in dry powder inhalers

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ABSTRACT

We investigated the feasibility of highly branched cyclic dextrin (HBCD) as an excipient matrix in dry powder inhalers (DPIs). The fine particles of HBCD and HBCD/active pharmaceutical ingredients (APIs) were prepared by spray-drying an ethanol-aqueous solution containing HBCD. The particle size of spray-dried HBCD itself was approximately 3.0 μm with a wrinkled shape. Solid-state fluorescence emission spectroscopy of 1-naphthoic acid (1-NPA) showed that it was dispersed in a molecular dispersion/solid solution, if the model compound of 1-NPA was spray-dried with HBCD. Powder X-ray diffraction and differential scanning calorimetry indicate that 1-NPA was in the amorphous state after spray-drying with HBCD, which is confirmed by the fluorescence measurements, 1-NPA could be incorporated into HBCD. When the antimycobacterial agent, rifampicin, was spray-dried with HBCD for the purpose of pulmonary administration, the emitted dose and fine-particle fraction of the spray-dried particles of rifampicin with HBCD were 95.7 ± 1.7% and 39.5 ± 5.7%, respectively. The results indicated that HBCD possessed a high potential as an excipient in DPIs, not only by molecular association of API molecules with HBCD, but also by that of API fine crystals.



## 1. Introduction

Inhalation formulations have been recently developed as an attractive alternative to oral and parenteral formulations for directly administering poorly water-soluble drugs to the lungs or delivering asthma drugs to the local bronchi (Weers et al., 2007; Sou et al., 2013; Stegemann et al., 2013). There could be several advantages to this route by avoiding first-pass metabolism and potentially enabling prompt onset depending on the physicochemical properties of the drug (Ong et al., 2011). There are three main pulmonary drug delivery systems: nebulizers, metered-dose inhalers, and dry powder inhalers (DPIs). In pulmonary drug delivery, DPI formulations offer easy use, more convenient portability, and lower costs than other formulations. To create the DPI formulations, either interactive mixtures of micron-sized drugs (<5 μm) that adhere to larger carrier particles like lactose, or drug-only agglomerates has been developed. Most of the DPI products have been developed as carrier-based formulations. Then, lactose has been commonly used as an excipient for DPI formulations. The presence of a carrier has aimed to overcome poor flowability and poor dispersibility of drugs. The carrier-based formulations depend on the lactose quality, lactose source, particle size, and particle-size distribution. In addition, a typical drug-to-carrier ratio is 1:67.5 (Larhrib et al., 1999; Zeng et al., 2000a, 2000b). To decrease the amount of carrier, other formulations for DPI have been developed. Furthermore, the excipients in any formulation have to be safe for use in humans. The development of carrier-free DPI formulations has the potential to overcome issues related to carriers including lactose as a critical component of the formulation, because blend uniformity is a critical issue for carrier-based formulations (Healy et al., 2014). Moreover, drug agglomerates have been used as one of the DPI formulations. However, the aerosolization of drug agglomerates highly depends on the API characteristics and performance of DPI device. Recently, carrier-free DPI formulations have been developed. Carrier-free DPI formulations contain soft aggregation, coated particles, spray-dried particles, and so on. Furthermore, other alternative particle-engineering approaches have been devised, such as the production of composite particles where API is embedded in an excipient. The currently-approved excipients for pulmonary formulations have been limited to a few sugars, hydrophobic additives, and lipids that naturally occur in the lungs and are used in surfactants (Pilcer and Amighi, 2010). Lipids such as dipalmitoylphosphatidylcholine, phosphatidylcholines, phosphatidylglycerol, phosphatidylinositol, and phosphatidylethanolamine are typical examples of surfactants present in the lungs (Possmayer et al., 2001). In addition, several amino acids, including glycine, alanines, and leucine, have been tried as excipients for pulmonary formulations because the addition of several amino acids has been shown to improve aerodynamic properties (Seville et al., 2007; Porta et al., 2011). In addition to lipids and amino acids, many sugars, such as

*Abbreviations:* API, active pharmaceutical ingredient; DPI, dry powder inhaler; DSC, differential scanning calorimetry; ED, emitted dose; FPD, fine-particle dose; FPF, fine-particle fraction; HBCD, highly branched cyclic dextrin; HPLC, high-performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; HPβCD, hydroxypropyl-β-cyclodextrin; NPA, naphthoic acid; PM, physical mixture; PXRD, powder X-ray diffraction; SDP, spray-dried particle; SEM, scanning electron microscopy.

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lactose, mannitol, glucose monohydrate, trehalose, dextrose, maltose, and dextrins, have been tested as candidate carriers in DPI formulations (Zeng et al., 1999, 2000a, 2000b; Tee et al., 2000; Li et al., 2014). As mentioned above, lactose is the most popular excipient for DPIs, and its safety, quality, and stability have been established. Pilcer and Amighi (2010) listed the sources of commercially available inhalation grade lactose for use in marketed DPIs. According to their report, most DPI products have relied on lactose as an excipient. In recent days, sugars other than lactose have been tested in feasibility studies, and it is expected that some of these sugars will be approved as excipients in pulmonary formulations (Matilainen et al., 2008; Kaialy et al., 2014; Amaro et al., 2015). To enhance the efficiency of pulmonary delivery, additional strategies based on the use of new excipients in DPIs are required. Our group took particular note of highly branched cyclic dextrin (HBCD), which is safe in humans and has been used as a food additive, as a new additive agent in DPIs (Takata et al., 1996a, 1996b; Takii et al., 2004). HBCD, which has a helical structure, was launched in the market as a food ingredient approximately several decades ago. HBCD is a new type of dextrin that is produced from waxy corn starch by the cyclization reaction of a branching enzyme tranferase previously reported by Fujii et al. (2003). This dextrin is highly soluble in water and has a relatively low propensity for retrogradation. A branching enzyme is involved in the formation of branch linkages (α-1, 6 linkages) of starch and glycogen, and the prospected structure of HBCD is composed of either a helical structure or cyclic cluster. Cyclodextrin, which is cyclic oligosaccharides consisting of six to eight glucose units linked by α-1, 4-glycosidic linkage, is sharply different from this HBCD. The molecular structure of cyclodextrin approximates a truncated cone with a hydrophilic exterior surface and a nonpolar interior cavity (Makhlof et al., 2008), where cyclodextrin with cyclic structure is essential for its chemical interaction with molecules, as well as for its functionality in enhancing the aqueous solubility of water-insoluble compounds. On the other hand, HBCD is a new type of dextrin that is produced from waxy cornstarch via the cyclization reaction of a branching enzyme transferase. HBCD has been considered to be a type of hydrodynamic aggregation structure with a diameter of several tens of nanometers in aqueous solution, as in many glycosylated food additives (Takii et al., 1999). HBCD could enhance the solubility or absorption of drugs by composite structure. Therefore, HBCD might embed the drug in aggregated structures irrespective of the hydrophobic and hydrophilic nature reported in our previous paper (Kadota et al., 2015).

In the present study, the feasibility of HBCD as an excipient matrix in DPIs was tested. We used fluorescence spectroscopy to investigate the incorporation of organic compounds into the helicalor net-like structure of HBCD, and 1-naphthoic acid (1-NPA) was selected as a model fluorescence compound to study its molecular state on HBCD (Lai et al., 2006; Tozuka et al., 2009). The changes in the molecular state of 1-NPA were investigated by powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC). A spray-dried powder of rifampicin, which is a first-line antibiotic for tuberculosis, with HBCD was prepared to investigate HBCD as an excipient in DPIs. The prepared particles of rifampicin with HBCD were characterized in the terms of aerodynamic properties.

## 2. Materials and methods

### 2.1. Materials

1-NPA and HBCD were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Rifampicin was supplied by Kaken Pharmaceutical Co., Ltd. (Tokyo, Japan). The average molecular weight of HBCD is 400,000 and has a narrow molecular weight distribution, whereas most commercial dextrins have a broad molecular weight distribution (Fujii et al., 2003). InhaLac®, α-lactose monohydrate (lactose), was provided by Meggle Co. Ltd. (Tokyo, Japan). All other chemicals and solvents were of reagent grade.

### 2.2. Preparation of particles via spray-drying

The particles of 1-NPA or rifampicin mixed with HBCD were prepared by spray-drying. Anethanolic 1-NPA or rifampicin solution was slowly added to an aqueous HBCD solution using a peristaltic pump (MP-2000; Eyela, Tokyo, Japan) at a flow-rate of 2.0 ml/min at room temperature. The ratio of ethanol to water was varied at a total constant volume of 300 ml. For the preparation of spray-dried particles (SDPs), 100 mg of 1-NPA or 200 mg of rifampicin and 1000 mg of HBCD were completely dissolved in an ethanol (99.5%) and water solution. The loading ratio of 1-NPA or rifampicin to HBCD was set at 1:10 or 1:5 as the weight volume, respectively. This solution was fed into a Büchi Mini Spray Dryer B-290 (Nihon Büchi K.K., Tokyo, Japan). The solutions were pumped into the drying chamber at a rate of 5.5 ml/min and atomized through a two-fluid external-mixing 0.5-mm nozzle using compressed air. The inlet and outlet temperatures of the drying chamber were maintained at 130 °C and 80 °C, respectively. The powders were collected and dried in a desiccator containing blue silica gel under reduced pressure before evaluating the physiochemical properties. The content uniformity for SDP samples was within 85–115%.

### 2.3. Preparation of evaporated particles

For the preparation of recrystallized 1-NPA powders by evaporation, 300 mg of 1-NPA crystals was dissolved in 300 ml of ethanol in a round-bottom flask. The ethanol and water were removed by rotary evaporation (Rotavapor R-3; Nihon Büchi K.K) to obtain evaporated 1-NPA particles under reduced pressure at 50 °C.

### 2.4. Preparation of carrier-based formulations

To compare SDPs of rifampicin with HBCD to carrier-based formulation, the micronized rifampicin was pulverized using a planetary mill (Pulverisette 6; Fritsch GmbH, Idar-Oberstein, Germany) at room temperature. A mixture of rifampicin with zirconia balls was performed in a 12-ml zirconia jar. The pulverization was performed using 3 zirconia balls with diameters of 1.0 mm. The revolution speed of the jar 500 (rpm) and the pulverizing time 60 (min) were selected in this study. The pulverizing process was stopped every 10 min to cool the jar for 10 min to prevent an excessive increase in temperature during the pulverizing process (Shimono et al., 2015). The pulverized samples were stored at room temperature with silica gel until further analysis. As mentioned in the introduction, blend uniformity is a critical issue for carrier-based formulations. The carrier-based formulations were prepared by blending lactose and rifampicin at a weight ratio of 10/1 using vortex mixture for 10 min. The content uniformity of used carrier-based formulations was within 70–130% at triplicated experiments.

### 2.5. Particle size distribution analyzed by dynamic light scattering

The particle size distribution of HBCD in the suspension before spray-drying was investigated. Its particle size distribution as a function of the ethanol ratio was measured at 25 °C via DLS using a Microtrac UPA (MicrotracBEL, Corp., Osaka, Japan) without dilution. The detection range of the UPA instrument was 0.003–6 μm. The measurement time was fixed to approximately 30 s, although the particle size distribution was nearly independent of the measurement time under this condition.

### 2.6. Scanning electron microscopy

The particle morphology of the samples was observed by SEM (VE-7800; Keyence Corporation, Osaka, Japan). The samples were sputter-coated with gold before observation using sputtering equipment (E-1045; Hitachi High-Technologies Corporation, Tokyo, Japan). All samples were observed at an operating voltage of 2–4 kV.