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Preparation of composite particles of hydrophilic or hydrophobic drugs with highly branched cyclic dextrin via spray drying for dry powder inhalers

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ABSTRACT

This study aimed to investigate the feasibility of using highly branched cyclic dextrin (HBCD) as an additive agent for dry powder inhalers (DPIs) because the currently approved excipients for pulmonary administration are limited in number. HBCD has a specific assembled structure of 20 to 30 nm in aqueous solution, and the aggregation size of HBCD gradually increased with ethanol concentrations of up to 35% in an ethanol–water solution. This aggregation of HBCD in mixed solution may have considerable potential for application as a new additive agent for DPIs. This aggregation of HBCD with a hydrophilic or hydrophobic drug in a mixed solution was investigated. Thereafter, spray-dried particles (SDPs) of theophylline/HBCD exhibited a halo pattern in X-ray diffraction, indicating that theophylline existed in an amorphous state or fine crystals. The results for each yield and drug content suggested that the mechanism of particle generation also differed between hydrophilic and hydrophobic drugs with HBCD during spray drying. Nevertheless, the average particle size of the SDPs of theophylline/HBCD or clotrimazole/HBCD prepared at any ethanol concentration was below 7 μm, suggesting that HBCD may be a carrier for DPIs. The average particle size of composite particles spray-dried at 35% ethanol was the smallest, measuring below 5 μm. HBCD may be a potential carrier for DPIs.

1. Introduction

Pulmonary delivery can directly administer drugs for treating local and systemic disorders. Treating lungs with antifungal drugs has certain advantages, such as a decreased therapeutic dose, the emergency control of resistant strains and the reduction of side effects throughout the body compared with traditional injection and oral administration [1,2]. Pulmonary delivery is a promising new pharmaceutical approach. Tobramycin and aztreonam have been approved for use as an inhalation formulation, and both inhalations have been administrated in nebulized form [3]. However, the portability and administration time of the conventional nebulizer formulation are inconvenient. Poor drug delivery remains the key issue for nebulizer formulation [4,5]. Dry powder inhalers (DPIs) have attracted attention as an alternative to nebulizer formulation over the years. Specifically, combined administration with antifungal drugs may enhance the effectiveness of treatment. Many recent studies that combined administration with antifungal drugs reported a synergistic effect on various diseases [6–8]. The low-dose usage of combined administration is expected to improve the therapeutic efficacy and high-dose usage while reducing the frequency of side effects.

Various methods have been utilized to produce fine composite particles for DPI formulations. Dry milling is often used to produce DPI formulations [9]. Recently, supercritical fluid technology has been used to manufacture fine particles of medicinal substances via a build-up process [10]. Spray drying is a one-step process that converts a liquid feed into a dried particle [11,12]. The liquid feed can be a solution or a suspension, which is first atomized to a spray that is placed in thermal contact with hot air, resulting in the rapid evaporation of the droplets. Various particles can be continuously produced from liquid using this process. The principal advantages of spray drying in regard to pulmonary formulation are the ability to manipulate and control various parameters, such as the solvent composition, solute concentration, temperature, size of the nozzle, and spray pressure [13]. Spray drying has been used in pharmaceutical processes to prepare DPIs [14,15]. Pilcer et al. [16] used spray drying to produce porous inhalation nanoparticles that contained tobramycin drugs surrounded by a matrix composed of amorphous clarithromycin. They succeeded in producing composite particles with an increased fine particle fraction. However, the currently approved excipients for pulmonary administration are limited in number [17] because the Food and Drug Administration (FDA) favors the

Abbreviations: CD, cyclodextrin; DLS, dynamic light scattering; DPIs, dry powder inhalers; FDA, Food and Drug Administration; GRAS, generally recognized as safe; HBCD, highly branched cyclic dextrin; HPLC, high performance liquid chromatography; PXRD, powder X-ray diffraction; SEM, scanning electron microscopy; SDPs, spray-dried particles.

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use of commercially established excipients as well as "generally recognized as safe" (GRAS) substances [18]. Despite the lack of regulatory guidance on pulmonary administration, the development of new excipients has been expanding in recent years. Lipids have been developed as safe excipients in the inhalation field because the surfactant present in the lungs consists of 90% lipids by weight [19]. Cyclodextrin (CD) has been shown to provide many benefits in pulmonary drug delivery, such as improvements in aqueous solubility and stability [20,21]. CD comprises cyclic oligosaccharides consisting of six to eight glucose units linked by α-1, 4-glycosidic linkage; moreover, the molecular structure of CD approximates a truncated cone with a hydrophilic exterior surface and a non-polar interior cavity [22], where CD with a cyclic structure is essential for its chemical interaction with molecules and for its functionality in enhancing the aqueous solubility of water-insoluble compounds.

To enhance the further efficiency of pulmonary delivery, a particle design based on the new concept and development of excipients for DPIs has been required. We focused our attention on highly branched cyclic dextrin (HBCD) as a new additive agent for DPIs, which have been used as a food excipient based on its safety to humans. HBCD was launched on the market as a food material with the trade name of cluster dextrin approximately ten years ago and has a molecular weight ranging from 30,000 to 1,000,000 [23,24]. The structure of HBCD is composed of the helix structure [25]. In marked contrast with CD, HBCD is a new type of dextrin that is produced from waxy cornstarch via the cyclization reaction of a branching enzyme transferase [26,27]. HBCD may play a role in seeding for the nucleation of active pharmaceutical ingredients in the solution because HBCD is considered a type of aggregation structure in solution, as trans-glycosylated food additives have been reported in our previous papers [28–31]. To apply composite particles of HBCD containing drugs as an inhalation formulation, we must understand the crystallization mechanism from solution and particle formation during spray drying for HBCD and hydrophilic or hydrophobic drugs.

The aim of the present study was to examine the feasibility of HBCD as a DPI excipient. Composite particles of a hydrophilic or hydrophobic drug with HBCD for DPIs were produced by spray drying. The crystallization of HBCD in solution or composite formation between drugs and HBCD was measured via dynamic light scattering. The particle properties, such as the average particle size, morphology and crystal forms, were evaluated to determine the relationship between aggregation structures in mixed solutions and the particle properties. The different mechanisms of particle formation between hydrophilic or hydrophobic drugs and HBCD were predicted based on the yields and drug contents of composite particles.

2. Materials and methods

2.1. Materials

Theophylline was purchased from Nacalai Tesque (Kyoto, Japan). Clotrimazole was purchased from Wako Chemical Co., Ltd. (Osaka, Japan). The chemical structures of theophylline and clotrimazole used in this study are presented in Fig. 1. Highly branched cyclic dextrin (HBCD) was supplied by Ezaki Glico (Osaka, Japan) (Fig. 2). All other chemicals and solvents were of reagent grade.

2.2. Preparation of composite particles via spray drying

The spray-dried particles (SDPs) of drugs with HBCD were prepared using the spray drying method. The preparation of the suspension before spray drying differs between hydrophilic and hydrophobic drugs. A hydrophilic drug (theophylline) was dissolved in distilled water, and a hydrophobic drug (clotrimazole) was dissolved in ethanol under magnetic stirring (400 rpm). To prepare the composite particles of theophylline with HBCD by spray drying, theophylline and HBCD were

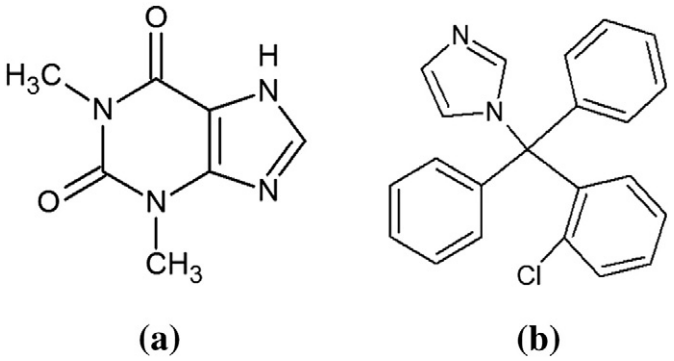

Fig. 1. Chemical structures of (a) theophylline (TH) and (b) clotrimazole (CLO).

dissolved in distilled water. Shortly thereafter, ethanol was added to the solution of dissolved theophylline and HBCD at rate of 2 mL/min using a pump (MP-2000, Eyela, Tokyo, Japan) at room temperature. In addition, HBCD was dissolved in distilled water before clotrimazole dissolved in an ethanol solution was added at rate of 2 mL/min using a pump. Both solutions of varying ethanol ratios were prepared at a total constant volume of 300 mL, and the loading rate of drugs/HBCD was fixed at 1/5 as a ratio of the weight volume. This suspension was fed to a spray dryer (B-290, Nihon Büchi K.K., Tokyo, Japan) at a rate of 5.5 mL/min. The inlet and outlet temperatures of the drying chamber were maintained at 130 °C and 80 °C, respectively. Air or N_2 gas under flow rate of 10 L/min was used for drying below or above 30% ethanol concentration, respectively. All SDPs were dried in a desiccator with blue silica gel under reduced pressure for 1 day before testing their physiochemical properties.

2.3. Particle size analysis of the suspensions

The particle size distribution of the suspensions as a function of the ratio of ethanol was measured at 25 °C via dynamic light scattering (DLS) using a Microtrac UPA (Nikkiso, Osaka, Japan). The detection rage of UPA was 0.003–6 μm. The measure time was fixed almost within 30 s. The particle size in the suspension was evaluated without dilution because this apparatus can be appropriate for the high concentration range.

2.4. Drug content in the suspension after filtration

The drug content of the suspension as a function of the ratio of ethanol was measured by high performance liquid chromatography (HPLC) (SPD-10A, Shimadzu Co., Ltd., Kyoto, Japan). The suspension

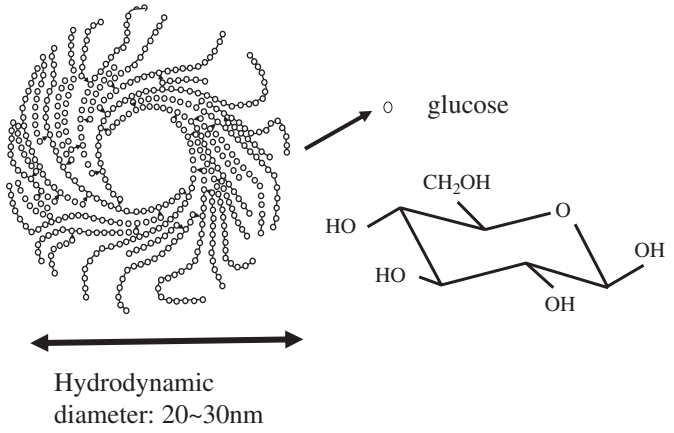

Fig. 2. A schematic representation of the HBCD structure.