The use of cyclodextrins in formulations for lung delivery

Cyclodextrins can solubilize poorly-soluble molecules for delivery in solution inhalers

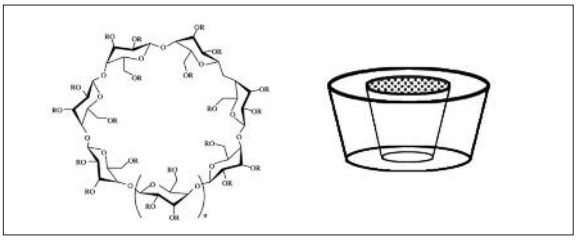
Helena Maria Cabral Marques

An overview of cyclodextrins

Cyclodextrins (CyDs) are water-soluble, non-reducing, macrocycle carbohydrate polymers constructed from α-(1-4)-linked D-glucopyranose units, in a ring formation[1,2] forming a toroidal, hollow, truncated cone structure (Figure 1). The most common CyDs are the α-(alpha), β-(beta) and γ-(gamma) CyDs formed by six, seven, and eight glucose units. Numerous CyD derivatives have been synthesized with the goal of identifying derivatives with improved safety and drug-complexation properties.

Figure 1

Cyclodextrins top and side view (α-, β- and γ- when n = 0, 1 and 2 respectively and R = H).



The most important property of CyDs is their ability to solubilize poorly water-soluble molecules and potentially alter release pharmacokinetics and bioavailability. The interior of the torus is a "hydrophobic cavity" that is able to form soluble, reversible inclusion complexes with water-insoluble compounds, resulting in compound solubilization.[3] The essential criterion is simply that the enclosed molecule or "guest" (or a portion of it) have a geometrical fitting, stereochemistry and polarity to fit into the cavity formed by the CyD or "host" molecule.[4,5] Several factors may influence inclusion complex formation, such as the type of CyD, cavity size, pH and ionization state, temperature and method of preparation.[6] The more stable a complex, the slower the initial release and consequently, the longer the time required for complete drug release. The drug release rate can be modified by combining both hydrophilic and hydrophobic β-CyD complexes into the drug product.

Worldwide, there are several commercial pharmaceuticals with CyD-based formulations for parenteral use: γ-CyD, hydroxypropylated-β-CyD and sulphobutylether-β-CyD,[7] but as far as it is known there aren't yet any approved for inhalation delivery to treat diseases of the lung. To improve treatment of lung disease, CyDs can be used to solubilize poorly-soluble molecules for delivery in solution inhalers. Alternatively, these solutions can be spray dried to create particles for inhalation in dry powder inhalers (DPIs).[8-12] In addition, CyDs may have the advantage of protecting labile molecules, such as proteins, from degradation. However, the safety of CyD for inhalation would have to be demonstrated.

A case study with salbutamol

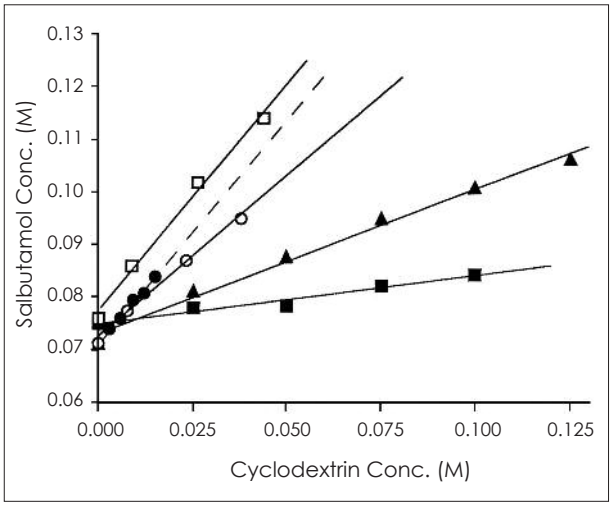
Selective β_2-agonists, of which salbutamol is an example, have been used for the symptomatic relief of attacks of acute asthma. However, although the onset of bronchodilatation is very rapid, the duration of action is short, so that multiple daily doses are often required. Prolongation of the duration of action of these short-acting β_2-agonists may provide improvement over the longer-acting β_2-agonists, like salmeterol, which are coming under increased scrutiny by regulators due to safety concerns.[13] The possibility of complexing salbutamol with a variety of cyclodextrins (CyDs), namely α-, β-, γ-, dimethyl (DM)-β- and hydroxypropyl (HP)-β-CyDs in order to extend the duration of action of salbutamol was studied.[14-22]

Phase solubility studies have shown that β-CyD and its derivatives presented the highest equilibrium constants,

meaning stronger interaction of CyD to salbutamol (Figure 2). Salbutamol solubility varied with the type of CyD used (HP-β- > Me-β- > β-≫ γ- > α-CyD).[14,15] As salbutamol is water soluble and yields an A_L type diagram,[23] the solid complex was prepared by both freeze drying (lyophilization) and spray drying techniques. Complexes of salbutamol and CyD in 1:1, 1:2 and 2:1 molar ratios were prepared by dissolving appropriate amounts of both constituents in water. Physical mixtures of both components in their respective proportions were also prepared as a control.

Figure 2

Phase solubility diagrams for salbutamol with α- (black square), β- (black circle), γ- (black triangle), DM-β-CyD (open circle) and HP-β-CyD (open square) at 37 °C. Each data point is the mean of duplicate samples (± < 5%) except for β-CyD which is the mean of three determinations (SEM < 0.0015).



Complex formation was verified by a cohort of physical techniques including differential scanning calorimetry (DSC)[14,21] and nuclear magnetic resonance (NMR).[16] When guest molecules are incorporated in the CyD cavity, their melting, boiling or sublimation points usually shift to a different temperature or disappear within the temperature range where the CyD is decomposed. The thermograms in Figure 3 show an endothermic peak for the freeze dried and spray dried salbutamol and for the physical mixture (salbutamol and β-CyD both freeze dried and spray dried) but this peak was eliminated when inclusion complexes were present.

The ability of a guest molecule to penetrate the CyD host is determined by its size, stereochemistry and polarity. Intermolecular interactions such as hydrophobic interactions, van der Waals forces, hydrogen bonding and other physical forces are involved in the inclusion complexation process. Proton-NMR was employed to assess the mode of inclusion of salbutamol within the β-CyD cavity. If inclusion does occur, protons located within or near the CyD cavity should be strongly shielded. The spectra showed upfield shifts of the CyD protons in the presence of salbutamol and the salbutamol protons shifted downfield in the presence of β-CyD. The downfield shifts of the aromatic protons were greater than those of the aliphatic protons, suggesting that the aromatic ring of salbutamol interacts more strongly with the β-CyD. The interior protons of the CyD molecule were shielded as a result of the anisotropy of the guest aromatic moiety. The highest shifts of β-CyD protons occurred for a molar ratio of 1:1 (salbutamol:β-CyD), indicating the most probable stoichiometry of the complex.

Complex formation was also corroborated theoretically by computer molecular modeling simulation: Molecular graphical computation showed that the minimum van der Waals energy positioning of salbutamol relative to β-CyD occurs when the aromatic ring of salbutamol penetrates the cavity leaving the aliphatic chain externalized (Figure 4).

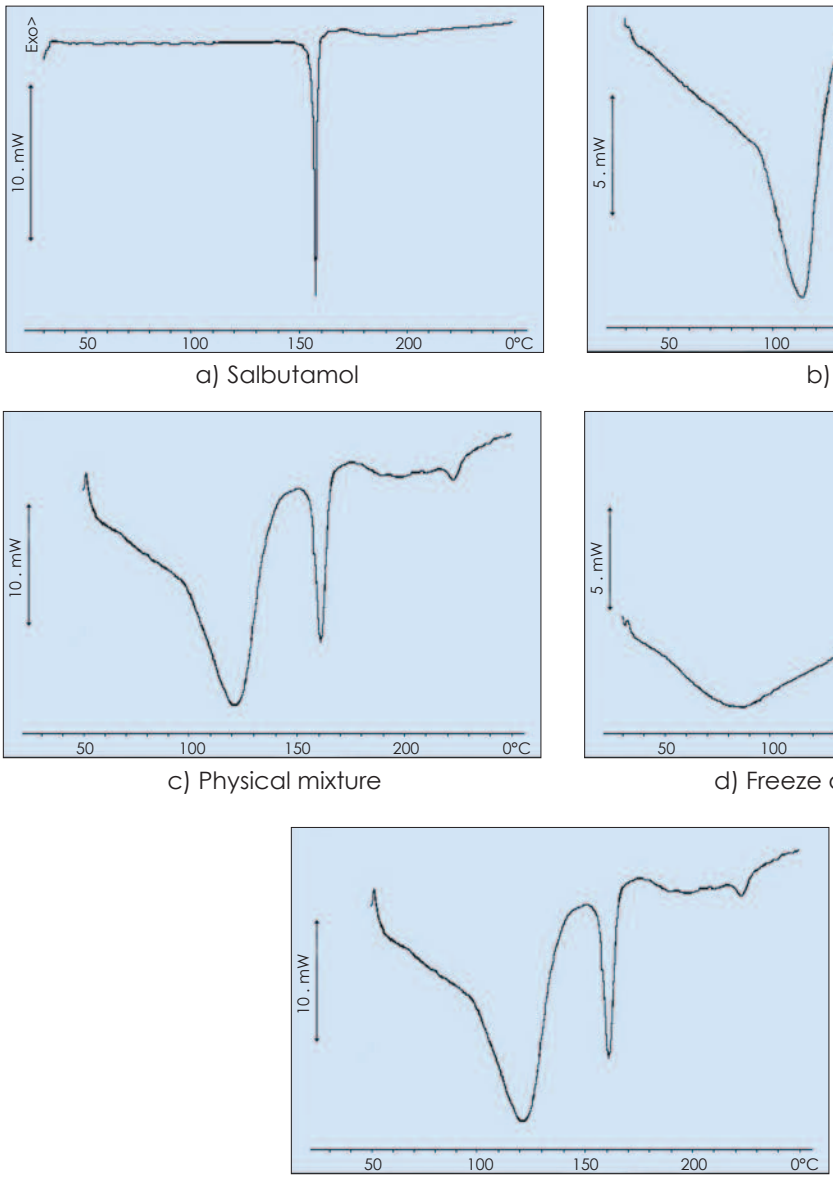
After concluding that β-CyD and its derivatives were the most promising, characterization of the pulmonary absorption of the CyDs following intratracheal (i.t.) instillation at the trachea bifurcation of NZW rabbits was performed. The bioavailability of β-CyD, DM-β-CyD and HP-β-CyD by intratracheal instillation in rabbits was very similar (about 80%) but HP-β-CyD appeared to be the most promising carrier because the carrier is absorbed more slowly, with a mean absorption time (MAT) of nearly 2 hours. The times required to reach the maximum plasma level for β-, DM-β- and HP-β-CyD were 30, 22 and 113 minutes, respectively.[17]

Investigation of the pharmacokinetics of the free salbutamol and the salbutamol-HP-β-CyD complex following intratracheal instillation was performed in order to evaluate the possibility of obtaining sustained release of salbutamol using HP-β-CyD as a carrier. Salbutamol and salbutamol complexed with HP-β-CyD were tested by i.t. instillation in rabbits, resulting in a maximum plasma concentration at 14 and 23 minutes, respectively, but the bioavailability of the complexed salbutamol was reduced to approximately 80% of that of the free drug. HP-β-CyD was also assayed showing a long lag time (34 minutes) before the start of absorption with an associated later T_{max} than that of salbutamol, indicating that the complex first dissociates within the lung followed by systemic absorption of the drug alone and then slower absorption of the carrier, CyD.[18]

Having shown that β-CyDs, particularly HP-β-CyD may provide a delayed release profile for salbutamol (C_{max} of 23 minutes versus 14 minutes), further studies were performed.[19-22] Salbutamol complexes obtained by spray

Figure 3

Thermograms of salbutamol, β-CyD, physical mixture, freeze dried and spray dried complexes obtained by DSC performed by a Mettler TA4000 apparatus equipped with a DSC 25 cell.



drying were formulated as dry powder inhalers. Respirable fractions below 6.4 μm using the Twin Stage Liquid Impinger (TSLI) at 60 L/min were 42.1 ± 5.97% for the salbutamol:HP-β-CyD complex and 33.6 ±2.12% for the salbutamol:β-CyD complex (as a percent of the nominal dose) using an experimental inhaler, the Microhaler. The same complexes obtained by freeze drying followed by micronization presented much lower respirable fractions. The respirable fraction was higher when spray dried, because the denser particles were finer in size and more regularly shaped. On the other hand, the complex particles obtained by freeze drying technique were larger in size, fluffier, less dense and more porous. It is noteworthy that spray drying resulted in lower final product yields for powder complexes compared to the freeze drying process. Although salbutamol:HP-β-CyD complexes were obtained by both freeze drying and spray drying methods, and characterized by DSC and NMR, complexes obtained by spray drying had a higher respirable fraction. Thus, this method may be useful in increasing the respirable fraction of DPI formulations.

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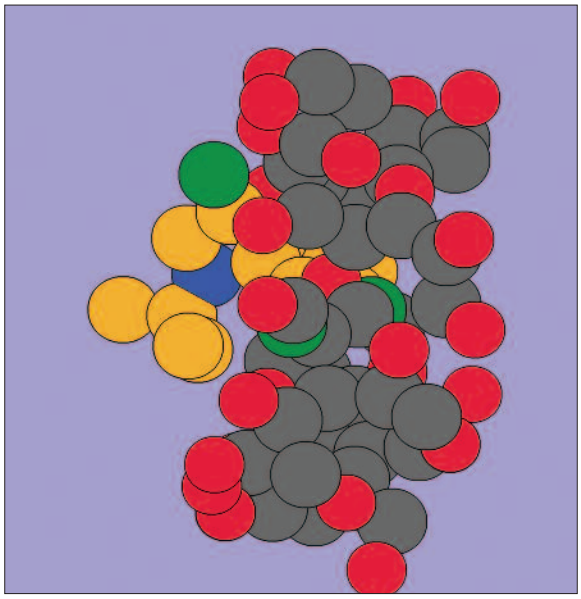
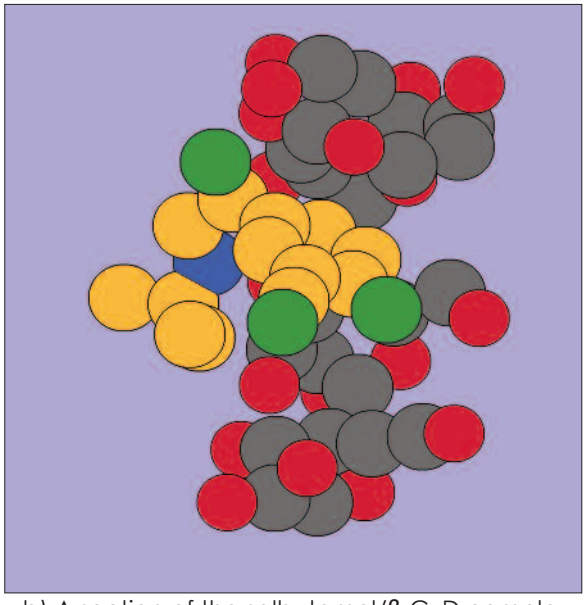
Figure 4

Relative position of salbutamol/β-CyD at minimum van der Waals. A section is also illustrated.



a) Salbutamol/β-CyD complex



b) A section of the salbutamol/β-CyD complex

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Dr. Helena Maria Cabral Marques is an Associate Professor of Pharmaceutics in the Nanomedicine & Drug Delivery Systems Group, {i Med.UL (Research Institute for Medicines & Pharmaceutical Sciences)}, Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649 - 003 Lisboa, Portugal. Tel: + 351 217946427. hcmarques@ff.ul.pt.