



# Do cyclodextrins bound to dextran microspheres act as sustained delivery systems of drugs?



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## ABSTRACT

The use of cyclodextrins (CDs) for controlled delivery of drugs is largely presented in the literature. However, the question of whether CDs themselves linked to a polymeric network are able to sustain the release of drugs still persists. Here, CD immobilization within dextran microspheres is reported, and CD-dextran complexes were packed in a glass column and then, the retention time of different drugs and drug model compounds was determined by liquid chromatography. The release profiles of drugs and of drug model compounds (indole, 3-nitrophenol, *p*-hydroxybenzoic acid, diclofenac), characterized by different values of the retention time (high, moderate or low), were investigated. The release rates were quite high even for drugs that exhibit very high retention time (high association equilibrium constant). Moreover, the volume of the release fluid strongly influences the rate of drug release. As a whole, "the sink conditions" must be continuously maintained, since at each drug concentration in the release medium, equilibrium occurs between the free and the CD-bound drug.

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## 1. Introduction

Cyclodextrins (CDs) are widely used in the pharmaceutical industry due to their specific properties to form inclusion complexes with a large variety of drugs (Misiuk and Zalewska, 2009; Xu et al., 2010; Zingone and Rubessa, 2005). Inclusion complexes improve chemical stability of drugs (Fundueanu et al., 2004), mask the drug unpleasant smell (Szejtli and Szenté, 2005), and affect the release rate of drugs in physiological fluids (Bibby et al., 2000). In most cases, CDs are not used as such, but grouped with polymeric materials such as hydrogels. These hydrophilic three-dimensional networks enhance the biocompatibility of CDs and prevent dilution in the physiological medium, increasing the stability of the inclusion complex (Concheiro and Alvarez-Lorenzo, 2013).

CD linking to a polymeric network could be obtained in a single step by covalent cross-linking of the two components (Fundueanu et al., 2003) or in two steps by coupling functionalized CDs to a polymeric backbone (Yuan et al., 2013). If the access of drugs to the CD cavity is not blocked, CDs in hydrogels can still form inclusion complexes. However, values of the association equilibrium constants for drug binding to CD-hydrogels may be lower (Sreenivasan, 1997) or higher (Crini et al., 1998) than those reported for free CDs. In CD-rich hydrogels, CDs can form complexes with higher association equilibrium constants than those observed for parent CDs dispersed in an aqueous medium. In fact, the guest molecule released from one CD may interact with another empty CD that it may meet during diffusion along the hydrogel network (Concheiro and Alvarez-Lorenzo, 2013).

The formation of CD-guest molecule complexes can be monitored in aqueous solution by several methods including NMR spectroscopy (Floare et al., 2013), UV-vis spectrophotometry (Borodi et al., 2008), spectrofluorimetry (Martínez et al., 2011), polarography (Taraszewska and Piasecki, 1987), and potentiometry (Diard et al., 1985). Values of the association equilibrium constants for binding of guest molecules to  $\alpha$ -,  $\beta$ - and  $\gamma$ -CDs are well known (Connors, 1995; Rekharsky and Inoue, 1998). In contrast, the determination of values of the association equilibrium constants

*Abbreviations:* CAB, cellulose acetate butyrate; CD, cyclodextrin; Dex, dextran; Dex ms, dextran microspheres; DT, dextran with standard molecular weights; ECH, epichlorohydrin; ESEM, environmental scanning electron microscopy; ISEC, inverse size exclusion chromatography; ms, microspheres; PB, phosphate buffer solution;  $T_R$ , retention time.

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