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# Sustained release applications of a fluoroalkyl ester-functionalized amphiphilic cyclodextrin by inclusion complex formation with water-soluble drugs in supercritical carbon dioxide

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ABSTRACT

An amphiphilic γ-cyclodextrin, selectively functionalized with perfluorobutanoyl group, octakis(6-*O*-perfluorobutanoyl)-γ-cyclodextrin (γ-CyD-F), was investigated as a potential sustained release carrier for hydrophilic drugs, taking molsidomine (MOL) as a model drug. Supercritical carbon dioxide, an environmentally benign solvent, was used for the preparation of MOL/γ-CyD-F inclusion complexes. The molecular encapsulation of MOL by the amphiphilic cyclodextrin was confirmed by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) studies. Additionally, $^1$H NMR spectroscopy was used to investigate the inclusion mode of drug with the γ-CyD-F. The *in-vitro* release of MOL from the peanut oil suspensions into aqueous phase was found to be significantly retarded by the complexation with γ-CyD-F, mainly due to the hydrophobic properties associated with the γ-CyD-F.



## 1. Introduction

There is an increasing interest in optimizing the efficiency of drug activity through the use of rationally designed drug carrier materials. Cyclodextrins (CyDs) are well known candidates for a role, modifying physical, chemical, and biological properties of drug molecules through their unique property of inclusion complex formation with a variety of drugs [1]. In general, hydrophilic CyDs are employed to enhance the dissolution rate of poorly water-soluble drugs for immediate release applications, whereas hydrophobic CyDs are used as sustained release carriers. However, as the potential use of CyDs in biological system often requires amphiphilic properties, several modifications have been made on CyDs with the aim of providing versatile carriers and delivery systems for hydrophilic and lipophilic drugs [2]. Amphiphilic CyDs can be obtained by the introduction of long alkyl or fluoroalkyl chains at primary face and/or secondary face of the CyDs, and they have been shown to form monolayers at the air–water interface and micelles or bilayer vesicles in water [3–6].

Fluorinated organic compounds have attracted much attention owing to their potential importance in industrial as well as in biomedical research. Because of the unique properties conferred by the fluorinated chains to molecules, several fluorine containing organic compounds have been reported for their promising pharmaceutical application such as oxygen delivery (liquid ventilation) and temporary blood substitutes and they are currently being investigated in phase-III clinical trials for the treatment of the diseases like respiratory distress syndrome [7]. At present more than two hundred fluorinated pharmaceuticals are available in the market and others are appearing [8]. Recently, fluorine containing β-cyclodextrins were prepared as a new class of amphiphilic carriers and they exhibited amphiphilic behavior at the air–water interface [3]. Nanocapsules and nanospheres of amphiphilic perfluoro-β-cyclodextrins and perfluoroalkylthio-β-cyclodextrins were also prepared and investigated for their potential role as oxygen carriers [9]. Additionally, fluorine containing cyclodextrins and their inclusion complexes were recently developed as novel drug carriers. They have been successfully tested for the *in-vivo* site-specific delivery of various fluorinated drugs including trifluridine and flutamide, a non-steroidal fluorinated nitrophenyl propamide used for its anti-androgen effects in prostate cancer chemotherapy [10].

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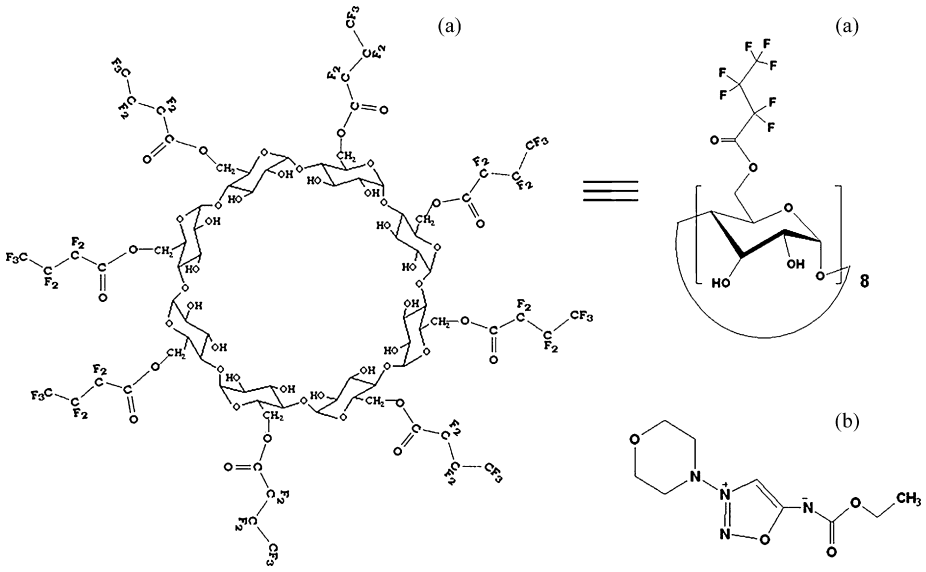


**Fig. 1.** Molecular structures of (a) γ-CyD-F and (b) MOL.

In general, several preparation methods in solution are available to prepare CyD–drug inclusion complexes. However, many of these methods are time consuming and need multistage processing, involving the evaporation of a large volume of liquid solvents, which are often found in the inclusion complex as harmful residues. Herein, we report a simple and organic solvent-free method to molecularly encapsulate water-soluble drugs by an amphiphilic cyclodextrin, octakis(6-*O*-perfluorobutanoyl)-γ-cyclodextrin (γ-CyD-F), using an environmentally benign solvent, supercritical carbon dioxide ($scCO_2$). Apart from the key advantages such as the lack of toxic solvent residues and the ease of product recovery, $CO_2$ is inexpensive, inert, non-flammable, and has recently been explored as a promising medium for protein extraction and bioconversion, polymer synthesis, material processing, and also in the particle engineering [11–14].

Molsidomine (MOL) or N-(ethoxycarbonyl)-3-(4-morpholinyl)sydnone imine), a prodrug, was selected as a model drug in this study. MOL is a peripheral nitrovasodilator and particularly useful for the treatment of angina pectoris [15]. The drug is freely soluble in water (0.25 g/dL$^{-1}$ at 25 °C) and the duration of antihypertensive action after single oral dosing is only 2.1–2.7 h which necessitates the clinical use of 38–75 mg to be taken at 3–4 times a day [16]. Due to its effectiveness and intensive use as a drug of choice, several controlled release methods of MOL have been reported in the past [17,18]. The combination of inclusion properties of the CyDs and the useful amphiphilic properties of fluorocarbon chains are expected to give molecules possessing novel physical, chemical and biological properties compared to their hydrocarbon analogs. Thus, it was anticipated that the γ-CyD-F could give thermodynamically stable inclusion complexes with hydrophilic drugs such as MOL, whereas the hydrophobic properties conferred by the fluorinated chains could be exploited as a tool to retard the release rate of highly water-soluble drugs [19].

In this study, the inclusion complex formation of γ-CyD-F with MOL was investigated using $scCO_2$ as a solvent. The complexes were further studied with the aid of differential scanning calorimetry (DSC), powder X-ray diffraction (XRD), and $^1$H NMR spectroscopic studies. Additionally, the potential use of γ-CyD-F as a drug carrier material was demonstrated by *in-vitro* controlled release of MOL from γ-CyD-F complexes.

## 2. Materials and methods

### 2.1. Materials

MOL was purchased from Aldrich and used as received. γ-CyD-F was synthesized by selective functionalization at C-6 position of the all glucose units of CyD by esterification with heptafluorobutyric acid [20]. Complete procedure for synthesis and characterization of γ-CyD-F was described in our previous report. Molecular structures of γ-CyD-F and MOL are shown in Fig. 1.

### 2.2. Preparation of MOL and γ-CyD-F inclusion complexes in $scCO_2$

The experimental apparatus used in the preparation of inclusion complexes in $scCO_2$ is shown in Fig. 2. It consists of a 10 cc high-pressure stainless steel reactor equipped with sapphire quartz window and a high-pressure syringe pump (ISCO model 260D series) for pressurizing carbon dioxide. Heating was provided by a water bath and the temperature was measured with a thermocouple (Doric Trendicator 400A). Teflon-coated magnetic stir bar was used to mix the cell contents. In a typical inclusion experiment, equimolar mixtures of MOL and γ-CyD-F were placed in the high-pressure reactor, and carbon dioxide was charged into the cell using the syringe pump until the pressure reached up to 34.5 MPa at 45 °C. After 6 h of stirring, the $CO_2$ was slowly vented off, and the powders were collected. The physical mixtures of MOL and γ-CyD-F were prepared by mixing both solids at 1:1 molar ratio (8 mg of MOL and 100 mg of γ-CyD-F) at room temperature.

### 2.3. Characterization of inclusion complexes

The inclusion complexes were investigated with the aid of differential scanning calorimetry (DSC-60 Shimadzu, Japan) and powder X-ray diffractometry (XRD Philips X'Pert-MPD, Japan). $^1$H NMR spectra were recorded using a JNM-ECP 400 (JEOL) spectrometer, with DMSO-$d_6$ as a solvent (internal reference $\delta_H$ = 2.5 ppm).

### 2.4. In-vitro drug release studies

The *in-vitro* release rate of MOL from an oily suspension of drug-γ-CyD-F complex was measured according to the paddle method of