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# Effect of alkylcarbonates of γ-cyclodextrins with different chain lengths on drug complexation and release characteristics

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**Abstract**

Alkylcarbonates of γ-cyclodextrins were produced and their inclusion complexes with four poorly water-soluble drugs of different structures and solubilities were prepared. The alkylcarbonates and the alkylcarbonate drug complexes were characterized by DSC and XRPD; the physical mixtures were used as control. Solubility capacities were evaluated by phase solubility studies. The effect of alkyl chain length on the complexation and release behaviour was investigated as well. The XRPD patterns of alkylcarbonates showed that the derivatives lose the original crystallinity of γ-cyclodextrins. The series of alkylcarbonates formed inclusion complexes with the drugs considered. Both XRPD and DSC analyses did not show neither the reflections of the crystalline structures nor the melting peaks of the drugs, respectively. These γ-cyclodextrin derivatives can improve drug solubility and influence the drug release rates while the alkyl chain length may affect these properties.
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*Keywords:* Inclusion complexes; Alkylcarbonate γ-cyclodextrins; DSC; XRPD; Release rate

## 1. Introduction

Cyclodextrin inclusion compounds (Duchêne, 1987; Uekama et al., 1998) have been widely used in the pharmaceutical field, particularly to improve solubility, dissolution rate and bioavailability of hydrophobic drugs. The possibility of modifying cyclodextrins to overcome their technological and toxicological limitations has been also examined (Loftsson and Brewster, 1996; Irie and Uekama, 1997). Recently, their application in different drug administration routes has been reported (Shimpi et al., 2005).

In a preceding work, we prepared a new type of γ-cyclodextrin (γ-CD) derivatives, i.e. their alkylcarbonates, with the goal of extending the physico-chemical properties and inclusion capacity of γ-CD, in particular to obtain drug complexes with good safety profiles. Actually, alkylcarbonates of γ-CD have a lower hemolytic effect than the parent CD (Trotta et al., 2002).

The role of the alkyl chain as substituent on cyclodextrins is important. Alkyl-substituted cyclodextrins show an increased complexation ability, which is probably due to the cavity extension (Thompson, 1997). The increase in cavity size appears to improve complexation by providing additional interaction surface. However, this improvement may be limited by steric hindrance induced upon addition of substituents close to the cavity entrance, as it was observed in the case of methylated and acetylated β-cyclodextrins (Harata et al., 1984; Liu et al., 1992). In this study, four alkylcarbonates (ethyl, butyl, hexyl and octyl) of γ-CD were prepared as drug carriers, to achieve faster dissolution rates, increased oral bioavailability and reduced side effects. The series of alkylcarbonates were employed to form inclusion complexes with some low-solubility pharmaceutically relevant molecules such as progesterone, dexamethasone, flurbiprofen and diazepam. Progesterone and dexamethasone are a hormone and an anti-inflammatory steroid, respectively, that can form soluble complexes with β and γ-CDs (Uekama et al., 1982). Flurbiprofen is a weakly acidic anti-inflammatory drug showing local gastrointestinal side-effects, which are attributed partly to the insoluble drug particles adhesion to the gastric mucosa, leading to high local concentrations of flurbiprofen. Diazepam is

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a benzodiazepine sparingly soluble in water and, consequently, its solutions must contain an organic solvent such as ethanol or propylene glycol. To avoid the need for organic solvents many approaches have been studied; for example, parenteral formulations have been developed using sub-micron o/w emulsions, in which diazepam is dissolved in the oily phase of the emulsion (Gajewska et al., 2001).

The aim of this study was to determine the effect of the alkyl chain length of γ-CD alkylcarbonates on their complexation and their release behaviour, with the ultimate goal of developing modified γ-CDs with complexation properties that can increase the oral bioavailability of the drugs.

## 2. Material and methods

### 2.1. Materials

γ-CD was a kind gift from Wacker Chemie (Münich, Germany); progesterone, dexamethasone, diazepam and flurbiprofen used as model drugs (Table 1) were from Fluka (Buchs, CH). All reagents (ACS grade) were from Sigma (USA) and were used without further purification. HPLC solvents were from Carlo Erba (Milan, Italy).

The alkylcarbonates were prepared as described elsewhere (Trotta et al., 1993) with an average degree of substitution (DS) of three per γ-CD molecule, e.g. 0.375 alkylcarbonate group per anhydroglucose repeat unit. Briefly, the selected alcohol was activated by reaction with carbonyldiimidazole in alcohol free chloroform; the required amount of the obtained product was allowed to react with the cyclodextrin in anhydrous pyridine at 80 °C for 3 h to obtain the corresponding alkylcarbonate of γ-CD by precipitation with diethyl ether.

The ethyl carbonate was also synthetized with a DS = 5 per γ-CD molecule. The average molecular weights of the alkylcarbonates were calculated on the basis of the average substitution degree. A scheme of the alkylcarbonate derivatives is reported in Fig. 1.

### 2.2. Solubility and stability of γ-CD alkylcarbonates

The solubility of the series of γ-CD alkylcarbonates was determined in water at 25 °C by weighing 20 mg of dry powder of each derivative and adding water under stirring until complete dissolution. The solution was stirred for one day and then the cyclodextrin concentration was determined in the supernatant by HPLC using an amino derivatised silica column with an acetonitrile:water mixture (70:30, v:v) as mobile phase and a refractive index detector (Zsadon et al., 1979).

Table 1
Characteristics of the model drugs

| | M.W. | log $P$[a] | Solubility (mg/ml) |
|---|---|---|---|
| Progesterone | 314.47 | 3.9 | 0.010 |
| Dexamethasone | 392.47 | 1.9 | 0.080 |
| Flurbiprofen | 244.70 | 4.1 | 0.012 |
| Diazepam | 284.74 | 2.7 | 0.050 |

[a] $P$ = octanol/water partition coefficient.

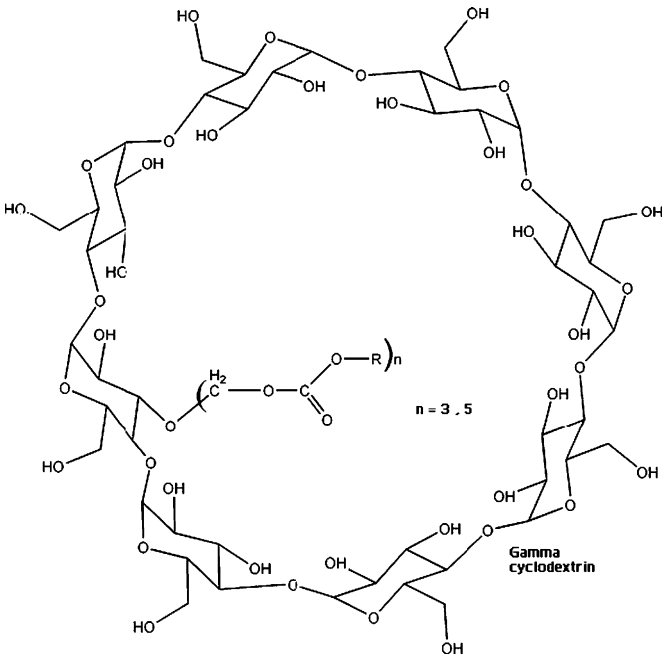


Fig. 1. Scheme of the alkylcarbonate structure (R = ethyl, butyl, hexyl or octyl).

The stability of γ-CD alkylcarbonates was evaluated at 25 and at 37 °C in phosphate buffer solutions at two different pH values: 1.1 and 6.8 that are those of stomach and duodenum, respectively. The experiments lasted 8 h to mimic the gastrointestinal transit. At fixed times (1, 2, 4, 6 and 8 h) the γ-CD alkylcarbonate concentration in the solutions was determined by the HPLC method previously reported. Moreover, the physical stability of ethylcarbonate aqueous solutions were determined over time; for this purpose the solutions were maintained at room temperature for 18 months.

### 2.3. Preparation of binary mixtures

Binary physical mixtures of the series of alkylcarbonate γ-CDs with each drug were prepared by mixing appropriate amounts of solid components (2:1 molar ratio) in a glass mortar.

### 2.4. Preparation of the complexes

Complexes of γ-CD alkylcarbonates with different alkyl chain lengths were obtained by adding an excess of the selected drug to an alkylcarbonate water/ethanol solution (70:30, v/v). For flurbiprofen the aqueous solution was corrected at pH 2.0 to prevent the dissociation of the drug. The complexes of ethylcarbonates DS = 3 were prepared in water. The mixtures were stirred at 25 °C for 48 h, then filtered, centrifuged and dried to obtain the complex as a powder.

### 2.5. Characterization of the alkylcarbonates and their complexes

The inclusion complexes and the γ-CD alkylcarbonates alone were characterized by differential scanning

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