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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.

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.

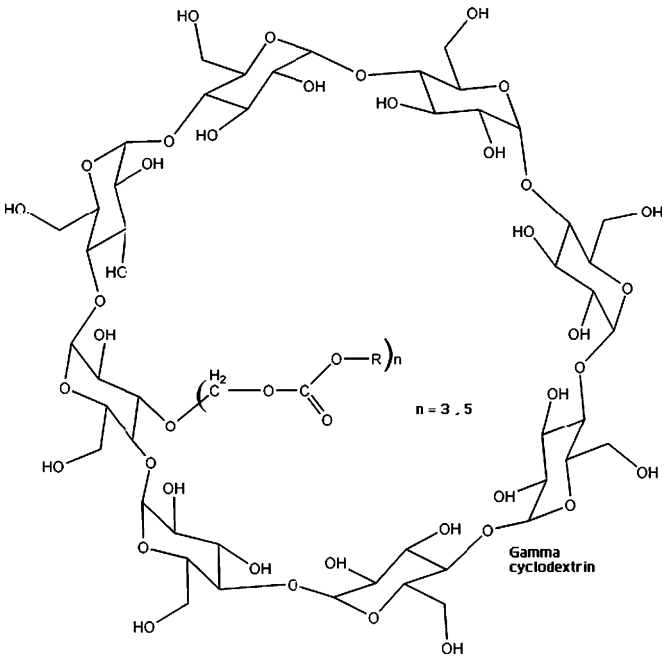

Fig. 1. Scheme of the alkylcarbonate structure (R = ethyl, butyl, hexyl or octyl).

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

calorimetry (DSC) and X-ray powder diffraction (XRPD) analyses.

Thermal analyses were performed using a DSC 7 system (Perkin-Elmer); samples of 5–6 mg were weighed in aluminum sample pans and then heated at a rate of 10 °C/min in the 25–350 °C range under a nitrogen purge. The X-ray powder patterns were obtained using a Siemens D-5000 diffractometer equipped with Bragg-Brentano geometry. The operative conditions were as follows: 40 kV, 30 mA, Cu Kα radiation (λ = 0.15418 nm). The samples were analyzed in the range 2.5–60° (2θ).

2.6. Drug quantitative determination

Drug concentrations were determined by suitable reverse phase HPLC methods reported in literature for each molecule. The instrument was a Perkin-Elmer Binary LC pump 250 Chromatograph equipped with a UV detector and a 5 μm Lichrosorb RP-18 column (250 mm × 4.6 mm).

2.7. Phase solubility studies

Phase solubility was studied to evaluate the apparent stability constants of the complexes as described by Higuchi and Connors (1965). Excess amounts of each drug were added to aqueous solutions containing increasing concentrations of alkylcarbonates (0.25, 0.5, 1.0, 2.5, 5.0, 7.0, 10.0 and 15 mM). After equilibration at 25 °C for 5 days, the supernatants were centrifuged, filtered and analyzed by HPLC.

Solubility capacities were determined in 0.5 M phosphate buffer at pH 7.4 for progesterone, dexamethasone and diazepam, while flurbiprofen ($pK_a = 4.2$) was studied in phosphate buffer at pH 2.5 so as to have the non-dissociated form of the drug.

Phase-solubility diagrams were obtained by plotting the experimental molar concentrations of the drugs as a function of the molar cyclodextrin concentrations. The apparent stability constants or binding constants for each drug were estimated by the methods of Higuchi and Connors by means of the slopes and the intercepts of the regression lines.

2.8. In vitro release studies

The *in vitro* release experiments were performed using powdered samples of the series of complexes and of the drugs as control. The solids were suspended at 37 °C in phosphate buffers at two different pH values (7.4 and 6.8) to simulate physiological fluids, and then incubated under gentle stirring. At fixed times, within a period of 2 h buffer samples were collected, centrifuged, filtered and the concentration of the released drug determined in the supernatants by HPLC analysis.

3. Results and discussion

γ-Cyclodextrin has the highest aqueous solubility of the parent CDs (about 23 g/100 ml at room temperature) but over time its solution becomes opalescent and a precipitate forms; this behaviour could affect its pharmaceutical applications. Both turbidity and precipitate-formation of γ-CD solutions are due to the self-aggregation of γ-CD monomers owing to intermolecular hydrogen bonds (Szente et al., 1998). One way to overcome this drawback is to modify the hydroxyl group on the γ-CD molecule forming derivatives, so as to avoid hydrogen bonds formation and increase the solution stability.

Table 2
Solubility of γ-CD alkylcarbonates at 25 °C

	M.W.	Degree of substitution	Solubility (mM)
γ-CD	1297	–	177.00[a]
Ethyl γ-CD	1513	3	16.00
Ethyl γ-CD	1657	5	2.16
Butyl γ-CD	1597		2.60
Hexyl γ-CD	1681	3	1.07
Octyl γ-CD	1765	3	0.45

[a] Apparent solubility.

The water solubility of γ-CD alkylcarbonates we prepared is related to the length of the alkyl chain on the cyclodextrin (Table 2). The solubility decreases significantly with the alkyl chain length and with the number of alkyl chains.

The aqueous solutions of γ-CD ethylcarbonate showed a physical stability for more than 18 months, at room temperature and at pH = 6.0, without any precipitate formation. This increase in solubility in respect to the parent γ-CD could be related to the weakening of the hydrogen bond network among cyclodextrin molecules, owing to the action of the alkyl chains.

The series of γ-CD alkylcarbonates showed a chemical stability with no degradation observed by HPLC analysis after 8 h at pH 1.1 and 6.8, which are the typical pH values of the stomach and duodenum, respectively. Alkaline pHs could favor the hydrolysis of the carbonates, but at pH 7.4 the alkylcarbonates are still stable. These results show that these γ-CD derivatives could be suitable for potential in vivo administration.

X-ray analysis showed that the series of alkylcarbonates are solids with a peculiar behaviour which is different from that of the strongly crystalline γ-CD (Fig. 2). In fact, they show a poor

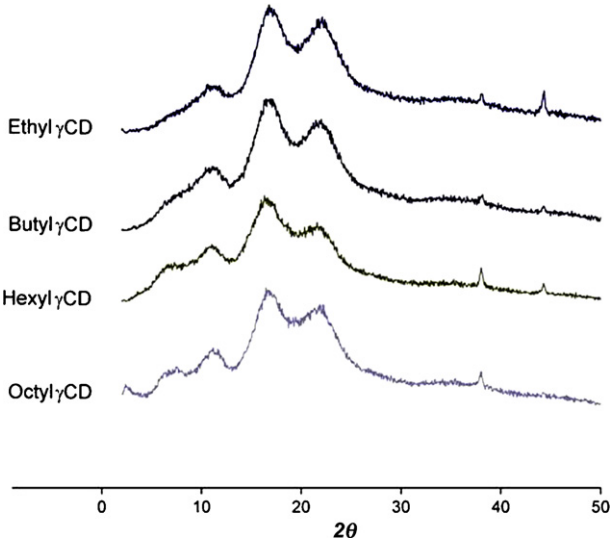

Fig. 2. XRPD diffraction patterns of the series of γ-CD alkylcarbonates.

Table 3
Experimental XRPD characteristic ratios (R/A: ratio between peak areas; R/H: ratio between peak heights) for the two most intense peaks at ∼2.36 and −2.04 Å

	R/A	R/H
Ethyl γ-CD	0.93	1.22
Butyl γ-CD	1.13	1.33
Hexyl γ-CD	3.62	2.14
Octyl γ-CD	2.17	1.42

long-range order and a sharp short-range packing in the same sample. At 2θ values ranging from 3° to 30° we observed the simultaneous disappearing of the XRPD reflections characterizing the cyclodextrin not derivatized and the appearance of new broad reflections with a M-shaped profiles.

In all diffraction patterns of derivatives, the peaks ranging between 3° and 30° are broad and in the general their profiles are similar. They show a high intensity of the second hump of the M-shaped profile at about 22°. At greater values of 2θ, corresponding to lattice spacings of 2.36 and 2.04 Å, two narrow peaks are always present varying only in their relative intensity. The largest difference is in the shape of the profile in between 4° and 20°, where a reflection at about 6° becomes more and more intense with the alkyl chain length.

Further information could be obtained from the decomposition of the XRPD patterns. To do that, we choose a Gaussian peak type. So we were able to assign the mean d_{hkl} position for the principal peaks (P1 and P2) at 2.36 and 2.04 Å, respectively, for all the XRPD pattern obtained.

When comparing the intensity ratio and the peak height ratio of the main reflections at about 22° and 17° (2θ) we can say, as it comes out from the peaks decomposition, that the hexylcarbonate behaviour represents a discontinuity in the series of γ-CD derivatives (see Table 3).

The DSC analyses showed that the series of γ-CD alkylcarbonates are thermally stable up to 300 °C.

The γ-CD alkylcarbonates can form inclusion complexes with all the model drugs, as confirmed by DSC and XRPD analyses. All the drugs present, before complexation, a high degree of crystallinity, as confirmed by narrow and sharp peaks

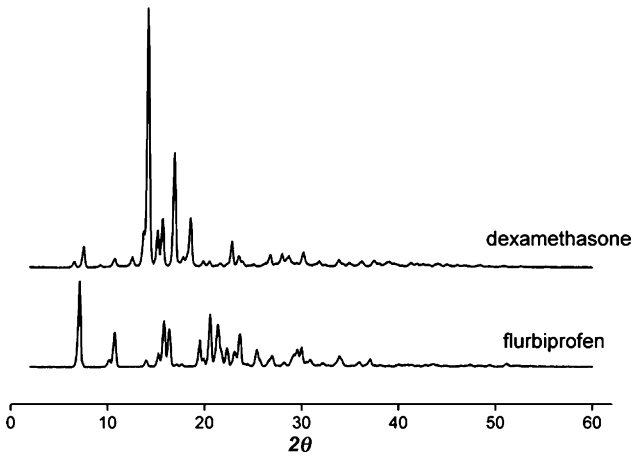

Fig. 3. XRPD diffraction patterns of dexamethasone and flurbiprofen.

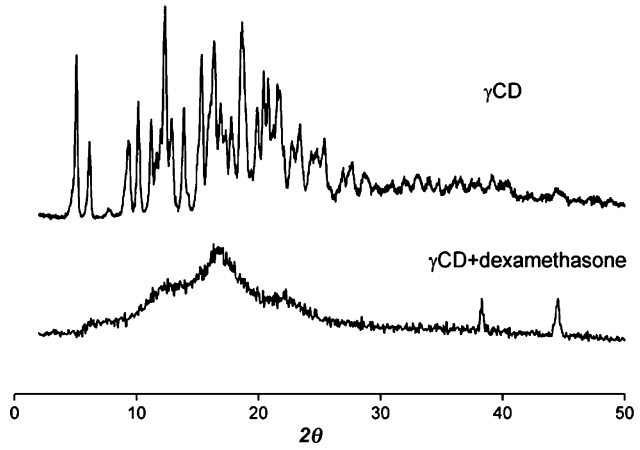

Fig. 4. XRPD diffraction patterns of γ-cyclodextrin and γ-cyclodextrin-dexamethasone complex.

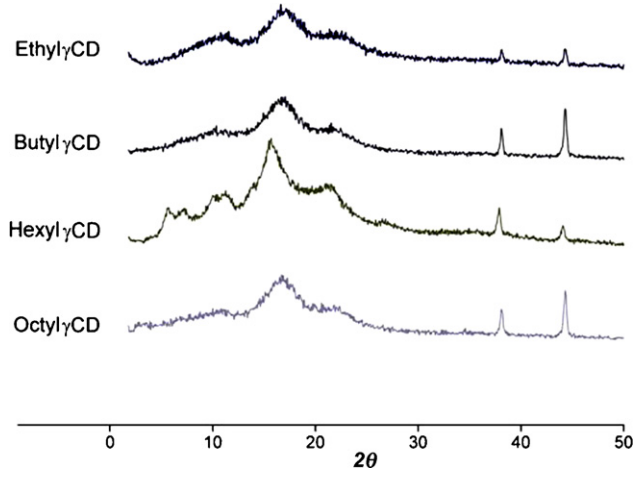

Fig. 5. XRPD diffraction patterns of dexamethasone complexes with the series of γ-CD alkylcarbonates.

and exemplified in Fig. 3 for dexamethasone and flurbiprofen. However, their crystallinity decreases after complexation. The X-ray patterns revealed the vanishing of the original peaks of the drug, while new broad reflections appear indicating the inter-

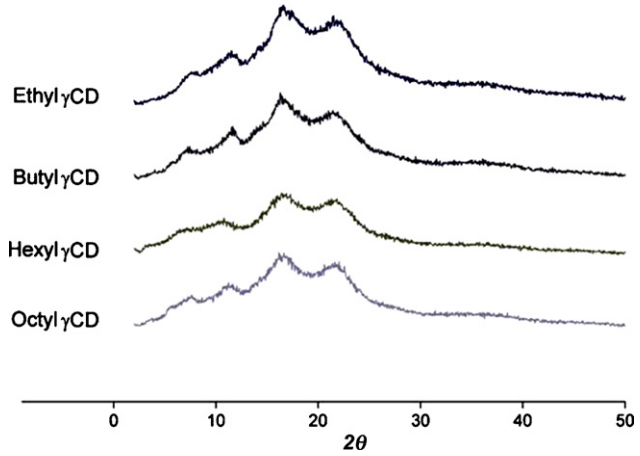

Fig. 6. XRPD diffraction patterns of flurbiprofen complexes with the series of γ-CD alkylcarbonates.

Table 4
Apparent stability constants of progesterone, dexamethasone, diazepam and flurbiprofen with the series of γCD alkylcarbonates

	Progesterone (M^{-1})	Dexamethasone (M^{-1})	Flurbiprofen (M^{-1})	Diazepam (M^{-1})
γ-CD	24,100	26,500	5240	2870
Ethyl γ-CD	11,870	12,500	3850	1200
Butyl γ-CD	19,500	13,400	4900	2580
Hexyl γ-CD	8,400	10,240	1200	895
Octyl γ-CD	25,900	28,200	2750	1750

Data represent the averaged values from three experiments.

action of the drug with the series of cyclodextrin derivatives. The same consideration applies when comparing the XRPD patterns obtained for the drug complexes with γ-CD, as reported in Fig. 4 for dexamethasone. The short-chain alkylcarbonate complexes with dexamethasone (and progesterone) show similar behaviour with at least five broad reflections at 11.77, 7.91, 5.30 and 4.10 Å. The introduction of a drug molecule in the short chain alkylcarbonates bring to a more relaxed packing resulting in a higher spaced structure. Nevertheless, more disordered structure maintains at high 2θ values, as it comes out at glance. Moreover, the short-range order becomes reinforced, as it may be seen from the intensity of the reflections at low 2θ values.

The long-chain alkylcarbonate complexes with dexamethasone and progesterone showed very different and more complicated behaviour compared with the short-chain ones. In

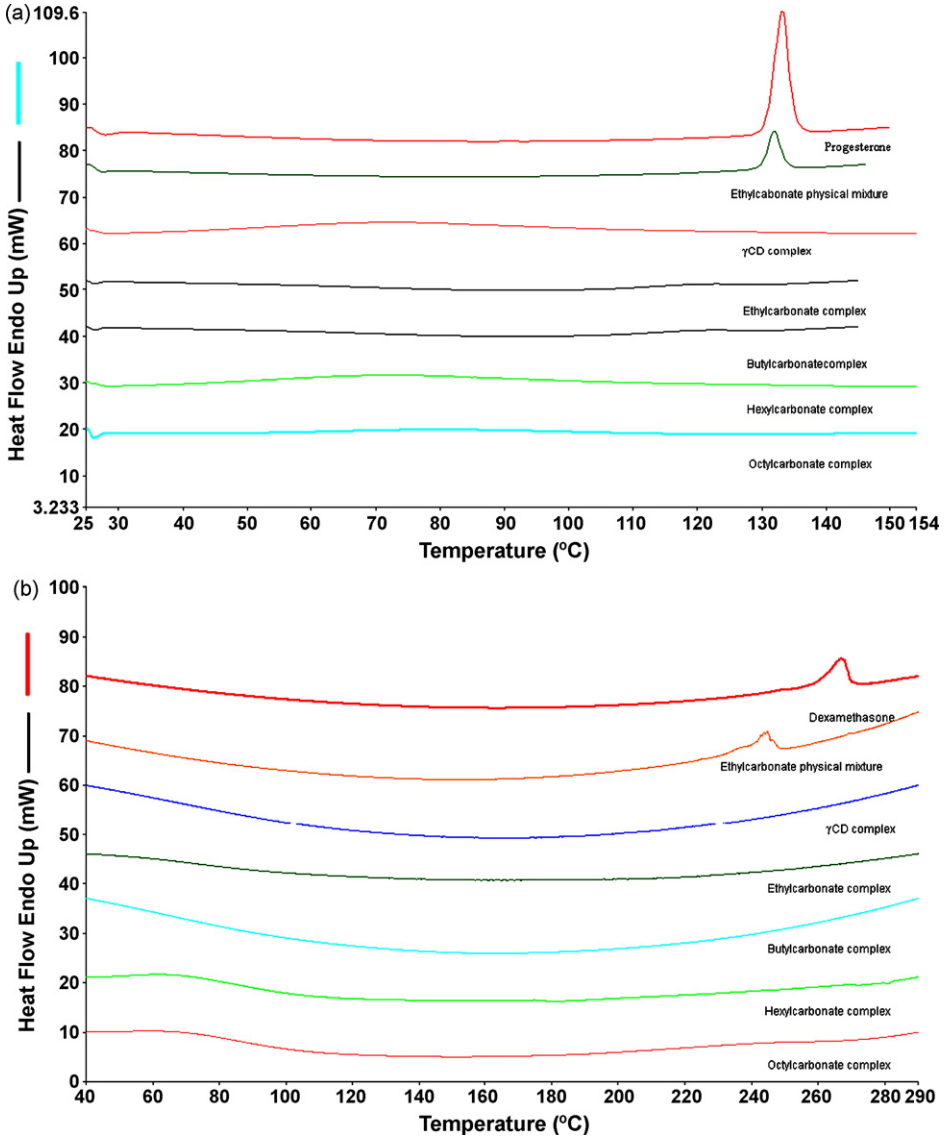

Fig. 7. (a–d) DSC thermograms of the series of γ-CD alkylcarbonate complexes with progesterone, dexamethasone, flurbiprofen and diazepam.

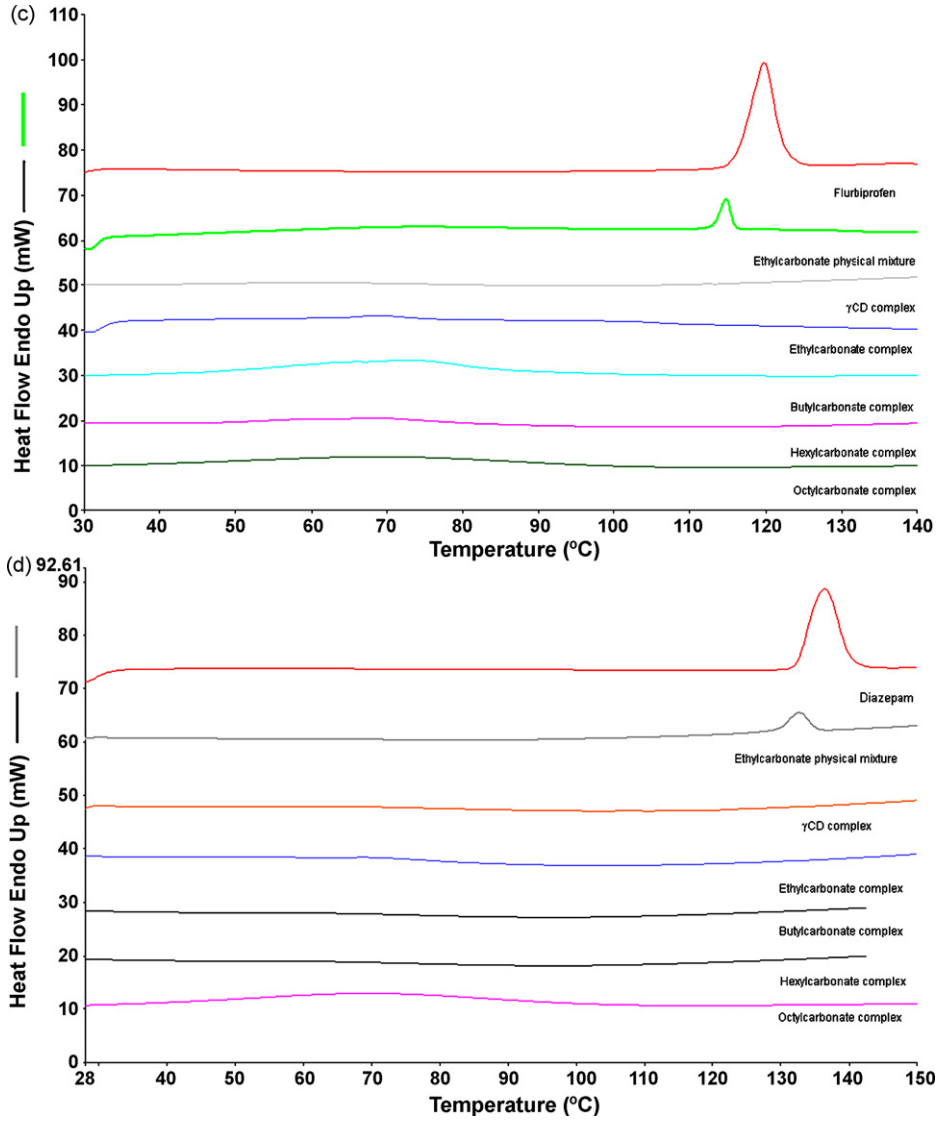

Fig. 7. (*Continued*).

Fig. 5 the diffraction patterns of the series of dexamethasone complexes are reported.

The hexylcarbonate complex shows a very different behaviour with no fixed reflections, which in the presence of the drug are generally displaced toward higher d_{hkl} values. Besides, each reflection splits into two peaks of the same intensity and FWHM (full width at half maximum), so revealing the discontinuity represented by this complex within the alkylcarbonate series.

Finally, the octyl carbonate complex with dexamethasone and progesterone shows a broad peak at 5.30 Å. The other peaks disappear, being replaced by one single more intense and broader reflection.

P1 and P2 sharp reflections could be associated with a short range well ordered packing confined in the γ-CD torus.

Broad reflections in the range 3–30° (2θ) are probably related to a long-range side by side packing between chains, whilst the interaction between γ-CD alkylcarbonates and drugs brings to weak but appreciable modifications in the long range packing.

The only occurrence of two slightly different coexisting structures is represented by the hexyl derivative complex, where every peak in the low 2θ range splits after the introduction of the dexamethasone in the cyclodextrin cavity.

At variance from what we recognized when working with progesterone and dexamethasone, the reflections at 2.36 and 2.04 Å disappeared when flurbiprofen is complexed, i.e. γ-CD alkylcarbonates lose their low spacing order, while maintained long range order (Fig. 6).

The introduction of a drug molecule in the γ-CD short chain alkylcarbonate complexes bring to a more relaxed packing which results in a higher spaced structure; however, the short spaced order still maintains when a molecule with a steroidic structure is added to form the complex. If a molecule with a very different structure like flurbiprofen or diazepam are used to obtain the complex, the low range order is lost as well.

Low spaced reflections could be associated with this short-range order, owing to the well ordered packing between the γ-CD torus. Splitting of XRPD peaks occurs in the hexylcarbonate

complex showing reflections that, in the presence of the drug, are displaced toward higher d_{hkl} values. Besides, each reflection splits into two peaks of same intensity and FWHM.

Generally, the XRPD patterns of the complexes with flurbiprofen are very similar, while are more complicated (as it comes out from the pattern decomposition) when compared to those of dexamethasone complexes which are dominated by two great peaks at 5.33 and 4.13 Å and show several less intense peaks at higher d_{hkl} values.

When summarizing, XRPD analysis might be fruitfully used to investigate the type of incorporation between drug with different structure and alkylcarbonate central cavity.

Fig. 7(a–d) shows the thermograms of progesterone, dexamethasone, diazepam and flurbiprofen and of their complexes with ethyl, butyl, hexyl and octyl carbonates of γ-CD. DSC thermograms of the complexes did not show the melting peaks corresponding to drug fusion: this indicates that the drugs are no longer crystalline and confirms their interaction with the alkylcarbonates of γ-CD showing the formation of the complexes. On the contrary, the thermograms of binary mixtures presented the melting peak of the drugs (data not shown), indicating that the drugs maintained their original crystallinity in the physical mixtures: hence, either they were not included or did not interact. Moreover, from Fig. 7 where the thermograms of the physical mixtures of ethylcarbonate with all the drugs have been reported as control, the endothermic peak of the drug fusion comes out.

All that agrees with the behaviour of the complexes we observed and discussed just now about XRPD analyses.

The water solubility of the four drugs was significantly increased by the interaction of alkylcarbonates. For example, the solubility enhancement for progesterone was about 8000-fold using butyl and hexyl derivatives and more than 3300-fold for flurbiprofen at the concentration of 15 mM.

The alkylcarbonates are surface active and have a CMC (data not shown); therefore, they could favor the drug solubilization also through the micelle formation. Both stoichiometry and apparent stability constants of the complexes were calculated from the phase-solubility diagrams. We obtain type A phase-solubility diagrams. In particular, A_L-type for ethyl and butyl derivatives. A_N type for the hexyl and octyl derivatives. Moreover, the octyl derivative showed a plateau level which it could be ascribed to its saturation because this alkylcarbonate is not very soluble. The stoichiometry was 1:1 alkylcarbonate:drug for the ethyl, butyl and hexyl derivates, while the ratio cyclodextrin:drug is greater for the octyl derivatives.

Table 4 illustrates the apparent stability constants of the series of alkylcarbonates with the four drugs. Flurbiprofen and diazepam showed the highest stability constants with the γ-CD butylcarbonates, with the only exception of that of the parent CD. On the contrary, the octylcarbonate gave the highest stability constant values with progesterone and dexamethasone.

Further, γ-CD hexylcarbonate showed lower stability constants with all tested drugs: this could indicate both the steric hindrance of the alkyl chain and the lower interaction with drugs, which could hamper the inclusion of the guest molecule in the CD cavity. Once again, the γ-CD hexyl carbonate confirms its peculiarity, as previously revealed by X-ray powder diffraction.

Stability constants increase, with the γ-CD octylcarbonate, probably as a consequence of the hydrophobic interaction of the drug with the octyl chains. Indeed, the alkyl chains may interact with hydrophobic portions of drugs not completely included in the cyclodextrin cavity. Stella and coworkers (Zia et al., 2000) reported that the alkyl chains of sulfobutylether β-cyclodextrins may provide additional hydrophobic regions for the stabilization of the inclusion complexes, potentially counterbalancing the negative effect of the steric hindrance. Moreover, alkyl chains may also provide an extension of the cyclodextrin cavity with which the guest molecules may interact.

The derivatization of cyclodextrins may also distort the cavity, so limiting the complexation with a guest molecules with the

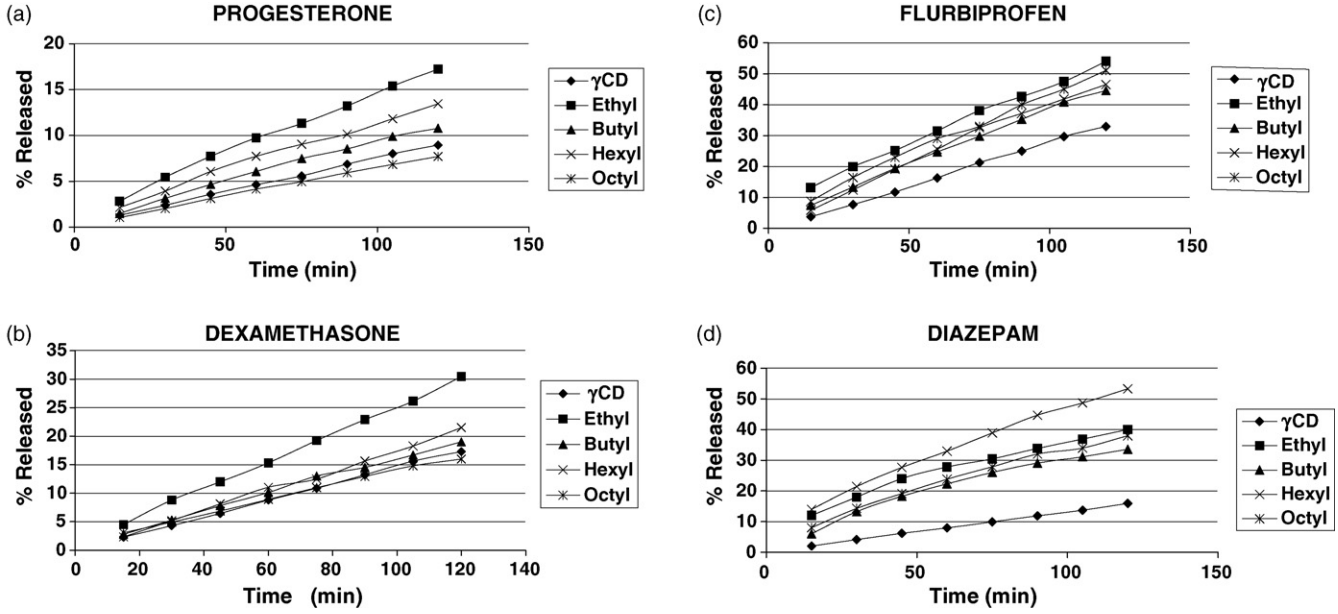

Fig. 8. (a–d) *In vitro* release profiles of the four drugs from γ-CD and the series of γ-CD alkylcarbonate complexes.

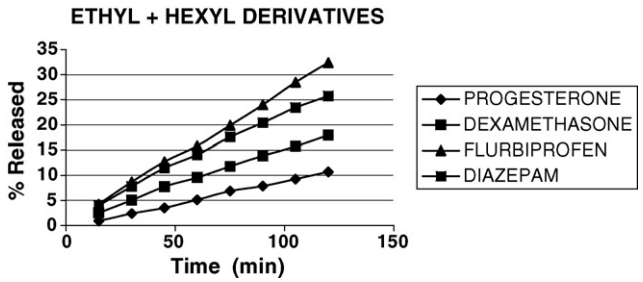

Fig. 9. *In vitro* release profiles of the four drugs from the mixture between γ-CD ethylcarbonate and γ-CD hexylcarbonate complexes.

interior cavity and inducing the interaction with the alkyl chain around the torus.

To verify the interaction of molecules with the modified cyclodextrin we prepared also the ethylcarbonates with DS = 5. The increased number of the alkyl chains did not favor the complexation capacity of alkylcarbonates.

The release rates of the drugs as complexes were significantly increased in respect to those obtained with the parent CD, in particular with butyl and ethyl derivatives. For instance, after 120 min the percentage of released progesterone was nearly 9% when complexed with γ-CD and about 18% when complexed with γ-CD ethylcarbonate. All the drugs tested showed a very low solubility in water; moreover, the complexation modified it significantly and consequently might increase the oral bioavailability.

Fig. 8(a–d) shows the *in vitro* release profiles of the drug complexes at pH 6.8. The release at pH 7.4 did not show sensible differences from those reported in Fig. 7 (data not shown).

The release rate increases with ethyl and butyl derivatives, when compared to the other alkylcarbonates, and this behaviour rather agrees with the apparent stability constants determined for the complexes.

The alkylcarbonates with lower aqueous solubility are carriers with a slower release. The combined use of complexes with alkylcarbonates having different chain length might allow to modulate the drug release. To verify this hypothesis, complexes of the four drugs with ethyl and hexylcarbonates were mixed and the mixed powder was used to determine the new release profiles at pH 6.8.

As it can be clearly seen from Fig. 9, the percentage of drug released lowers when hexyl complex is added. As an example, the percentage of released dexamethasone from ethylcarbonate reaches near 30% after 2 h, while reduces to 18% using the two complexes. Consequently, it might be possible to control the drug release, obtaining fast or prolonged release, by mixing suitable alkylcarbonate complexes.

4. Conclusions

Alkylcarbonates could be employed as drug carriers, since they form inclusion complexes. The comparison among the X-ray powder patterns of the γ-CDs, alkylcarbonates and drug complexes showed the sensible structural differences of these solid compounds, pointing out a discontinuity in the series as well. The stability constants of these complexes show that the more stable ones form with butyl and octyl derivatives, depending on the molecular structure of the guest drug, except for flurbiprofen. The γ-CD derivatives we considered can improve both solubility and release rate of poorly water-soluble drugs; the alkyl chain length may affect these properties. Moreover, the combination of various ratios of different alkylcarbonate complexes in a pharmaceutical formulation could enable drug release to be modulated.

Acknowledgement

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