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Polymorphism, pseudopolymorphism, and amorphism of peracetylated α-, β-, and γ-cyclodextrins☆

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Abstract

Polymorphism, pseudopolymorphism, and amorphism of hexakis(2,3,6-tri-*O*-acetyl)-α-cyclodextrin (TAαCyD), heptakis(2,3,6-tri-*O*-acetyl)-β-cyclodextrin (TAβCyD), and octakis(2,3,6-tri-*O*-acetyl)-γ-cyclodextrin (TAγCyD) were investigated using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffractometry (XRPD), Fourier transform infrared spectroscopy (FTIR) and optical microscopy. An anhydrous and a bi-hydrate crystalline forms of TAαCyD, two monotropic anhydrous polymorphs and three pseudopolymorphs (i.e. methanolate, hydrate, and isopropanolate-hydrate) of TAβCyD, as well as two monotropic anhydrous polymorphs and isostructural pseudopolymorphs (e.g. hydrate and isopropanolate-hydrate) of TAγCyD were isolated and characterized. The amorphous forms of each TACyD were also obtained. Thermal data for desolvation of TAαCyD·2H_2O and TAβCyD·CH_3OH were reconciled with their crystal packing features. Melting temperatures and enthalpies of the crystalline forms of each TACyD can be referred to for possible solid-state interactions with drugs.

Keywords: Peracetylated cyclodextrins solid-state forms; Differential scanning calorimetry; Thermogravimetric analysis; Powder X-ray diffractometry; Microscopic analysis; Fourier transform infrared spectroscopy

1. Introduction

Solid form diversity of pharmaceutical substances may influence the efficacy and safety of drug products. Physical chemical characterization of different solid phases that may occur during crystallization and pharmaceutical formulation processes (i.e. polymorphs, solvates, desolvated solvates, and amorphous materials [1]) is therefore advisable for both drugs and excipients. In case of hydrophilic cyclodextrins (CyDs), the amorphous or crystalline nature affects their technological properties as pharmaceutical excipients for tablets [2–4], as well as their solid-state interactions with hydrophobic drugs, which in turn influence the dissolution rate and drug stability [5–8]. On the other hand, hydrophobic CyD derivatives such as peracylated αCyDs, βCyDs, and γCyDs (see [6] and refs. therein) can be used as bioabsorbable sustained-release carriers for hydrophilic drugs. In the present work our previous investigations on thermal and structural characterization of the most common [9] and less common large-ring [10] native CyDs were extended to the hydrophobic hexakis(2,3,6-tri-*O*-acetyl)-α-cyclodextrin (TAαCyD), heptakis(2,3,6-tri-*O*-acetyl)-β-cyclodextrin (TAβCyD), and octakis(2,3,6-tri-*O*-acetyl)-γ-cyclodextrin (TAγCyD). Solid-state properties, namely polymorphism, pseudopolymorphism and amorphism of peracetylated CyDs were investigated using thermal [differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)], structural [powder X-ray diffraction (XRPD)], spectroscopic [Fourier transform infrared spectroscopy (FTIR)] and optical [polarized light microscopy (PLM)] characterization of TAαCyD, TAβCyD, and TAγCyD samples prepared by recrystallization from various solvents. Analysis was also performed on samples isolated by processing each TACyD alone under the experimental conditions of kneading, evaporative crystallization, and spray-drying used by us for preparing interaction products of vancomycin hydrochloride (VCM·HCl) with peracetylated CyDs [11–14].

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2. Experimental

2.1. Materials

TAαCyD, TAβCyD, and TAγCyD (a gift from Wacker-Chemie Italia SpA, Milan, Italy) were used. Their physicochemical features were: (a) TAαCyD (CAVASOL W6 TA): molecular weight on anhydrous basis $M(C_{72}H_{96}O_{48})$ = 1729.6 g mol^{-1}; mass loss (by TGA, see below) 1.19 ± 0.26% (w/w) (corresponding to ≈1 mol H_2O per TAαCyD mol); apparent density 400 kg m^{-3}; virtually insoluble in water at 25 °C; (b) TAβCyD (CAVASOL W7 TA): molecular weight on anhydrous basis $M(C_{84}H_{112}O_{56})$ = 2017.8 g mol^{-1}; mass loss (by TGA, see below) 0.79 ± 0.02% (w/w) (corresponding to ≈0.8 mol H_2O per TAβCyD mol); apparent density 350 kg m^{-3}; virtually insoluble in water at 25 °C; (c) TAγCyD (CAVASOL W8 TA): molecular weight on anhydrous basis $M(C_{96}H_{128}O_{64})$ = 2306.1 g mol^{-1}; mass loss (by TGA, see below) 0.97 ± 0.28% (w/w) (theoretical value for TAγCyD·H_2O 0.77%); apparent density 400 kg m^{-3}; virtually insoluble in water at 25 °C.

All other materials and solvents were of analytical reagent grade.

2.2. Sample preparation

Recrystallization experiments were carried out using saturated solutions of each TACyD (<180 μm sieve granulometric fraction) in various solvents (methanol, methanol/water 4/1 (v/v), ethanol, ethanol/water 1/1 (v/v), ethyl acetate, acetone, acetone/water 1/1 (v/v), 1-propanol, 2-propanol, 2-propanol/water 4/1 (v/v)) at the respective boiling points by spontaneous cooling to room temperature (Table 1). Kneading samples were prepared using ≈500 mg of each pure TACyD which were wetted with ≈1 mL of acetone/water 1/1 (v/v) solution, ground in a glass container for 3 min and microwave irradiated (Pabisch CM-Aquatronic, microwave power input 425 W) for 15 min. Microwave irradiation is reported to be a convenient method for carrying out inclusion reactions [15] and was used for preparing interaction products of VCM·HCl with peracetylated CyDs [11,12]. Pure TACyDs were dissolved by gently heating in methanol/water 4/1 (v/v) (≈50 mL g^{-1} of TACyD), acetone/water 1/1 (v/v) (≈20 mL g^{-1} of TACyD), and in 2-propanol/water 4/1 (v/v) solutions (≈30 mL g^{-1} of TAαCyD, ≈100 mL g^{-1} of TAαCyD, ≈150 mL g^{-1} of TAγCyD), which were evaporated under the same conditions of microwave heating used for the kneading samples. Spray-drying (Mini Spray Dryer B-191, Buchi, Flawil, CH) was carried out on acetone/water 1/1 (v/v) solutions of each TACyD under the following experimental conditions: T_{inlet} 130 °C, pump feed rate 3 mL min^{-1}; aspirator efficiency 32 m^3 h^{-1}. Microwave drying and spray-drying were also carried out on aqueous suspensions of each pure TACyD (≈100 mL g^{-1} of TACyD).

Table 1
Amount of solvent (mL g^{-1}) of peracetylated CyD used in the recrystallization experiments

Solvent	TAαCyD	TAβCyD	TAγCyD
Methanol	6	–	10
Methanol/water 4/1 (v/v)	50	60	25
Ethanol	4	70	10
Ethanol/water 1/1 (v/v)	–	–	12
1-Propanol	3	23	7
2-Propanol	9	–	–
2-Propanol/water 4/1 (v/v)	22	86	120
Acetone	4	3	2
Acetone/water 1/1 (v/v)	6	20	12
Ethyl acetate	4	4	2

2.3. Differential scanning calorimetry (DSC)

Temperature and enthalpy values were measured with a Mettler STAR^e system equipped with a DSC821^e Module and an Intracooler device for subambient temperature analysis (Julabo FT 900) on 3–5 mg (Mettler M3 Microbalance) samples in sealed aluminium pans with pierced lid (β = 10 K min^{-1}, static air atmosphere, −10 to 300 °C temperature range). Measurements were carried out at least in triplicate.

2.4. Thermogravimetric analysis (TGA)

Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell on 8–10 mg samples in open alumina crucibles (β = 10 K min^{-1}, static air atmosphere, 30–300 °C temperature range). Measurements were carried out at least in triplicate.

2.5. Microscopic analysis (PLM)

Microscopic observation of the sample morphology was performed under a Reichert (Arnsberg, Germany) polarized light microscope. Images were taken with a MOTICAM 2000 video-camera and elaborated with Adobe Photoshop 7.0.

2.6. Powder X-ray diffractometry (XRPD)

XRD powder patterns were taken at ambient temperature with a computer-controlled Philips PW 1800/10 apparatus (powdered samples in Al holders; $CuK_{\alpha,1}$ = 1.54060 Å, $CuK_{\alpha,2}$ = 1.54439 Å; 2–50° 2θ scan range; 0.02° 2θ s^{-1} scan speed; monochromator: graphite crystal). The program LAZY PULVERIX [16] was used to generate the idealized XRPD patterns for CuK_α radiation (1.5418 Å) of TAαCyD·2H_2O [17] and TAβCyD·CH_3OH [18].

2.7. Fourier transform infrared spectroscopy (FTIR)

Mid-IR (650–4000 cm^{-1}) spectra were recorded on powder samples using a Spectrum One Perkin-Elmer FTIR spectrophotometer (resolution 4 cm^{-1}) equipped with a MIRacle^{TM} ATR device (Pike Technologies).

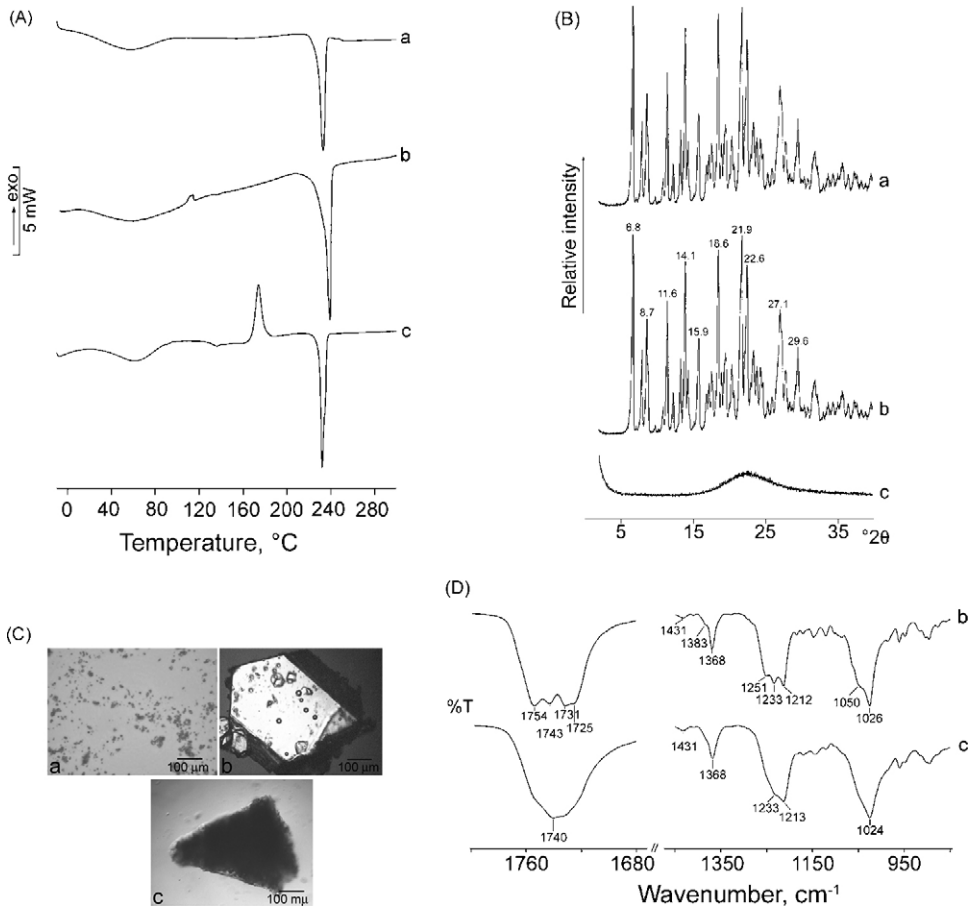

Fig. 1. Physical chemical characterization of commercial TAαCyD (a), TAαCyD·2H_2O by recrystallization from 2-propanol/water 4/1 (b), and amorphous TAαCyD by microwave-drying of a 2-propanol/water 4/1 (v/v) solution (c). Key: (A): DSC curves. (B): XRPD patterns with 2θ values of the most intense diffraction peaks for (b). (C): Photomicrographs. (D): FTIR spectra in the 1800–1680 cm^{-1} and 1450–850 cm^{-1} wavenumber regions.

3. Results and discussion

3.1. TAαCyD

TAαCyD is commercially available as a pseudopolymorph with a TGA mass loss corresponding with a monohydrate stoichiometry (see Section 2), which by heating between −3.5 and 103 °C transformed into a crystalline anhydrous form melting at 232.5 ± 0.5 °C with an associated fusion enthalpy of 43 ± 3 J g^{-1} (curve (a) in Fig. 1(A)). By evaporative crystallization or recrystallization of commercial TAαCyD from 2-propanol/water 4/1 (v/v) or methanol/water 4/1 (v/v) solutions, as well as by kneading, crystalline TAαCyD·2H_2O with a DSC profile very similar as that of the commercial product was isolated (curve (b) in Fig. 1(A)). The exothermal accident which follows the dehydration endotherm can be attributed to crystallization of a small portion of amorphous TAαCyD present in the crystalline sample. The XRPD pattern of crystalline TAαCyD·2H_2O recrystallized from 2-propanol/water 4/1 (v/v) solution (pattern (b) in Fig. 1(B)) was substantially superimposable to that of commercial TAαCyD (pattern (a) in Fig. 1(B)) and in good agreement with the theoretical pattern drawn from single-crystal X-ray data [17]. Water content (by TGA) of TAαCyD·2H_2O was generally lower than the theoretical value of 2.04% by weight (for example, 1.43% by weight for the kneading product) because during TGA runs at a starting temperature of 30 °C samples begun losing water at room temperature (≈23 °C). This can be expected by the weak hydrogen bonds involving one of the water molecules in the dihydrate crystal [17]. X-ray amorphous TAαCyD was isolated by recrystallization from acetone, acetone/water 1/1 (v/v), ethanol, 1-propanol, 2-propanol or ethylacetate, by spray-drying of acetone/water 1/1 (v/v) solutions (which is the preparation method of the interaction products between TACyDs and VCM·HCl [11,12]), and by microwave-drying of 2-propanol/water 4/1 (v/v) solutions (pattern (c) in Fig. 1(B)). During DSC runs, after water loss, amorphous TAαCyD showed a glass transition at $T_{midpoint}$ = 135.4 °C and then crystallized at about 180 °C into the above described TAαCyD anhydrous form (pf 232.8 °C, ΔH_{fus} = 42 J g^{-1}) (curve (c) in Fig. 1(A)). A well developed prismatic crystal of TAαCyD·2H_2O (picture (b)) compared with microcrystalline commercial TAαCyD (picture (a)) and an opaque glassy chip of amorphous TAαCyD (picture (c)) are shown in Fig. 1(C). The FTIR spectrum of crystalline TAαCyD·2H_2O (spectrum (b) in Fig. 1(D)) was very similar as that of the commercial product (not shown), as it can be expected from similarity of the respective XRPD patterns (a) and (b) in Fig. 1(B). The dominant absorption bands were

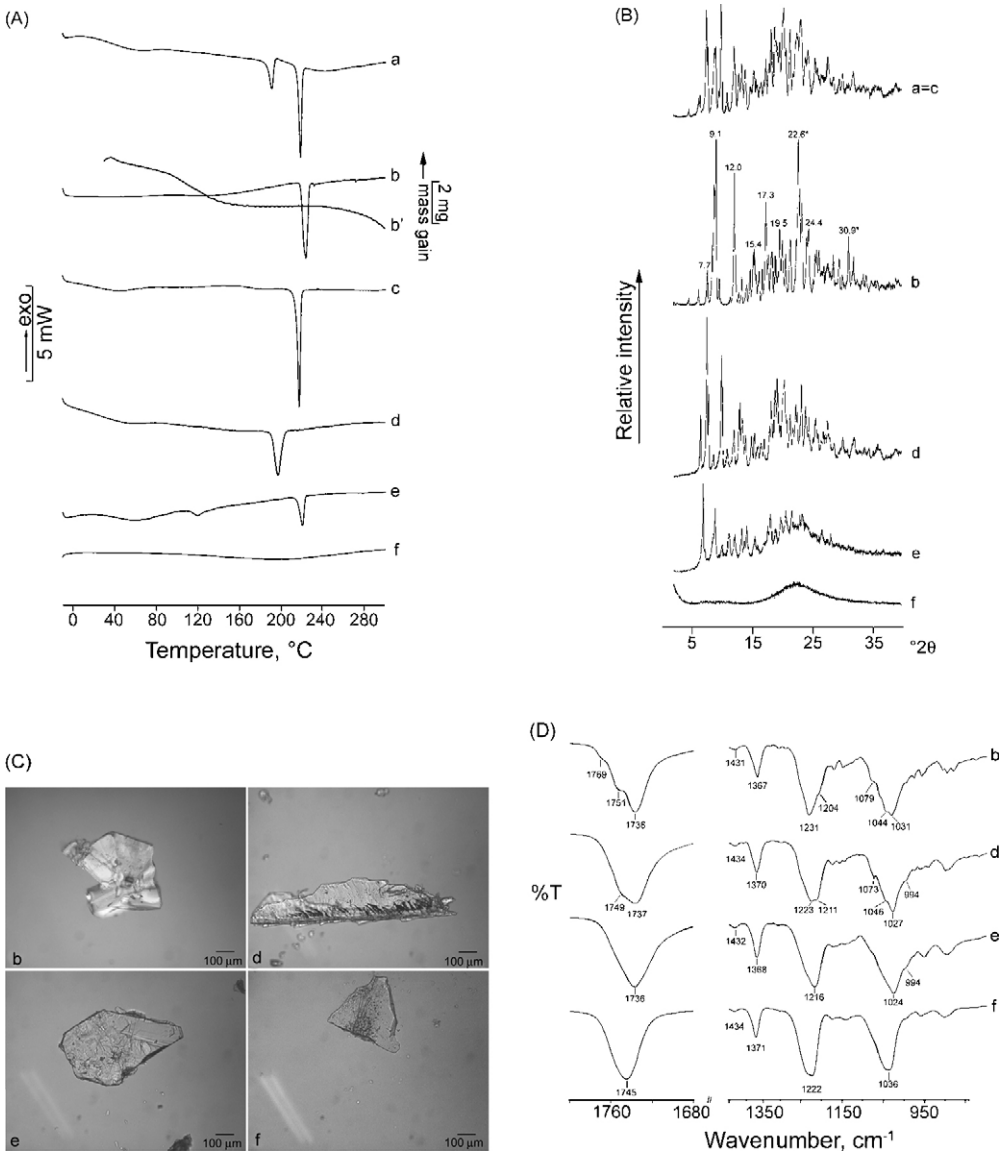

Fig. 2. Physical chemical characterization of commercial TAβCyD (a), TAβCyD·CH_3OH by recrystallization from methanol/water 4/1 (b), TAβCyD hydrate by spray-drying of aqueous suspensions (c), TAβCyD hydrate by microwave-drying of methanol/water 4/1 (v/v) solution (d), TAβCyD 2-propanolate-hydrate by recrystallization from 2-propanol/water 4/1 (v/v) (e), and amorphous TAβCyD by spray-drying of acetone/water 1/1 (v/v) solutions (f). Key: (A): DSC curves (TGA curve for (b) superimposed to DSC). (B): XRPD patterns with 2θ values of the most intense diffraction peaks and peaks of higher intensity than the theoretical value – see text – marked with stars for (b); pattern (c) superimposable to (a). (C): Photomicrographs. (D): FTIR spectra in the 1800–1680 cm^{-1} and 1450–850 cm^{-1} wavenumber regions.

those due to C=O stretching vibration over the wavenumber range 1800–1680 cm^{-1}, C–O asymmetric stretching vibration of acetates at 1251 cm^{-1}, and asymmetric stretching of the O–CH_2–C groups for acetates of primary alcohols at 1026 cm^{-1}, whilst medium and weak bands at 1368 and 1431 cm^{-1} can be attributed to symmetric and asymmetric deformation of the CH_3 group for acetates [19] (spectrum (b) in Fig. 1(D)). The FTIR spectrum (c) of amorphous TAαCyD resembled that of the crystalline sample, though the absorption bands were not so well resolved and sharp but broader suggesting a wide range of hydrogen bond lengths and orientation due to a less ordered structure [20].

3.2. TAβCyD

Thermal behaviour of commercial TAβCyD was typical of a crystalline (see pattern (a) in Fig. 2(B)) pseudopolymorph that after solvent loss between 13 and 97 °C transformed into a lower-melting anhydrous polymorph I ($T_{fus,I} = 192.2 \pm 1.8$ °C, $\Delta H_{fus,I} = 25 \pm 1$ J g^{-1}) which in turn recrystallized at about 200 °C into a higher-melting form II ($T_{fus,II} = 218.5 \pm 0.8$ °C, $\Delta H_{fus,II} = 41 \pm 2$ J g^{-1}) (curve (a) in Fig. 2(A)). Crystalline TAβCyD monomethanolate from methanol/water 4/1 (v/v) desolvated following a smooth deflection of the baseline over the 99–179 °C temperature range (curve (b) in Fig. 2(A)), with a

corresponding TGA mass loss of $1.58 \pm 0.03\%$ by weight (theoretical value 1.56%) (curve (b′)), giving the pure anhydrous TAβCyD higher-melting polymorph II ($T_{fus,II} = 220.4 \pm 1.2\,^{\circ}C$, $\Delta H_{fus,II} = 40 \pm 2\,J\,g^{-1}$). The rather high desolvation temperature of TAβCyD·CH_3OH ($T_{onset} \approx 126\,^{\circ}C$) can be expected by the rather strong O–H. . .O hydrogen bonds of 2.76 and 2.82 Å in which the methanol molecule is involved in the crystal [18]. The theoretical XRPD pattern of TAβCyD·CH_3OH drawn from single-crystal data [18] was in agreement with the experimentally recorded pattern (b) in Fig. 2(B). The higher diffraction intensity of the peaks marked with stars with reference to the theoretical values can be ascribed to preferred orientation of the powder in the sample holder, i.e. non-random distribution of the crystal orientation [21]. The difference in desolvation temperature for TAβCyD·CH_3OH and commercial TAβCyD was an indirect experimental proof that the commercial product was composed of a different pseudopolymorph, probably a hydrate (see Section 2). Spray-drying of aqueous suspensions of TAβCyD gave a product with an XRPD pattern superimposable with that of commercial TAβCyD (pattern (c) in Fig. 2(B)), which dehydrated during DSC runs to pure TAβCyD higher-melting polymorph II (pf 220.5 °C, fusion enthalpy $41\,J\,g^{-1}$) (curve (c) in Fig. 2(A)). By evaporation or microwave-drying of a saturated solution of TAβCyD in methanol/water 4/1 (v/v), a pseudopolymorph with a XRPD pattern very similar as that of commercial TAβCyD (pattern (d) in Fig. 2(B)) which however desolvated to pure lower-melting anhydrous polymorph I (curve (d) in Fig. 2(A)) was isolated. Thermal

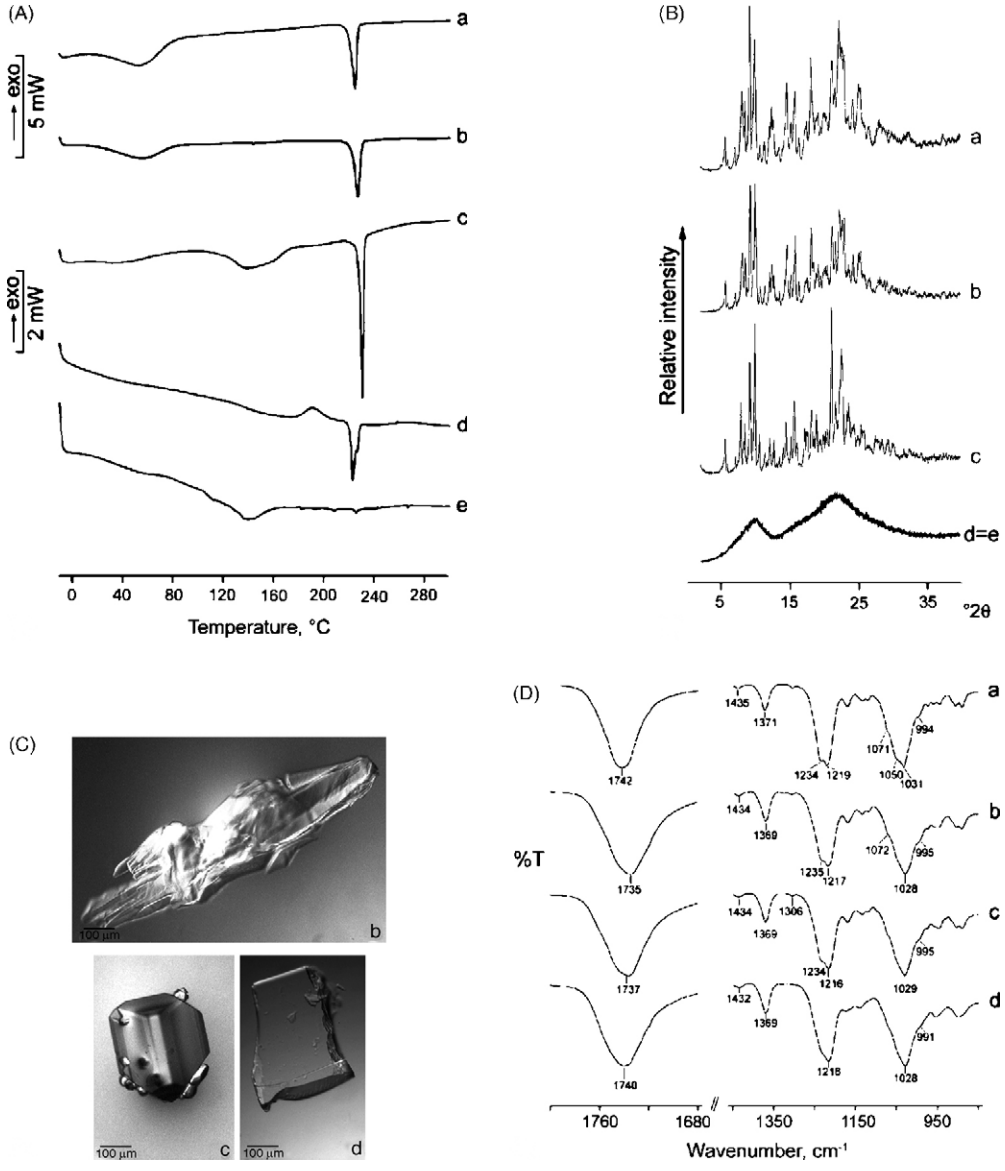

Fig. 3. Physical chemical characterization of commercial TAγCyD (a), TAγCyD·H_2O by recrystallization from methanol/water 4/1 (v/v) (b), TAγCyD isopropanolate-hydrate by recrystallization from 2-propanol/water 4/1 (v/v) (c), amorphous TAγCyD by spray-drying of acetone/water 1/1 solutions (d), and amorphous TAγCyD by recrystallization from ethyl acetate (e). Key: (A): DSC curves. (B): XRPD patterns; pattern (e) superimposable to (d). (C): Photomicrographs. (D): FTIR spectra in the 1800–1680 cm^{-1} and 1450–850 cm^{-1} wavenumber regions.

data ($T_{fus,I} = 192.9 \pm 2.2\,^{\circ}C$, $\Delta H_{fus,I} = 24 \pm 2\,J\,g^{-1}$) suggested a monotropic relationship with the higher melting form II according to the Heat of Fusion Rule [22]. Recrystallization of commercial TAβCyD from 2-propanol/water 4/1 (v/v) gave a pseudopolymorph which, after two distinct DSC desolvation steps between 18–103 °C (TGA mass loss 2.8% by weight) and 109–136 °C (TGA mass loss 1.05% by weight), transformed into the pure anhydrous TAβCyD higher-melting polymorph II (curve (e) in Fig. 2(A)). Thermal data accounted for a 2-propanolate-hydrate TAβCyD crystalline form (overall theoretical mass loss 3.72% by weight), as confirmed by its distinct XRPD pattern which revealed concomitantly a lower crystallinity degree than that of other crystalline forms (pattern (e) in Fig. 2(B)). Recrystallization from acetone or ethyl acetate, spray-drying of acetone/water 1/1 (v/v) solutions or microwave-drying of 2-propanol/water 4/1 (v/v) or ethanol solutions of the commercial product led to an X-ray amorphous form of TAβCyD (pattern (f) in Fig. 2(B)) which showed no tendency to recrystallize during DSC scans (see curve (f) in Fig. 2(A)). Fig. 2(C) shows that crystals of the TAβCyD pseudopolymorphs recrystallized from methanol/water 4/1 (v/v) (picture (b)) and 2-propanol/water 4/1 (v/v) (picture (e)) had significant bulk in all directions and are well developed. The crystal isolated by microwave-induced evaporative crystallization of a methanol/water 4/1 (v/v) saturated solution (picture (d)) was elongated in one axis, while amorphous TAβCyD (picture (f)) appeared as a transparent glassy chip. FTIR spectra of the TAβCyD solid forms presented in Fig. 2(D) showed the same main features as those for TAαCyD solid forms (see Fig. 1(D)). Distinct differences in some absorbtion bands can be found among TAβCyD crystalline pseudopolymorphs, i.e. methanolate, hydrate and 2-propanolate-hydrate, as well as between each crystalline pseudopolymorph and the amorphous form.

3.3. TAγCyD

TAγCyD is commercially available as a pseudopolymorph characterized by the XRPD pattern (a) in Fig. 3(B), which after solvent loss between 6 and 88 °C around 1% by weight (see Section 2), transformed into a crystalline anhydrous form melting at $225.6 \pm 1.1\,^{\circ}C$ with an associated fusion enthalpy of $25.3 \pm 0.2\,J\,g^{-1}$ (curve (a) in Fig. 3(A)). TAγCyD recrystallized from methanol/water 4/1 (v/v) showed thermal (curve (b) in Fig. 3(A)) and X-ray diffraction (pattern (b) in Fig. 3(B)) behaviour very similar as those of commercial product, though an exact monohydrate stoichiometry resulted from TGA (mass loss $0.77 \pm 0.02\%$ by weight, theoretical value for TAγCyD·H_2O 0.77%). Thermal behaviour of TAγCyD recrystallized from 2-propanol/water 4/1 (v/v) showed both a DSC (curve (c) in Fig. 3(A)) and TGA two-step desolvation profile which can be attributed to a double solvate, i.e. hydrate (TGA mass loss between 7 and 81 °C $0.90 \pm 0.23\%$ by weight, theoretical for TAγCyD·H_2O 0.77%) and 2-propanolate (TGA mass loss between 102 and 180 °C $3.84 \pm 0.6\%$ by weight, theoretical for TAγCyD·$1.5CH_3CHOHCH_3$ 3.76%). Similar biphasic desolvation profiles (not shown) were observed for TAγCyD samples recrystallized from 1-propanol, acetone or acetone/water 1/1 (v/v), so that an isostructural relationship between these crystalline pseudopolymorphs can be desumed [23]. Thermal behaviour of TAγCyD samples isolated by spray-drying of acetone/water 1/1 (v/v) solutions or by recrystallization from ethyl acetate (or acetone), which were both amorphous showing the same XRPD pattern (d) and (e) in Fig. 3(B), demonstrated, respectively, the tendency (curve (d) in Fig. 3(A)) or no tendency (curve (e) in Fig. 3(A)) to recrystallize by heating. The recrystallization product during a DSC scan ($T_{exo} \approx 190\,^{\circ}C$) of the amorphous sample obtained by spray-drying of acetone/water 1/1 (v/v) solutions showed a distinct melting peak at 222.5 °C with a shoulder at 227.0 °C (close to the fusion temperature of the common desolvation product of TAγCyD pseudopolymorphs) (curve (d) in Fig. 3(A)). The presence of a lower-melting anhydrous TAγCyD polymorph with a fusion enthalpy of $18.9 \pm 0.3\,J\,g^{-1}$ in monotropic relationship with the higher melting form according to the Heat of Fusion Rule [22] can be therefore assumed. An irregularly shaped crystal elongated in one axis of TAγCyD·H_2O (picture (b)), a well developed chunky prismatic crystal of TAγCyD 2-propanolate hydrate (picture (c)), and a transparent glassy chip of amorphous TAγCyD (picture (d)) are shown in Fig. 3(C). FTIR spectra of the TAγCyD solid forms in Fig. 3(D) showed the same main features as those for the other TACyDs solid forms (see Figs. 1(D) and 2(D)). The very similar FTIR spectra of TAγCyD·H_2O and TAγCyD 2-propanolate hydrate and the similarity of the respective XRPD patterns (b) and (c) in Fig. 3(B) accounted for an isostructural relationship also between these crystalline solvates of TAγCyD.

4. Conclusion

A number of crystalline forms of TAαCyD (anhydrous and dihydrate), TAβCyD (two monotropic anhydrous polymorphs and three pseudopolymorphs, i.e. methanolate, hydrate, and isopropanolate-hydrate) and TAγCyD (two monotropic anhydrous polymorphs and two pseudopolymorphs, i.e. a hydrate isostructural with an isopropanolate-hydrate), as well as the amorphous forms of each TACyD, were isolated and characterized from the thermal and structural point of view. Thermal data for desolvation of TAαCyD·$2H_2O$ and TAβCyD·CH_3OH can be reconciled with the reported crystal packing features. Melting temperatures and enthalpies of the crystalline forms of each TACyD can be referred to for possible solid-state interactions between peracetylated α-, β-, and γ-CyD with drugs.

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