Journal of Thermal Analysis and Calorimetry, Vol. 68 (2002) 517–529

THERMAL AND STRUCTURAL CHARACTERIZATION OF COMMERCIAL α-, β-, AND γ-CYCLODEXTRINS

G. Bettinetti[1*], *Cs. Novák*[2] *and M. Sorrenti*[1]

[1]Dipartimento di Chimica Farmaceutica, Università di Pavia, Viale Taramelli 12, I-27100 Pavia, Italy
[2]Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, Research Group for Technical Analytical Chemistry of the Hungarian Academy of Sciences, Szent Gellért tér 4, H-1111 Budapest, Hungary

Abstract

α-, β-, and γ-cyclodextrins (CDs) marketed by five different companies were characterized from the thermal and structural point of view. Three αCD samples showed two-step DSC dehydration profiles and their XRD patterns were characteristic for αCD·6H_2O form I, whereas one brand with an apparent three-step DSC dehydration behaviour was a mixture of αCD·6H_2O form I and anhydrous αCD. The differences in the DSC profiles after dehydration and EGA onset decomposition temperatures recorded for the five βCD brands were attributed to different manufacturing and purification processes. The five γCDs brands showed a common thermal behaviour and very similar XRD patterns. The patterns did not match the idealized pattern of γCD·14.1H_2O, indicating the occurrence of two different hydrated crystal structures.

Keywords: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, differential scanning calorimetry (DSC), evolved gas analysis (EGA), simultaneous thermogravimetry and differential thermal analysis (STA), thermomechanical analysis (TMA), X-ray diffractometry (XRD)

Introduction

Cyclodextrins (CDs) are well known to provide enhanced bioavailability and physical and chemical stability of poorly water soluble and chemically unstable pharmaceuticals [1]. In addition, CDs have been proposed as pharmaceutical excipients [2], and monographies for αCD [2] and βCD [2, 3] are included in official compendia. αCD, βCD, and γCD hydrates are commercially available in a quality suitable for use in pharmaceutical oral, topical/transdermal and transmucosal formulations. αCD is most frequently encountered as hexahydrate form I [4], but it

* Author for correspondence: Phone: (39-0382) 507-368; Fax: (39-0382) 507-368; E-mail: gpbettinetti@unipv.it

1418–2874/2002/ $ 5.00
Akadémiai Kiadó, Budapest

can be also found as the polymorph form II [5] and the non-stoichiometric hydrate with 7.57 waters per αCD molecule [6]. Various structural studies have been carried out for βCD [7–10] which is a non-stoichiometric hydrate [11] with variable water content from 12.3 H_2O at 100% to about 9.4 H_2O at 15% humidity without altering its ordered crystalline structure [12, 13]. Crystal structures of γCD·17H_2O at 120 K [14], γCD·14.1H_2O at room temperature [15], and γCD·15.7H_2O at 110 K [16] have been reported. The solid state properties of a material to be used as pharmaceutical excipient may influence some physicochemical characteristics such as particle size, specific surface area, flowability, compactibility, etc., which in turn influence the quality (i.e., stability, bioavailability, efficacy, safety) of the dosage forms. Hence the crystal form and/or the water content of the used CD may be critical factors in the excipient functionality and/or performance [17, 18]. Since CDs are produced by many suppliers through different manufacturing processes and may exhibit source-to-source and/or batch-to-batch variability, solid-state characterization of five commercially available brands of αCD, βCD, and γCD was carried out using various thermoanalytical techniques and X-ray diffractometry. Evolved gas analysis (EGA), a technique which has been employed to investigate inclusion complexation [19] and gives information about the purity and stability of the cyclodextrins, was used to detect possible organic contamination and/or impurities related to different crystal forms, manufacturing processes, and storage conditions. Such organic impurities were probably responsible for the initially assumed toxicity of CDs [20]. Simultaneous thermogravimetry and differential thermal analysis (STA), differential scanning calorimetry (DSC), and thermomechanical analysis (TMA) were also employed to give a comprehensive thermoanalytical description of such commercially available CDs. The X-ray diffraction (XRD) powder patterns of commercial CDs were also recorded and compared to the computer calculated patterns reported for αCD·6H_2O form I [4], βCD·12H_2O [7, 12], and γCD·14.1 H_2O [15].

Experimental

Materials

Commercial samples of αCD, βCD, and γCD from different firms (Archemia, I-Milan; Mercian Corporation, Japan-Tokyo; Nihon Shokuhin Kako, Japan-Tokyo; Roquette-Frères, F-Lille; Wacker-Chemie GmbH, D-München) were used as received. According to the light microscopic observations, the particle size of powders were similar. Their average diameters were in the range of 100–300 μm. αCD, βCD, and γCD of the same brand were indicated with a number from one to five, without referring to the order in which the firms are reported.

Evolved Gas Analysis

Evolution of organic compounds from CDs as a function of temperature was detected using a DuPont 916 Thermal Evolution Analyzer equipped with a hydrogen-air flame

ionization detector which is very sensitive for the organic components and gives no sign for inorganic compounds (water, carbon dioxide). The sample mass was about 5 mg samples in open aluminium pans. Besides β=8 K min^{-1} heating rate and nitrogen purge gas with a flow rate of 1.8 L h^{-1} have been applied. The thermoanalytical runs have been carried out between 30–350°C. Duplicate measurements were made for each sample.

Simultaneous Thermogravimetry-Differential Thermal Analysis

Simultaneous measurements of mass changes and transition temperatures were performed with a TA Instruments 2960 STA, simultaneous DTA-TG unit. The applied experimental conditions were: about 6 mg samples were placed into a platinum crucible with a heating rate of 5 K min^{-1} from 30 to 300°C under an argon flow (flow rate 10 L h^{-1}). Duplicate measurements were made for each sample.

Differential Scanning Calorimetry

Temperature and enthalpy values were measured with a TA Instruments 2920 MDSC apparatus on about 6 mg samples in open aluminium pans under argon with a flowing rate of 10 L h^{-1}. An opened empty pan was used as reference. The applied heating rate was 5 K min^{-1} over the 30–300°C temperature range. Duplicate measurements were made for each sample.

Thermomechanical Analysis

TMA was done with a Mettler TA4000 apparatus equipped with a TMA 40 cell on tablets ≈1 mm thick which were obtained by compressing in a hydraulic press with a 1.0 cm diameter die ≈200 mg of sample at 5 t for 3 min. The instrument operated as a dilatometer under negligible (or zero) load, and the expansion of the sample was evaluated by measuring the increase in sample thickness consequent to water loss over the 30–220°C temperature range under static air atmosphere at a heating rate of 10 K min^{-1}. At least four replicate measurements were made for each sample.

X-ray Diffractometry

X-ray powder diffraction patterns were taken at ambient temperature and atmosphere with a computer-controlled Philips PW 1800/10 apparatus equipped with a specific PC-APD software with powdered samples placed in Al holders. Wavelengths: $CuK_{\alpha,1}$=1.54060 Å, $CuK_{\alpha,2}$=1.54439 Å. Scan range: 2–50° 2θ. Scan speed: 0.02° 2θ s^{-1}. Monochromator: graphite crystal. The unit cell data for αCD·6H_2O form I [4], βCD·12H_2O [7, 12], and γCD·14.1H_2O [15] were used as input to a local computer program to generate the idealized XRD patterns for these species.

Results and discussion

Thermal characterization of α-, β-, and γ-cyclodextrins

CDs are known to crystallize as hydrates, with water molecules in part included in the cavity of the macrocycle and in part localized in the interstices between macrocycles within the crystal lattice. CDs are also able to form inclusion complexes with a variety of guest molecules, including organic solvents such as methanol [21, 22], ethanol [23], and *n*-propanol [24].

αCDs

Despite that the sample named to brand #5 is about 20 years old, its EGA curve (Fig. 1a) indicates the evaporation of organic, volatile compound(s), probably trace(s) of aromatic or chlorinated solvents used in the preparation and separation of CDs [20]. It evolves right after the three-step dehydration of the α-cyclodextrin sample. Three samples (brands #1, #3 and #4) of αCD showed flat EGA profiles between room temperature and 250°C (before their decomposition) and two-step of dehydration DSC patterns were characteristic for the hexahydrate form I [25–29]. The sharp endotherm peak at ≈140°C (the corresponding enthalpy value is about 7.5 J g^{-1}) without any mass loss effect can be attributed to a phase transition of the anhydrous αCD to another form [27]. The characteristic of the phase transition mentioned above will be even more investigated in future work. (The thermal behaviour of brands #1 and #4 were very similar to brand #3, Fig. 1b, so far, these curves here are not presented.)

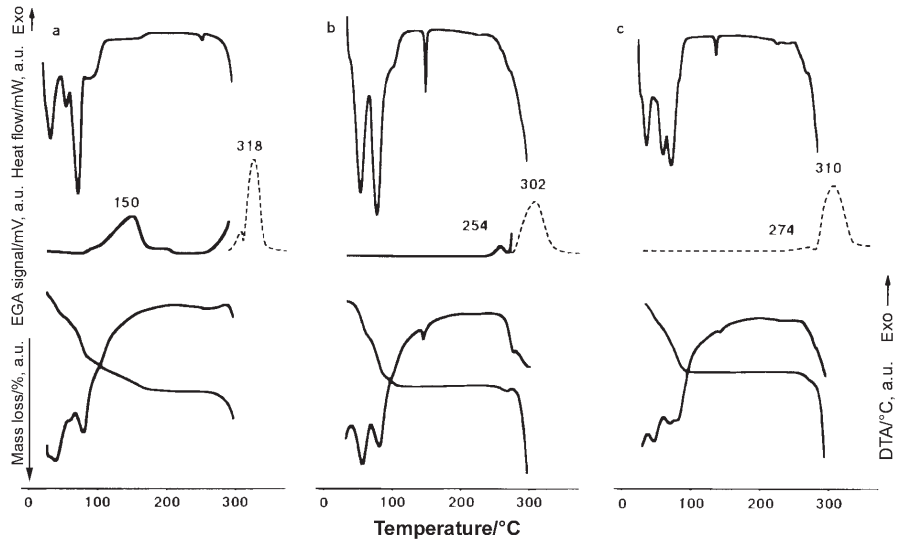

Fig. 1 DSC (top), EGA (middle), and STA (bottom) curves of αCD brands. (a – #5 brand containing organic compound, b – #3 brand, αCD·6H_2O Form I and c – #2 brand is a mixture of αCD·6H_2O Form I and anhydrous αCD

The DSC curve of brand #2 αCD shows the characteristics of a mixture of αCD hexahydrate (Form I) and anhydrous αCD (see later) and exhibited a peculiar three-step dehydration profile (Fig. 1c).

β*CDs*

According to their EGA profiles, no any traces of evaporation of organic compounds have been observed below their decomposition. This latter started between 230–280°C as it has proven by Fig. 2a.

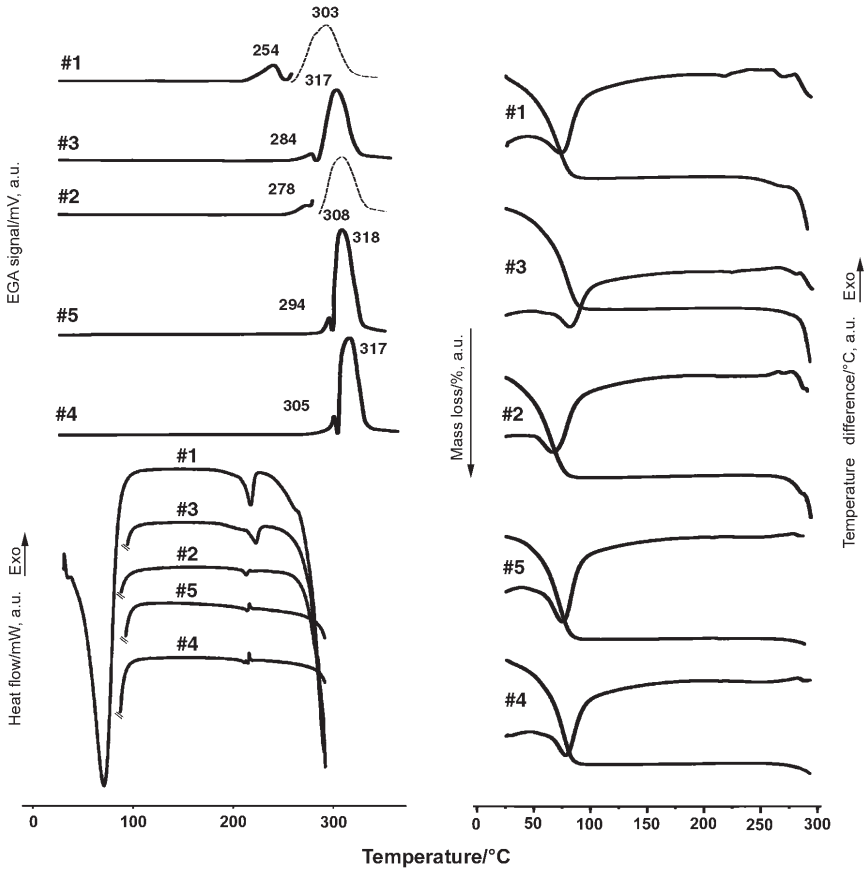

Fig. 2 EGA (top, left), DSC (bottom, left) and STA (right) curves of βCD brands

γ*CDs*

Similarly to βCDs, the examined γCDs gave also a flat EGA curves below their decomposition. The onset values of their decomposition temperatures varied from 265°C for #1 brand to 280°C (for #3 and #5 brands) and 287°C (for #2 and #4 brands)

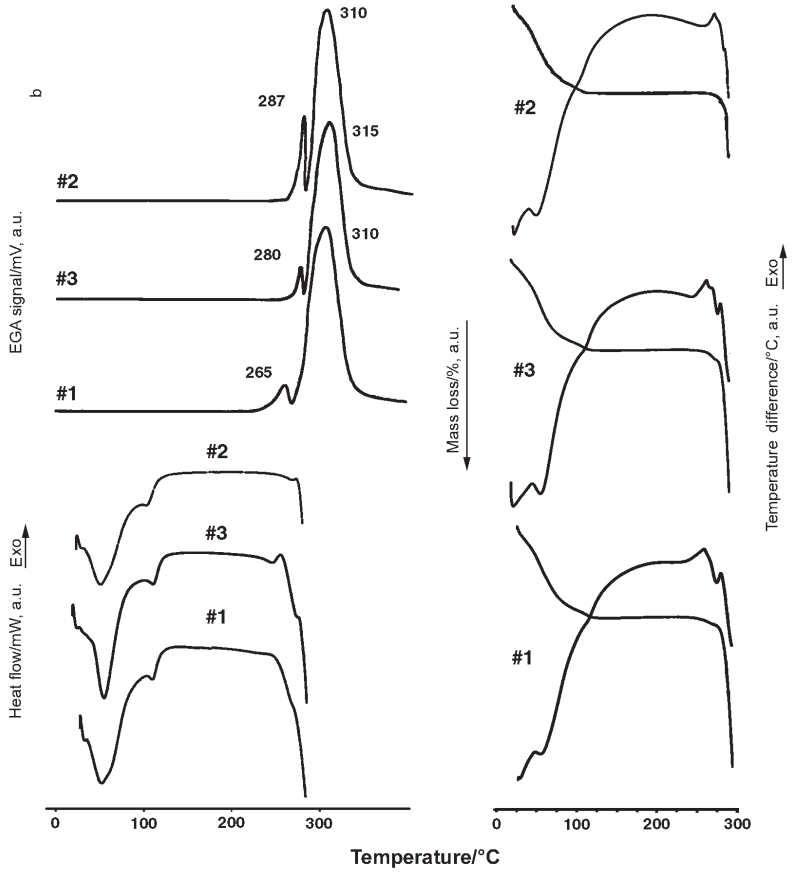

Fig. 3 EGA (top, left), DSC (bottom, left), and STA (right) curves of γCD brands

(Fig. 3). (The thermoanalytical behaviour of #5 and #4 brands are very similar that of #3 and #2 brands, respectively, curves here are not presented.)

For the evaluation of the total mass loss due to water (or water and organic contaminants in case of the old αCD batch) evolution, the representative initial temperature values were determined as 30°C (according to the STA experiments), whereas the corresponding end-temperatures were determined on the base of the onset decomposition temperatures observed on the EGA curves for each CD samples (Figs 1, 2, and 3). The results were in agreement with ≈6 water molecules per αCD molecule [25–29], ≈11 water molecules per βCD molecule [25, 26, 29, 30–36], and ≈7 water molecules per γCD molecule [25, 26, 29]. The specific dehydration enthalpy ΔH_i (in J mol^{-1}_{water}) of each CD was calculated from Eq. (1)

$$\Delta H_{\mathrm{i}} = \left[\frac{\Delta H_{\mathrm{i,exp}} 100}{\Delta m_{t_1 - t_2} \%} \right] M_{\mathrm{W}} \quad (1)$$

where $\Delta H_{\mathrm{i,exp}}$ is the total enthalpy change (in J g^{-1}_{sample}) experimentally determined over the integration limits of the DSC dehydration peak, $\Delta m_{t_1 - t_2}$ % is the mass loss obtained over the same temperature range, and M_{W} is the molecular mass of water (18.016 g mol^{-1}). Specific dehydration enthalpies higher than that of pure water, namely 40.7 kJ $mol^{-1}_{\mathrm{water}}$ at 100°C, were obtained for αCD (53±1 kJ $mol^{-1}_{\mathrm{water}}$), whereas values of 40±2 kJ $mol^{-1}_{\mathrm{water}}$ and of 36±8 kJ $mol^{-1}_{\mathrm{water}}$ were obtained for βCD and γCD, respectively.

Thermomechanical analysis

αCDs

TMA, a technique which has been proposed for characterization of pharmaceutical excipients for solid dosage forms [37, 38], was applied to investigate the commercial CDs. It was already observed that dehydration of βCD is accompanied by a sharp expansion of the material [30, 39], whereas αCD expands to a much lesser extent under the same de-

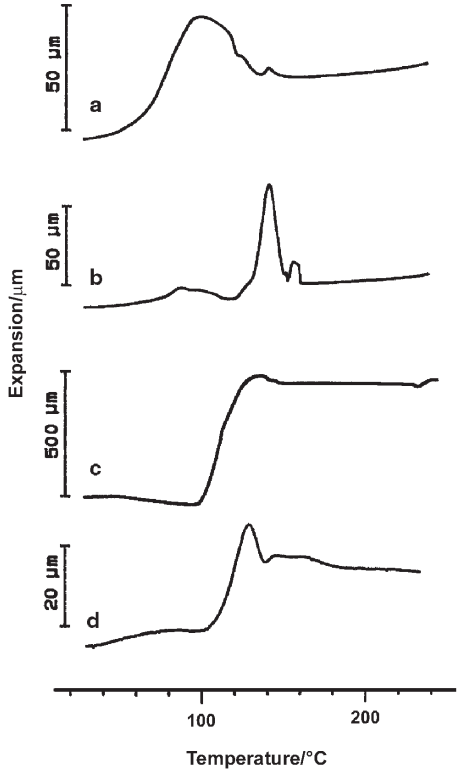

Fig. 4 TMA curves of various cyclodextrins (a – αCD, brand #2; b – αCD brand #1; c – βCD, brand #2 and d – γCD, brand #3)

hydration conditions [27, 28]. The TMA profiles of four αCD brands are very similar to each other as it looks like in Fig. 4, curve a, αCD #2 brand. The initial expansion, which is (4.0±0.5)% of the initial thickness of the sample at about 90–100°C, was followed by a gradual contraction of the substance between 100–140°C, until a plateau value was reached. (TMA curves of brands #3, #4 and #5 are very similar to brand #2, curve a.) The TMA behaviour of αCD brand #1 was found completely different (Fig. 4, curve b). After a small initial expansion ((0.53±0.22)% of the initial thickness of the sample), a more pronounced effect was observed between 120–140°C followed by a nearly symmetric contraction of the sample. An overall (3.4±0.4)% expansion related to the initial thickness of the sample has been observed.

β*CDs*

The TMA behaviour of the βCD brands was characterized by a sharp and remarkable expansion (≈30% the initial thickness of the sample) in a relatively narrow temperature range (100–130°C) (Fig. 4, curve c). No contraction of the dehydrated sample

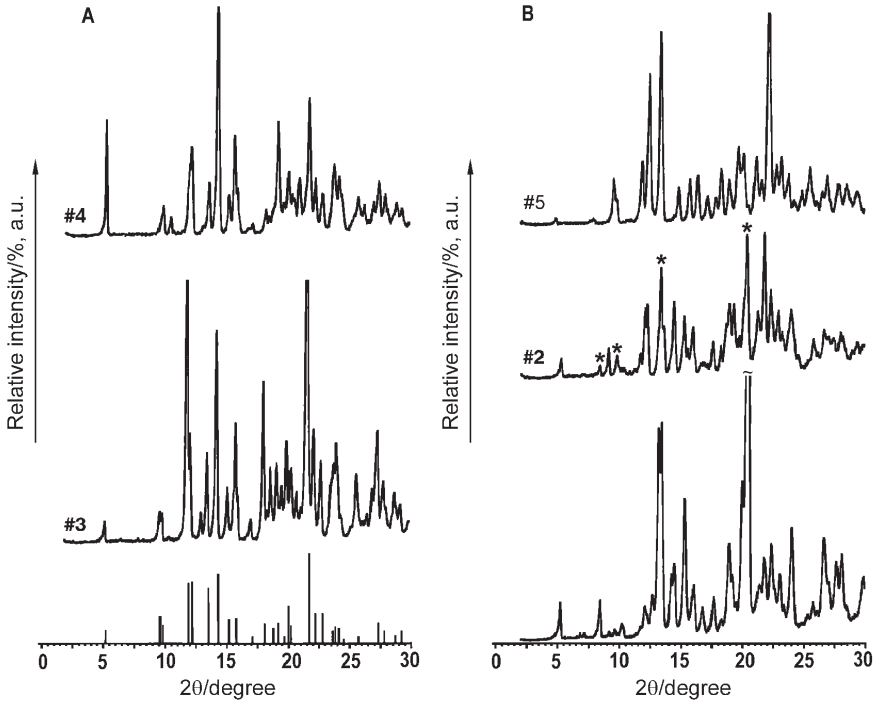

Fig. 5 XRD powder patterns of αCDs. A: αCD·6H_2O Form I (bottom – calculated, middle – measured for #3 brand; top – measured for #4 brand). B: bottom – anhydrous αCD [29], middle – #2 brand containing αCD·6H_2O Form I and anhydrous αCD, top – #5 brand containing organic compound). (The characteristic peaks of anhydrous αCD in brand #2 are marked with asterisks.)

was observed below 200°C. All further TMA curves recorded about the other βCD brands are very similar as that of brand #2.

γCDs

The γCD brands show a TMA profile which in the ascending part qualitatively resembles that of the unique αCD #1 brand (Fig. 4, curve b), with a two-step increase in sample thickness during the transformation to anhydrate (Fig. 4, curve d). The overall increase was (2.3±0.5)% the initial thickness of the sample, about a half of that was observed for γCD. (TMA curves of other γCD brands are very similar as that of brand #3.)

X-ray powder diffraction studies

αCDs

The experimental XRD powder patterns of three αCD brands matched the idealized pattern of αCD hexahydrate Form I [4] (Fig. 5A, bottom). Preferred orientation of the powder sample in the holder [40], i.e., non random distribution of crystal orientations, was probably responsible for the higher intensities of some diffraction peaks. In

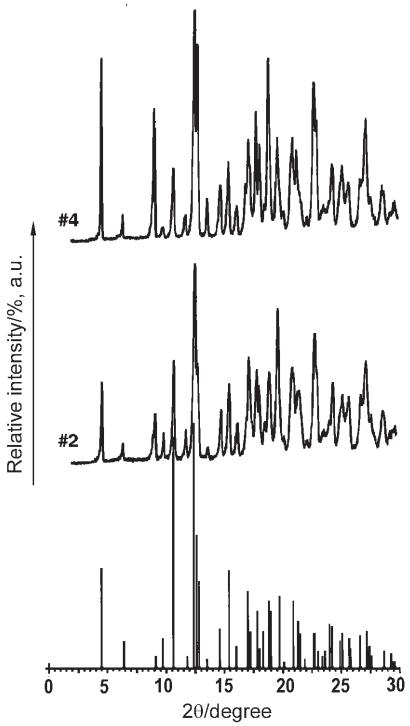

Fig. 6 XRD powder patterns of βCDs (bottom – calculated pattern for βCD·12H_2O, middle – pattern of #2 brand, top – pattern of #4 brand)

the XRD pattern of the αCD brand characterized by a three-step DSC dehydration profile (see preceding), some diffraction effects peculiar of anhydrous αCD can be seen [29], for example those at 8.3, 10.3, and 13.3 °2θ (Fig. 5B, bottom). A remarkable increase of the intensity of the second peak of the doublet at 20.1–20.4 2θ values was also due to the anhydrous αCD, whose amount in the #2 brand probably depends on the process of manufacturing and/or storage conditions. The peculiar XRD pattern of the old αCD batch with a characteristic EGA profile (see preceding) was attributed to the inclusion complex formation between an organic compound (e.g. impurity, contamination, solvent) and the αCD (Fig. 5B).

β*CDs*

The experimental XRD patterns of the βCD brands resembled that of βCD·11H_2O [29] and were in reasonably good agreement with the calculated pattern of βCD·12H_2O [7, 12] (Fig. 6, bottom). The diffraction patterns of brands #1 and #3 are very similar to brand #2 (Fig. 6, middle), while the pattern of brand #5 is very similar to brand #4 (Fig. 6, top). Preferred orientation effects on the intensities of some diffraction peaks are also evident. The computer generated patterns from the crystal structures of βCD hydrates at lower water contents, i.e., 11.6H_2O, 11H_2O, and 9.4H_2O, were substantially identical as

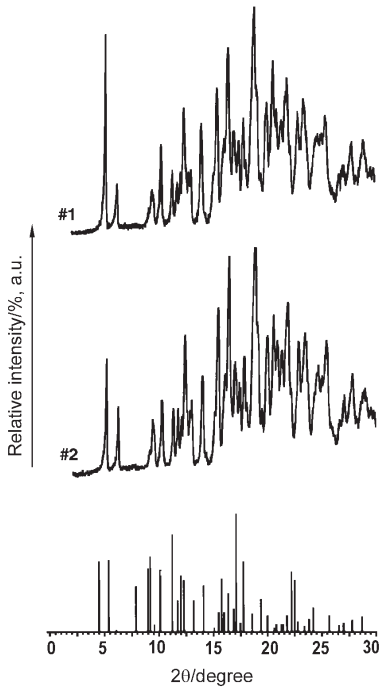

Fig. 7 XRD powder patterns of γCDs (bottom – calculated pattern of γCD·14.1H_2O, middle – pattern (corresponding to that reported for γCD·7H_2O [29]) for #2 (middle) and #1 (top) brands

that of βCD·12H_2O because continuous and reversible hydration of βCD did not affect the ordered crystalline structure [12].

γCDs

The experimental XRD patterns of the γCD brands matched that reported for γCD·7H_2O [29], which has been considered an intermediate form between anhydrous γCD and the crystal form containing ≈17 mole of H_2O (Fig. 7, bottom). The X-ray pattern of brand #5 is very similar to brand #2 (Fig. 7, middle), while brands #3 and #4 are very similar to brand #1 (Fig. 7, top). By the comparison of XRD pattern of γCD·17H_2O [29] with the theoretical pattern of γCD·14.1H_2O [15] (Fig. 7). It can be stated, that the basic structure of the 14.1H_2O hydrate was maintained despite some more water molecules built in the crystal lattice.

Conclusions

In general the thermoanalytical techniques, especially the simultaneous methods (TG-DTA, TG-DSC) permits the real-time measurement of the mass loss and enthalpy effects within one sample. The supplement of these results with evolved gas analysis (EGA) experiments is useful to characterize CDs. Besides they provide well comparable quality data about the properties of individual different batches. The differences in thermoanalytical behaviour of CDs were probably caused by the large variety of different preparation and purification procedures as well as the different storage circumstances.

TMA results provid data about the compaction properties of different CDs, which have technological importance (e.g. in tablet making). βCD expands much more extensively than αCD and γCD, exhibits better compaction properties. However, they are lost when the compound transformed into anhydrous βCD but are recovered and enhanced by rehydration [18]. Therefore, the TMA measurements can also provide a useful complement of DSC and TG results for the characterization and quality control of cyclodextrins produced for commercial purposes.

Characterization of commercial products of α-, β-, and γCD using X-ray powder diffraction allows to distinguish the different crystalline forms within the samples. By the evaluation of the XRD powder patterns it was noticed that some diffraction peaks exhibited larger intensities than those of the calculated pattern owing to the non-random distribution of crystal orientations (i.e., preferred orientation effects).

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The financial support of the OTKA T 026 459, U 31 277 and the Soros Foundation to CsN and of FAR to GB is gratefully acknowledged.

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