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CHARACTERIZATION OF SOME CYCLODEXTRIN DERIVATIVES BY THERMAL ANALYSIS

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Abstract

Acetyl-cyclodextrins, maltosyl-β-cyclodextrin, methyl-β-cyclodextrin and hydroxypropyl-cyclodextrins were characterized from data obtained with hot stage microscopy, differential scanning calorimetry and thermogravimetry. Phase transformation processes were studied by thermomicroscopy. Enthalpy values of dehydration processes have been explained with the different chemical composition of the substituent groups of cyclodextrins.

Keywords: acetyl-cyclodextrins, hydroxypropyl-cyclodextrins, maltosyl-cyclodextrin, methyl-cyclodextrin, thermal characterization

Introduction

Cyclodextrins are cyclic molecules constituted by 6, 7 or 8 units of glucose, giving rise to α, β and γ-cyclodextrin (natural cyclodextrins) respectively. They have a hydrophobic central cavity able to incorporate different molecules (guest molecules) with appropiated size and shape. The resulting compound has been named inclusion compound or inclusion complex. The inclusion compounds show physicochemical parameters completely different from which are exhibited by the free guest molecules.

As the field of application of natural cyclodextrins increases, new cyclodextrins have been created, from natural cyclodextrins through chemical synthesis or enzymatic reactions [1].

In pharmaceutical technology cyclodextrins are used to improve certain properties of several drugs (solubility, bioavailability, stability, taste, side effects, etc.) forming the corresponding drug/cyclodextrin inclusion compound [2–4].

Like other excipients, cyclodextrins must be carefully characterized. The physicochemical properties of natural cyclodextrins are well known, but there is not enough information in the scientific literature about the physicochemical behaviour shown by cyclodextrin derivatives [5–7].

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The aim of this paper is to characterize some chemically modified cyclodextrins using different thermoanalytical techniques as differential scanning calorimetry (DSC), thermogravimetry (TG) and hot stage microscopy (HSM).

Experimental

Acetyl-α-cyclodextrin (AC-α-CD), acetyl-β-cyclodextrin (AC-β-CD), acetyl-γ-cyclodextrin (AC-γ-CD) and 6-O-maltosyl-β-cyclodextrin (MA-β-CD) were gifts from Cyclolab (Budapest, Hungary). Methyl-β-cyclodextrin (ME-β-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) were kindly supplied by Wacker Chimie (Munich, Germany). Hydroxypropyl-β-cyclodextrin (HP-β-CD) was also a gift from Cerestar (Hammond, IN, USA).

To carry out hot stage microscopic analyses about 1 mg of sample was placed on a microscopic slide, with cover and heated at a rate of 2°C min^{-1} on a Kofler stage. Samples were studied between 30 and 350°C. Microscopic examinations were carried out by using a Thermogalen microscope fitted with the Kofler stage.

DSC curves were recorded on a Mettler TA 3000 differential scanning calorimeter (model DSC 20). About 5–10 mg of sample were placed in a pinholed aluminium sample pan with lid and heated in atmospheric air at a rate of 10°C min^{-1} between 30 and 350°C.

Thermogravimetric analyses were carried out using a Mettler TA 3000 (TG-50). Samples (10 mg) were placed in a crucible of alumina β=10°C min^{-1} heating rate has been applied between 30 and 600°C.

Results and discussion

Hot stage microscopy

Thermomicroscopic observation of AC-α-CD at room temperature revealed that the sample was constituted of needle-like and flat particles which appeared coloured under polarized light. During heating no changes were detected until the temperature of phase transition was reached (200–205°C).

The sample of AC-β-CD was formed by grey irregular particles. Under polarized light they also appeared grey, with some coloured points. The process of solid→liquid transformation between 210–218°C was the only observed one during heating.

Spherical and amorphous particles of similar size were found in the microscopic view of the AC-γ-CD sample. During heating, no change of particle appearance was observed until its fusion (220–230°C).

The sample of MA-β-CD was constituted by spherical particles. As the temperature reached 270°C a softening process began and finished at 298°C.

The particles of ME-β-CD were spherical and their appearance was very similar to those which AC-γ-CD and MA-β-CD samples showed. However, its solid→liquid transition has been observed at much lower temperatures, in the range of 171–185°C.

By the microscopic observation of HP-β-CD two different types of particles have been distinguished, namely black sphericals and other long, hair-like ones. The special appearance of this sample can be useful to differentiate this amorphous substance from other amorphous

cyclodextrins. The melting of the crystalline part took place when softening the amorphous particles has occurred. Perhaps, this is the reason why a relatively wide temperature interval (220–257°C) has been observed for phase transition.

HP-γ-CD was constituted by grey spherical particles which formed aggregates. During heating, a softening (and a possible melting) between 230–260°C was only detected.

Differential scanning calorimetry

DSC curves obtained from all the studied cyclodextrins are shown in Fig. 1. In each case the first endotherm peak corresponds to the dehydration process. The second large endotherm peak over 240°C (with the exception of Me-β-CD, curve 5 in Fig. 1) probably represent the decomposition of the samples. According to the thermo-

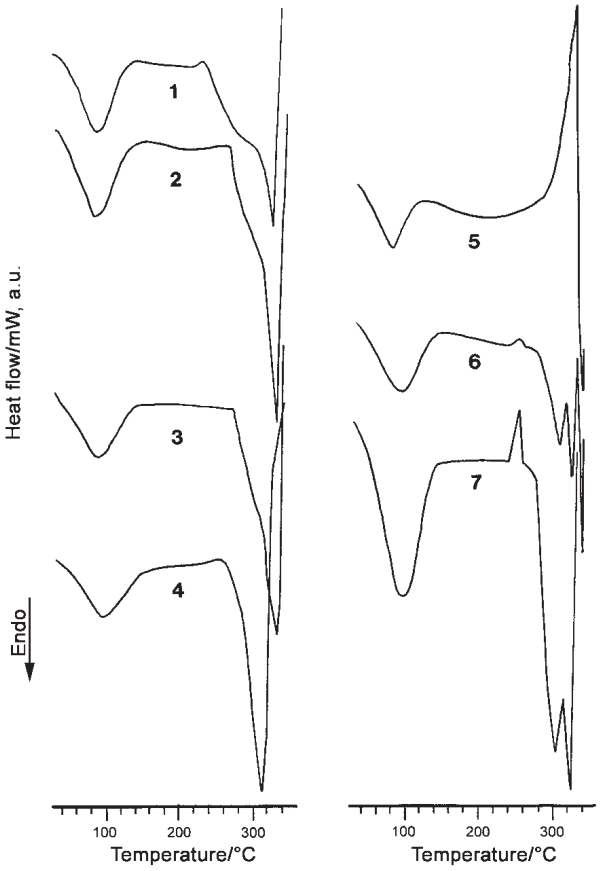

Fig. 1 DSC curves from 1 – acetyl-α-cyclodextrin, 2 – acetyl-β-cyclodextrin, 3 – acetyl-γ-cyclodextrin, 4 – maltosyl-β-cyclodextrin, 5 – methyl-β-cyclodextrin, 6 – hydroxypropyl-β-cyclodextrin and 7 – hydroxypropyl-γ-cyclodextrin

microscopic observations, the phase change of these cyclodextrin derivatives occurred at lower temperatures. In the DSC curve of ME-β-CD an exotherm decomposition can be observed. However, the Authors should point out, that the DSC curves of Ac-α-CD and Ac-β-CD show an exotherm deviation from the baseline before the large endotherm effect. It can be attributed to the slow oxidative decomposition, which started even in the solid state of the samples (curves 1 and 2 in Fig. 1).

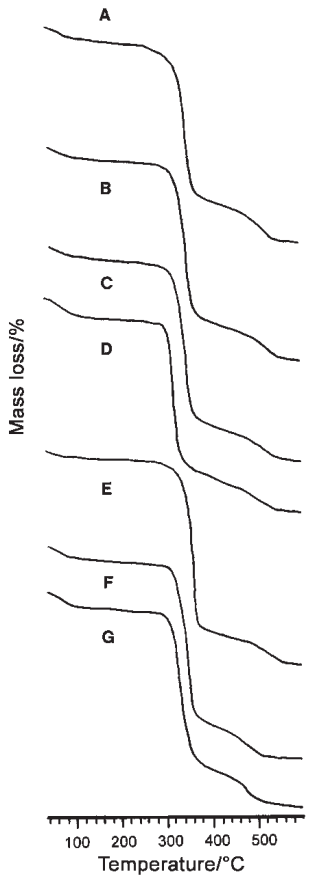

Fig. 2 TG curves from A – acetyl-α-cyclodextrin, B – acetyl-β-cyclodextrin, C – acetyl-γ-cyclodextrin, D – maltosyl-β-cyclodextrin, E – methyl-β-cyclodextrin, F – hydroxypropyl-β-cyclodextrin and G – hydroxypropyl-γ-cyclodextrin

Table 1 shows the temperature intervals and the values of the corresponding enthalpies. Because of experimental conditions and the thermal behaviour of the examined samples the temperature limits of integration could not be adequately determined. This is the reason why the obtained enthalpies cannot be exactly compared, but they are rather informative values.

Table 1 Data obtained from DSC analysis

Substance	Temperature range/°C	Peak temperature/°C	Enthalpies/J g^{-1}
AC-α-CD	40–140	87.8	78.99
	240–350	328.2	268.26
AC-β-CD	40–140	86.2	89.17
	260–350	331.7	208.29
AC-γ-CD	40–150	93.2	107.55
	260–350	334.8	307.59
MA-β-CD	40–160	96.7	197.35
	260–350	309.8	–651.40
ME-β-CD	40–120	80.7	62.79
	280–350	338.8	260.45
HP-β-CD	40–160	96.8	135.79
	240–260	251.5	–1.89
	270–320	308.3	39.93
HP-γ-CD	40–160	102.2	157.84
	240–270	259.6	–10.03
	270–350	327.9	237.74

Thermogravimetry

TG curves of all the cyclodextrin derivatives are shown in Fig. 2. Three representative mass loss steps could be observed. The first step belongs to the process of dehydration between 30–120°C. The second and third ones are representative for the primary and secondary decomposition, respectively between 240–400°C, after the phase change. Mass loss data are collected in Table 2.

Table 2 Data obtained from TG analysis

Substance	Temperature range/°C	Mass loss/%	Process
AC-α-CD	30-100	5.44	dehydration
	240-400	74.85	decomposition
AC-β-CD	30-100	5.39	dehydration
	240-400	77.68	decomposition
AC-γ-CD	30-100	6.01	dehydration
	240-400	79.83	decomposition
MA-β-CD	30-100	8.44	dehydration
	240-400	75.45	decomposition
ME-β-CD	30-100	3.26	dehydration
	240-400	84.75	decomposition
HP-β-CD	30-100	6.46	dehydration
	240-400	79.03	decomposition
HP-γ-CD	30-100	7.34	dehydration
	240-400	79.64	decomposition

In order to generalize we have calculated the average energy corresponding to the loss of 1% water in each cyclodrextrin derivative. The results are summarised in Table 3.

Table 3 Data obtained from dehydration process

Substance	Energy/J g^{-1}*
AC-α-CD	14.52
AC-β-CD	16.54
AC-γ-CD	17.89
MA-β-CD	23.38
ME-β-CD	19.26
HP-β-CD	21.02
HP-γ-CD	21.50

*Average energy absorbed to remove 1% water from the sample

If the comparison was established among the derivatives from the same natural cyclodextrin (β-derivatives), it can be observed that maltosyl derivative showed higher value of energy to remove 1% of water, followed by hydroxypropyl derivative and after methyl and acetyl derivatives. These differences could be due, in general, to the chemical structure of the substitution group, which allows the formation of a hydrogen bond with the hydration water molecules, because the maltosyl is the substitution group which gives rise to more intense bonding.

Conclusions

Thermomicroscopic study has proved to be very useful in order to know the melting process of clyclodextrin derivatives. The apparently unlike results obtained from DSC and TG with respect to the dehydration processes, could be explained in accordance with the nature of the substitution groups of the cyclodextrin derivatives included in this study.

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