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# Thermal stability of the linoleic acid/α- and β-cyclodextrin complexes

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**Abstract**

This paper presents a thermal stability study of the linoleic acid/α- and β-cyclodextrin (α- and βCD) complexes. Bionanoparticles were obtained by a solution method and were characterized by differential scanning calorimetry and transmission electron microscopy. The pure linoleic acid, the corresponding thermally (50–150 °C) degraded raw linoleic acid samples or those recovered from the complexes were analyzed by gas chromatography–mass spectrometry, after conversion to the methyl esters. Nanoparticles were obtained with good yields of 88% and 74% for α- and βCD complexes, respectively. The main degradation products (for the thermally degraded raw samples) were aldehydes, epoxy, dihydroxy derivatives, homologues, and isomers of linoleic acid. A good thermal stability of nanoparticles can be observed, especially for the linoleic acid/αCD complex, which contains a relative concentration above 98% fatty acid in the case of temperature degradations of 50 and 100 °C. A lower concentration of 92% can be observed in the case of the linoleic acid/βCD complex but, for the temperature degradation of 150 °C, the linoleic acid was partially converted to more stable geometrical isomers.


*Keywords:* Nanoparticles; Thermal stability; Linoleic acid; Cyclodextrins; DSC analysis; TEM analysis; GC–MS analysis

## 1. Introduction

The application of oligo- and polysaccharides in the drug, cosmetic, and food industries represents a very large field. Some of the most used systems for protecting and controlled release of biomolecules are liposomes (Grabielle-Madelmont, Lesieur, & Ollivon, 2003; Kim & Baianu, 1991; Loukas & Gregoriadis, 1997; Saarinen-Savolainen, Järvinen, Taipale, & Urtti, 1997), especially in the pharmaceutical industry and in medical practice. In recent last years, liposomes have been extensively obtained and used as biological membranes and as transporters for various biocompounds (Puglisi, Fresta, Mazzone, Furneri, & Tempera, 1995; Saravolac, Kournikakis, Gorton, & Wong, 1996). Some studies were performed in the immunoisolated cell transplantation field (Li, 1998; Rihova, 2000) and for the encapsulation of proteins, enzymes and antigens (Bollag, Rozycki, & Edelstein, 1996; Gombotz & Wee, 1998).

A very interesting field of supramolecular chemistry is the complexation of organic molecules (guest) in organic structures which contain cavities (host), the process being known as host–guest chemistry, molecular encapsulation, or nanoencapsulation (Szejtli, 1988; Venema, 1996). Most used as host molecules are the cyclodextrins (CDs), which are natural cyclic oligosaccharides, containing 6 (αCD), 7 (βCD), 8 (γCD) or more glucopyranose moieties; they all have the structure of a truncated cone with a hydrophobic inner cavity, which can interact with a hydrophobic organic molecule (geometrically compatible) and form a more

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stable, protective (to air, temperature, light), and controlled releasing supramolecular system (Nepogodiev & Stoddart, 1998; Szejtli, 1988). These matrices were especially used for the encapsulation of drugs (Bocanegra, Seijas, & Yibirín, 2003; Diakur, Zuo, & Wiebe, 1999; Kinnarinen, Jarho, Järvinen, & Järvinen, 2003; Veiga & Merino, 2002), odorant and flavouring compounds (Eckert, 1996; Goubert et al., 2001; Liu, Furuta, Yoshii, Linko, & Coumans, 2000; Szejtli, 1982), food additives (Crittenden & Playne, 1996; O'Boyle, Aladin-Kassam, Rubin, & Diosady, 1992), and biomacromolecules (Miertus et al., 1998). Very interesting applications of cyclodextrins are for the microencapsulation, in liposomes, of the complexes with various drugs (Kim & Baianu, 1991) and in the biosensor field (transducers) (Culha, Lavrik, Schell, Tipple, & Sepaniak, 2003).

In our previous work (Hădărugă, Hădărugă, Bandur, & Lupea, 2003, 2004a, 2004b), we have studied the nanoencapsulation of the oleic acid and different volatile oils and odorant compounds in CDs in order to establish the capacity of encapsulation of oligosaccharides and evaluate the stability of complexes. In this study, we have investigated the thermal stability of linoleic acid encapsulated in α- and βCD, using differential scanning calorimetry (DSC) and gas chromatography–mass spectrometry (GC–MS) analyses. Some linoleic acid degradation products, which appear in the presence of air and humidity, at different temperatures, play an important role in human health and could be responsible for various diseases, e.g., neoplasia. In order to establish the type and the concentration of these degradation products, and to evaluate the protective capacity of CDs, a thermal stability study of the linoleic acid/CDs complexes was carried out.

## 2. Materials and methods

### 2.1. Materials

*Linoleic acid* (>99%, standard for GC) and *$C_8$–$C_{20}$ alkane standard solution* were purchased from Fluka Chemie AG (Switzerland), α- and β-*cyclodextrin* (αCD and βCD, respectively; >99%, reagent grade), were purchased from Merck Co., Inc., New Jersey, as well as the *methanol · $BF_3$* reagent used for deriving the fatty acids esters.

### 2.2. Complexation

The complexation of the linoleic acid with α- or βCD was performed by dissolving α- or βCD in distilled water at 50 ± 1 °C in a thermocontrolled minireactor, equipped with a reflux condenser, and by adding an ethanolic linoleic acid solution (the weight corresponding to the linoleic acid:CDs ratio of 1:1, Table 1). After 15 min of stirring, the complex suspension was slowly cooled to 20 °C in about 4 h; the complex crystallization was completed in the refrigerator at 4 °C for 24 h. The complex was then filtered, washed with ethanol and dried.

Table 1
Linoleic acid and CD quantities used for complexation

| No | Complex | $m_{\text{linoleic acid}}$ (mg) | $m_{\alpha/\beta\text{CD}}$ (mg) | $m_{\text{complex}}$ (mg) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Linoleic acid/αCD | 140.2 | 540 | 598.2 | 87.94 |
| 2 | Linoleic acid/βCD | 140.2 | 671 | 599.9 | 73.95 |

### 2.3. Fatty acid ester derivatives

In order to establish the linoleic acid content (in the raw sample and in the degraded or complex recovered ones) by GC–MS analysis, samples were esterified to the corresponding more volatile methyl esters using the methanol · $BF_3$ method: the raw sample, or the hexane solution containing fatty acids, was treated with MeOH · $BF_3$ solution, refluxed 2 min on a water bath, and the more hydrophobic esters were extracted in hexane using a saturated NaCl solution for a good separation. The organic layer was separated and dried over anhydrous $CaCl_2$.

### 2.4. Fatty acid extraction from the complex

The linoleic acid/α- or βCD complex was dissolved in distilled water in a minireactor equipped with a reflux condenser and a magnetic stirrer, a small volume of hexane was added to the solution, and the emulsion was stirred for 20 min at 69 °C. After cooling, the organic layer was separated and the aqueous layer was extracted another three times with the same volume of hexane. All organic layers were dried over anhydrous $CaCl_2$ and analyzed by GC–MS.

### 2.5. Free and complexed linoleic acid degradation

Free and complexed linoleic acid thermal degradations were achieved on glass plates, in a thin film for liquid samples and as fine powder for solid complexes, in a thermocontrolled oven, at a temperature in the range of 50–150 °C, in the presence of air (70% relative humidity) at normal pressure, for 2 h (Table 2).

### 2.6. DSC analysis

Differential scanning calorimetry (DSC) was carried out on a DSC 204 Netzsch apparatus, with a temperature

Table 2
Degradation conditions for free and complexed linoleic acid

| No | Sample name | $m_{\text{sample}}$ (mg) | Temperature (°C) | Time (min) |
|---|---|---|---|---|
| 1 | Linoleic acid | 100 | 50 | 120 |
| 2 | Linoleic acid | 100 | 100 | 120 |
| 3 | Linoleic acid | 100 | 150 | 120 |
| 4 | Linoleic acid/αCD | 100 | 50 | 120 |
| 5 | Linoleic acid/αCD | 100 | 100 | 120 |
| 6 | Linoleic acid/αCD | 100 | 150 | 120 |
| 7 | Linoleic acid/βCD | 100 | 50 | 120 |
| 8 | Linoleic acid/βCD | 100 | 100 | 120 |
| 9 | Linoleic acid/βCD | 100 | 150 | 120 |

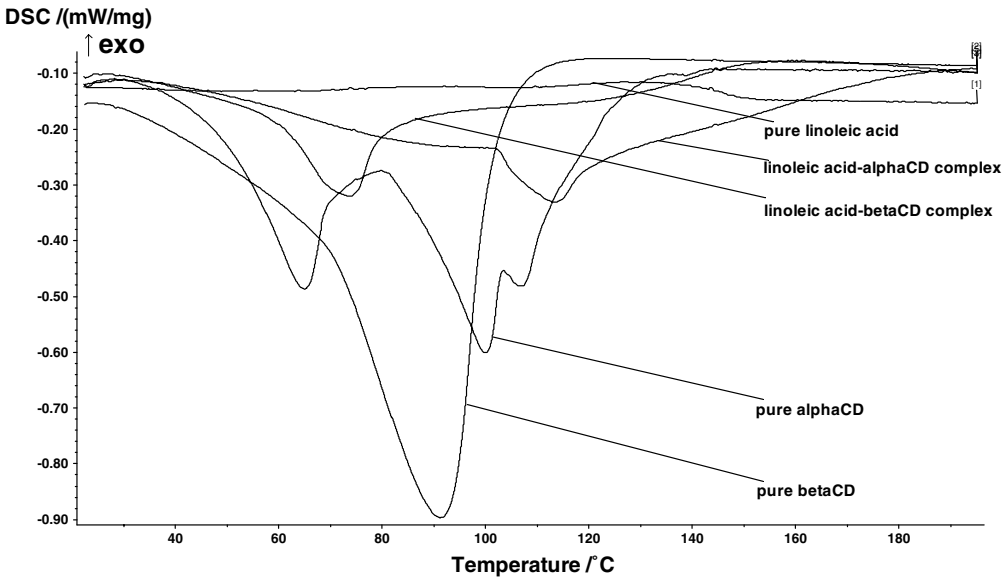


Fig. 1. DSC analysis of the linoleic acid/α- and βCD complexes comparatively with those of the pure linoleic acid, αCD, and βCD.

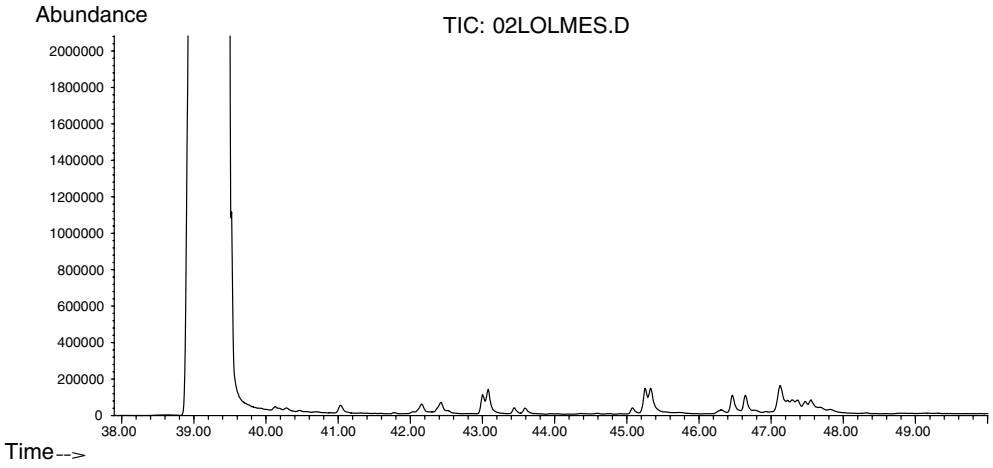


Fig. 2. Gas chromatogram for the linoleic acid (raw) for the KI in the range 2000–2600.

Table 3
MS identification, quantification, and Kovats indices of the main compounds from the methyl ester derived linoleic acid sample

| No | MS identification | Concentration (%) | Kovats index (KI) |
|---|---|---|---|
| 1 | Nonanoic acid, 9-oxo-, methyl ester | 0.02 | 1436 |
| 2 | Octanoic acid, 6,6-dimethoxy-, methyl ester[a] | 0.06 | 1601 |
| 3 | Linoleic acid, methyl ester | 97.3 | 2121 |
| 4 | 7,10-Octadecadienoic acid, methyl ester | 0.03 | 2152 |
| 5 | 8,11-Octadecadienoic acid, methyl ester | 0.08 | 2196 |
| 6 | 9,12-Octadecadienoic acid, methyl ester (isomer)[a] | 0.01 | 2233 |
| 7 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 1) | 0.09 | 2253 |
| 8 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 2) | 0.10 | 2267 |
| 9 | Linolenic acid, methyl ester | 0.15 | 2299 |
| 10 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 3) | 0.24 | 2303 |
| 11 | Oxiraneundecanoic acid, 3-pentyl-, methyl ester, *cis*-[a] | 0.21 | 2437 |
| 12 | Methyl (*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate[a] | 0.17 | 2525 |
| 13 | 9,12-Octadecadienal, dimethyl acetal[a] | 0.33 | 2579 |
| 14 | (*E*)-8-methyl-9-tetradecen-1-ol acetate[a] | 0.02 | 2609 |

[a] Identified with lower probability matching by NIST MS Search algorithm (see supporting information).

programme of −50 to 200 °C, the heating rate being 4 °C/min. Data acquisition was performed with the DSC Netzsch 204-Acquisition Soft, and the analysis of the data was performed with the Netzsch-Proteus Analysis ver. 4.0 programme (see supporting information for full range DSC analyses).

### 2.7. TEM analysis

Transmission electron microscopy (TEM) was performed on a Tesla BS-613 apparatus, with an acceleration voltage of 80 kV. One hundred particles were take into account in order to establish the mean particle size and the

Table 4
MS identification, quantification, and Kovats indices of the compounds from the methyl ester derived linoleic acid sample degraded at 50, 100 and 150 °C

| No | MS identification | KI | $c_1$[a] (%) | $c_2$[b] (%) | $c_3$[c] (%) |
|---|---|---|---|---|---|
| 1 | Malonaldehyde, bis(dimethyl acetal) [d] | 883 | | 0.12 | 0.87 |
| 2 | Methyl caproate[e] | 925 | 0.01 | 0.24 | 1.83 |
| 3 | 2-Heptenal, (*Z*)- | 958 | | 0.01 | |
| 4 | Hexanal dimethyl acetal | 980 | 0.15 | 1.58 | 10.6 |
| 5 | Methyl enanthate | 1026 | | 0.04 | 0.25 |
| 6 | 2-Octenal, (*E*)- | 1059 | | 0.07 | |
| 7 | Heptane, 1,1-dimethoxy-[e] | 1080 | 0.00 | 0.04 | 0.27 |
| 8 | Caprylic acid methyl ester | 1126 | 0.02 | 0.55 | 1.39 |
| 9 | 2-Nonenal, (*E*)- | 1160 | | 0.02 | |
| 10 | 2,4-Decadienal | 1317 | | 0.01 | |
| 11 | Methyl 8-oxooctanoate | 1334 | | | 0.53 |
| 12 | 2,4-Hexadiene, 1,6-dimethoxy-, (*E*,*E*)-[d] | 1354 | 0.01 | | |
| 13 | Methyl caproate? (isomer)[e] | 1394 | | 0.02 | 0.27 |
| 14 | Heptane, 1,1-dimethoxy- ? (aldehyde, dimethyl acetal)[e] | 1400 | 0.01 | | |
| 15 | Nonanoic acid, 9-oxo-, methyl ester | 1436 | 0.02 | 1.09 | 6.07 |
| 16 | Octanedioic acid, dimethyl ester | 1449 | | 0.02 | 0.85 |
| 17 | Octanoic acid, 6,6-dimethoxy-, methyl ester | 1500 | 0.01 | 0.15 | 0.56 |
| 18 | 3-Hexanone, 1,5,6,6-tetramethoxy- | 1515 | | | 0.31 |
| 19 | Nonanedioic acid, dimethyl ester | 1550 | 0.00 | 0.55 | 8.41 |
| 20 | 2-Octanol, 8,8-dimethoxy-[d] | 1600 | 0.21 | 2.51 | 10.5 |
| 21 | Methyl 8-(2-furyl)octanoate | 1624 | | | 0.67 |
| 22 | Decanedioic acid, dimethyl ester | 1650 | | | 0.30 |
| 23 | Methyl 11-oxo-9-undecenoate | 1698 | | 0.04 | 0.27 |
| 24 | 12,12-Dimethoxydodecanoic acid, methyl ester[d] | 1700 | | 0.08 | |
| 25 | Methyl 12-oxo-9-dodecenoate | 1800 | | 0.10 | |
| 26 | Octanoic acid, 6,6-dimethoxy-, methyl ester | 1817 | | 0.04 | |
| 27 | Heptanal, 7,7-dimethoxy-[d] | 1884 | 0.03 | 0.18 | |
| 28 | 6-Nonenal, 3,7-dimethyl-[d] | 1905 | | 0.04 | |
| 29 | Tetradecanoic acid, 10,13-dimethyl-, methyl ester[d] | 1926 | 0.00 | 0.02 | 0.12 |
| 30 | Butanoic acid, 2-ethyl-, methyl ester[d] | 1954 | | 0.02 | |
| 31 | 2-Hydroxyhexadecyl butanoate[d] | 1963 | | 0.03 | |
| 32 | 9,12-Octadecadienal, dimethyl acetal[d] | 1970 | | 0.12 | |
| 33 | Methyl (*Z*)-11-tetradecenoate | 2001 | | 0.07 | |
| 34 | 3-Hexanone, 1,5,6,6-tetramethoxy-[d] | 2017 | 0.01 | | |
| 35 | Linoleic acid, methyl ester | 2107 | 97.5 | 86.2 | 54.5 |
| 36 | 8,11-Octadecadienoic acid, methyl ester | 2112 | 0.59 | 0.40 | |
| 37 | 9,12-Octadecadienoic acid, methyl ester (isomer 1) | 2147 | 0.01 | | |
| 38 | 9,12-Octadecadienoic acid, methyl ester (isomer 2) | 2192 | 0.04 | | |
| 39 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 1) | 2294 | | 0.22 | 0.50 |
| 40 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 2) | 2299 | | 0.38 | |
| 41 | 6,9,12-Octadecatrienoic acid, methyl ester (isomer 3)[d] | 2320 | 0.31 | | |
| 42 | Cyclopropaneoctanoic acid, 2-[[2-[(2-ethylcyclopropyl)methyl]cyclopropyl]methyl]-, methyl ester[d] | 2350 | 0.01 | | |
| 43 | Olealdehyde, dimethyl acetal[d] | 2374 | 0.02 | 0.35 | 0.98 |
| 44 | 9,12-Octadecadienal, dimethyl acetal (isomer 3)[d] | 2422 | 0.18 | | |
| 45 | Methyl (*Z*)-12,13-epoxy-11-methoxy-9-octadecenoate[d] | 2521 | 0.53 | 4.65 | |
| 46 | Octadecanoic acid, 9,10-dihydroxy-, methyl ester[d] | 2612 | 0.30 | | |

[a] Relative concentration of compounds from the linoleic acid sample degraded at 50 °C.
[b] Relative concentration of compounds from the linoleic acid sample degraded at 100 °C.
[c] Relative concentration of compounds from the linoleic acid sample degraded at 150 °C.
[d] Identified with lower probability matching by NIST MS Search algorithm (see supporting information).
[e] Identified with higher probability matching by NIST MS Search algorithm, but they are the same compounds (probably isomers) (see supporting information).

standard deviation value for each case (see supporting information for TEM images).

### 2.8. GC–MS analysis

For the analysis of the methyl esters of fatty acids, a Hewlett–Packard HP 6890 Series gas chromatograph coupled with a Hewlett–Packard 5973 mass spectrometry detector (GC–MS) system was used (see supporting information for full range gas chromatograms).

A HP-5 MS capillary column (30 m length, 0.25 mm i.d., 0.25 μm film thickness) was used for the GC system. The temperature programme was set up from 50 to 250 °C at 4 °C/min, both the injector and detector temperatures were

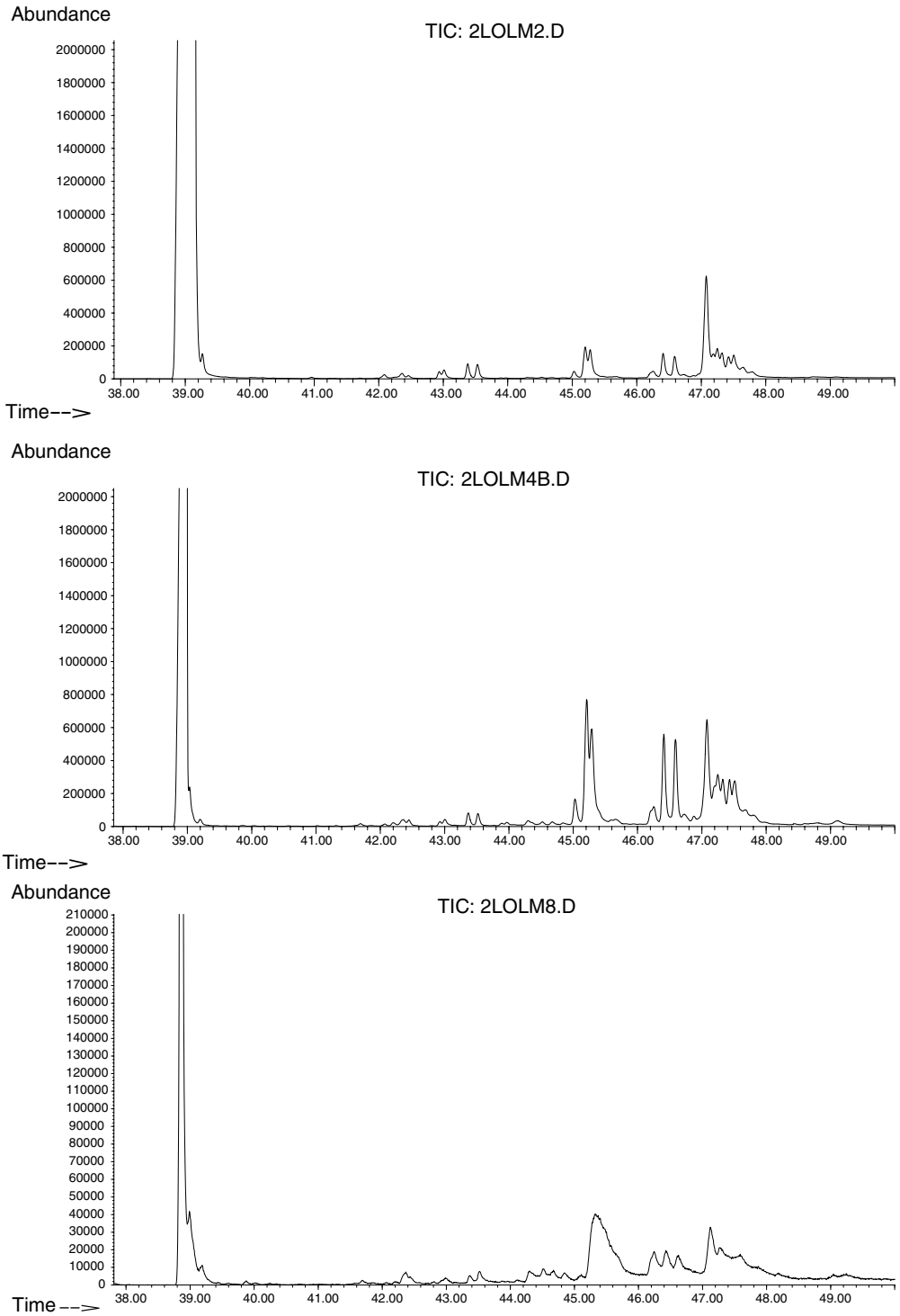


Fig. 3. Gas chromatograms for the linoleic acid samples degraded at 50 °C (top), 100 °C (middle), and 150 °C (bottom) for the KI in the range 2000–2600.

280 °C and He was used as carrier gas. The injection volume was 2 μl. For quantification, dodecane was used as external standard.

Ionization energy EI of 70 eV was used for the mass spectrometry detector, with a source temperature of 150 °C, scan range 50–300 amu, scan rate 1 $s^{-1}$. The mass spectra were compared with the NIST/EPA/NIH Mass Spectral Library 2.0 (see supporting information for experimental and NIST database mass spectra).

## 3. Results and discussion

The linoleic acid/α- and βCD complexes were obtained with good yields of 88% and 74%, respectively. Rhombic crystals with a mean side dimension of 230 ± 57 nm were obtained in the case of the linoleic acid/αCD complex (revealed by TEM analysis). In the case of the linoleic acid/βCD complex, the same analysis revealed hexagonal crystals with a mean side dimension of 236 ± 86 nm. The differential scanning calorimetry (DSC) analysis revealed that the linoleic acid had a melting point of −12.8 °C, with a transition energy of 0.63 J/g/K. The DSC analyses (Fig. 1) of the complexes, comparatively with those of the pure linoleic acid and α-/βCD, indicate the formation of the complex, the dehydration energy for the pure αCD and βCD being 119.2 J/g (in the temperature range 80–130 °C) and 56.35 J/g (in the temperature range 70–115 °C), respectively (Fig. 1). For the linoleic acid/αCD complex, the interaction energy was 19.44 J/g (in the temperature range 101–130 °C), and for the linoleic acid/βCD complex this energy was 34.13 J/g, corresponding to the decomplexation and/or rearrangement of the fatty acid in the complex (Rysanek, Coquillay, Bourgaux, & Ollivon, 2002).

In order to establish the free and degraded linoleic acid composition, the pure sample and the samples degraded at temperature values in the range 50–150 °C were analyzed by GC–MS. The concentration of the linoleic acid in the raw sample was 98% (as methyl ester), the main impurities being the corresponding 7,10- and 8,11-dien isomers of the linoleic acid, linolenic acid and some geometric isomers (Fig. 2 and Table 3). The Kovats indices (KI) were obtained according to the retention time of the sample compounds by evaluation from the correlational equation

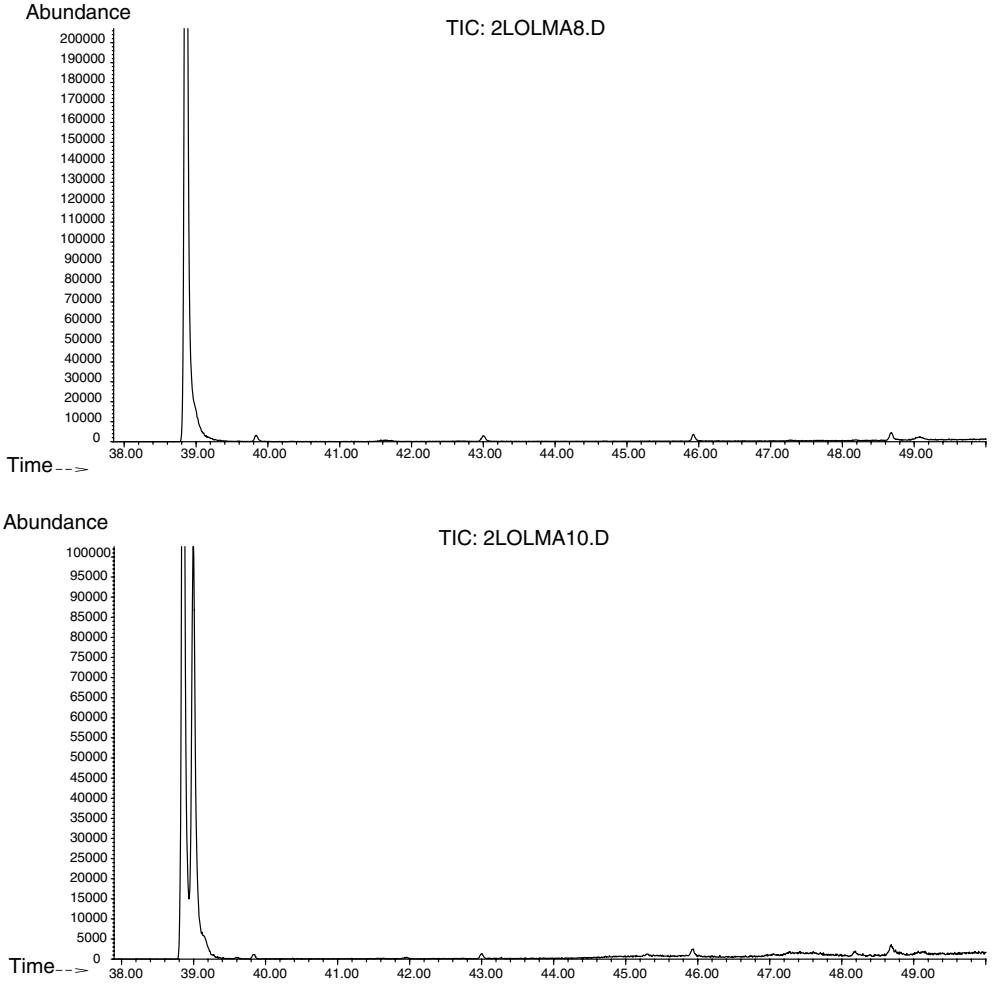


Fig. 4. Gas chromatograms for the degraded (at 50 °C – top and 100 °C – bottom) linoleic acid/αCD complexes, recovered, and methyl ester derived samples for the KI values in the range 2000–2600.

corresponding to the $C_8$–$C_{20}$ alkane standard solution. These KIs were calculated in order to confirm the MS identification of the main sample compounds, some KIs being previously determined for the pure compounds under the same conditions.

After thermal degradation of the linoleic acid sample at a temperature within the range 50–150 °C (in air at atmospheric pressure, 70% relative humidity), some degradation products can be identified, especially at temperatures above 100 °C, the main compounds being aldehydes (resulting from oxidation), epoxides and vicinal dihydroxy-acids. The concentration of linoleic acid in the sample degraded at 50 °C was 97.5%, the degradation compounds being in low concentrations, while the sample degraded at 100 °C revealed a linoleic acid concentration of 86.2%. The lowest linoleic acid concentration was observed for the sample degraded at 150 °C (54.5%) (Table 4).

The main aldehydes identified in the degraded samples (as acetals) were: malondialdehyde at a concentration of 0.1% for the sample degraded at 100 °C and in a higher concentration of 0.9% in the sample degraded at 150 °C. The same increasing concentrations were observed in the case of hexanal (concentration in the range 0.15–10.5% for the sample degraded at 50–150 °C), heptanal (0–0.3%), 9-oxononanoic acid (0.02–6%), octanedioic acid (0–0.9%), 6-oxooctanoic acid (0.01–0.6%), nonandioic acid (0–8.4%), and some linoleic and linolenic acid isomers (octadecadienoic and octadecatrienoic acids). In the case of the sample degraded at 100 °C, a small concentration of the 12,13-epoxi derivative can be identified.

The GC chromatograms for the raw linoleic acid and for the samples degraded at 50, 100, and 150 °C, corresponding to the Kovats index range of 2000–2600 (oxidation, epoxidation, epoxidation–hydrolysis degradation products) are depicted in Figs. 2 and 3, respectively. At higher temperatures the linoleic acid and some degradation products were probably polymerized.

A higher concentration of linoleic acid (as methyl ester) was detected in the recovered samples from the linoleic acid/α- and βCD complexes (99.3% and 99.6%, respectively).

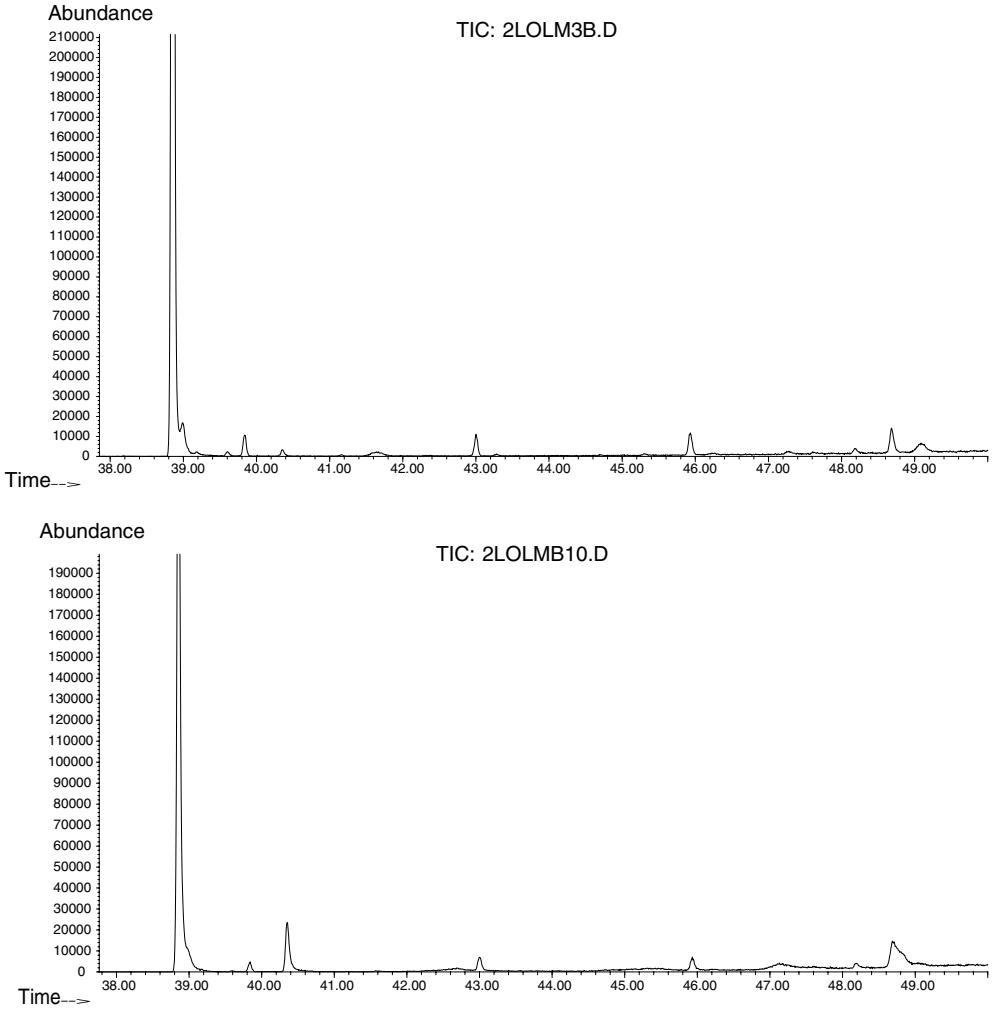


Fig. 5. Gas chromatograms for the degraded (at 50 °C – top and 100 °C – bottom) linoleic acid/βCD complexes, recovered, and methyl ester derived samples for the KI values in the range 2000–2600.

A good protection against the environmental degradation factors (especially against oxygen and humidity at higher temperature) can be observed in the case of nanoencapsulated fatty acid in cyclodextrin matrices. For the linoleic acid/αCD complex degraded at 50 °C no major degradation product can be identified (only malondialdehyde was present at the low relative concentration of 0.6%). The concentration of the linoleic acid was 99.4% while, for the sample degraded at 100 °C, the concentration of the fatty acid (as mixture of linoleic and one of its geometric isomers) was 98.4%; the main degradation compound was malondialdehyde (1.5%). In the case of the sample degraded at 150 °C, the concentration of linoleic acid was only 80%, this fatty acid being partially polymerized.

In the samples recovered from the linoleic acid/βCD complex degraded at 50 and 100 °C, small relative concentrations of malondialdehyde and hexanal could be identified, the concentrations of the linoleic acid being 94% and 92%, respectively. In the case of the sample degraded at 150 °C, the concentration of the linoleic acid was only 74%.

Figs. 4 and 5 show the gas chromatograms for the linoleic acid/α- and βCD samples (which can be compared with the gas chromatograms of the raw and degraded linoleic acid samples from Figs. 2 and 3) at the KI values in the range 2000–2600, corresponding to linoleic acid and its superior homologues or similar derivative peaks. The peaks corresponding to the degradation products from the non-encapsulated sample, degraded at 150 °C, can be clearly observed (see Fig. 3).

## 4. Conclusion

Very good yields were obtained for the complexation process, especially in the case of αCD, probably due to the best fit of the linoleic acid in the αCD cavity, that provides a higher interaction between the fatty acid and cyclodextrin.

Higher relative concentrations of degradation products can be identified in the case of thermally degraded linoleic acid samples, the main compounds being aldehydes (malondialdehyde, hexanal, heptanal, octanal, nonanal, decanal) probably resulted from oxidation processes, especially at higher temperature, and linoleic acid epoxidation and epoxidation–hydrolysis products.

A relatively high amount of the linoleic acid was transformed (probably by hydration–dehydration processes) to the more stable isomers of linoleic acid, most of them in the case of samples degraded at 100 and 150 °C.

Very good thermal stability was observed for both linoleic acid/α- and βCD complexes, the relative concentration of the fatty acid recovered from the complex with αCD being 99.4% and 98.4% in the cases of complexes degraded at 50 and 100 °C, respectively, comparatively with the non-encapsulated samples degraded at the same temperatures, where these concentration were 97.5% and 86.2%. In the case of the complex with βCD, the stability of the linoleic acid was lower, the relative concentrations of the fatty acid being 94% and 92% for the degradation temperatures of 50 and 100 °C, respectively.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.foodchem.2005.08.012.

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