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Detailed molecular characterization of castor oil ethoxylates by liquid chromatography multistage mass spectrometry

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ABSTRACT

The molecular characterization of castor oil ethoxylates (CASEOs) was studied by reverse-phase liquid chromatography (RPLC) mass spectrometry (MS) and multistage mass spectrometry (MS^n). The developed RPLC method allowed the separation of the various CASEO components, and especially, the baseline separation of multiple nominal isobars (same nominal mass) and isomers (same exact mass). MS and MS^n were used for the determination and structure elucidation of various structures and for the discrimination of the isobars and isomers. Different ionization techniques and adduct ions were also tested for optimization of the MS detection and the MS^n fragmentation. A unique fragmentation pathway of ricinoleic acid is proposed, which can be used as a marker of the polymerization process and the topology of ethoxylation in the CASEO. In addition, characteristic neutral losses of ricinoleic acid reveal its (terminal or internal) position in the molecule.

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1. Introduction

Non-ionic surfactants are widely used in the polymer industry. They are used as detergents, solubilizers and components of pharmaceutical and cosmetic products. Their success is based on: (1) the big variety of starting material (*e.g.*, alcohols, fatty alcohols and acids, and natural fats and oils) that can be polymerized, (2) the use of ethylene oxide and/or polypropylene oxide, forming homopolymers and block or random copolymers, and (3) the production of compounds of any size. This versatility allows the custom synthesis of polymers with specific physicochemical properties. Among the non-ionic surfactants commercially available, castor oil ethoxylate (CASEO) has found an extensive use in the pharmaceutical industry as a component of drug delivery systems. It is produced by the ethoxylation of castor oil, a natural oil rich in ricinoleic acid (*i.e.*, (9*Z*,12*R*)-12-hydroxyoctadec-9-enoic acid). As any other natural oil, castor oil is a mixture of different mono-, di-, and triacylglycerols and fatty acids many of which can be polymerized. Thus, the end product is a mixture of different polymeric structures. The use of these materials in the pharmaceutical sector requires a complete determination of its polymeric components. Besides the regulatory issues, a comprehensive analysis will also improve the understanding of the polymerization processes that facilitate the design of custom made products.

Liquid chromatography (LC) is an analytical technique that can meet the challenge of characterizing complicated mixtures of synthetic polymers, such as non-ionic surfactants [1–9]. Various LC methods were developed, such as gradient polymer elution chromatography (GPEC), liquid chromatography at critical conditions of adsorption (LCCC) [3–5,7,8], and two-dimensional LC (2D-LC) [3–5,9], which provide detailed molecular characterization of synthetic polymers. Nevertheless, the efficacy of these methods is inversely related to the complexity of the analytes. With increasing complexity, challenges as peak capacity and necessary time for method development become more important. In addition, the lack of chromatographic standards for all the possible polymeric structures renders their identification based on the elution time problematic.

Among the analytical techniques that do not require standards (*i.e.*, direct methods of identification) and can be easily coupled to LC, mass spectrometry (MS) has had a prominent position as a preferred tool in the last two decades. MS can provide detailed information about the end-group [10–13] the average molar mass (to some extent) [14] and the copolymer distribution [15–17]. Lattimer et al. [18,19] paved the way for the analysis of non-ionic surfactants by studying simple polyether systems by fast atom bombardment. Studies with electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) combined with collision-induced dissociation (CID) followed, showing that detailed structure information of the polyethers can be obtained [20–27]. Examples of coupling of high performance liquid chromatography (HPLC) with its various modes (*e.g.*, reverse-phase,

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normal-phase, and at critical conditions) to MS for the analysis of non-ionic surfactants have recently been demonstrated [28–32]. By careful selection of the chromatographic conditions the separation of the non-ionic surfactant components was made according to the end-group [28,31] or the copolymer distribution [31].

Although the MS analysis of the majority of the commercially available non-ionic surfactants has been demonstrated extensively, there are only limited reports on the analysis of CASEO. To the best of our knowledge, Meyer et al. [33–35] was the only group that used MS for the analysis of CASEO. They developed two different techniques for the analysis of CASEO: (1) separation of the mixture in a hydrophilic and hydrophobic fraction and consecutive MS analysis by using statistical approaches [33], and (2) a cyclodextrin-modified micellar electrokinetic capillary chromatography (CD-MEKC) method (developed in an earlier stage [36]) combined with delayed extraction MALDI time-of-flight MS (DE-MALDI-TOF-MS) using a fractionating robot [37,38]. These techniques allowed a more detailed analysis of the CASEO mixture, after the initial identification approach of Müller back in 1966 [39]. Although successful, the developed methods require complex instrumentation, robotic systems and statistical processing and are not ideal for routine analysis.

The aim of this work is to develop a simpler and more straightforward method for the analysis of CASEO, to the best of our knowledge, for the first time HPLC coupled to various MS instruments (*e.g.*, ion traps, time-of-flight mass analyzers and Orbitrap). A variety of MS methods (*e.g.*, different ionization techniques, positive/negative ion mode and cationization agents) are investigated to explore their added value and identify the optimal conditions for detailed molecular characterization. The use of multistage mass spectrometry (MS^n) is also investigated as a tool for detailed structural analysis of the various CASEO components.

2. Materials and methods

Commercially available CASEOs with different degrees of polymerization were kindly donated by Joke Speelman (AkzoNobel Surface Chemistry, The Netherlands). Sodium iodide (NaI) and ammonium chloride (NH_4Cl) were from J.T. Baker (Deventer, Netherlands). Lithium chloride (LiCl) and formic acid (FA) were purchased from Fluka (Buchs, Switzerland). Tetrahydrofuran (THF) was of HPLC-grade (Sigma–Aldrich, Germany). Ultra-pure water with a resistivity of 18.2 MΩ cm (at 25 °C) was obtained from a Millipore Direct-Q 3 (Molsheim, France) water purification system. All reagents and solvents were used without further purification.

HPLC was carried out using an Agilent 1100 series HPLC system (Palo Alto, CA) equipped with a binary pump and controlled by the Agilent Chemstation software for LC systems. Chromatographic separation was performed on a Alltech Kromasil C_{18} column (5 μm particle size, 4.6 × 150 mm). Because CASEO oligomers are partially soluble in acetonitrile, THF was used as a solvent. Initial chromatographic separations starting with a high percentage of water (*e.g.*, 90, 70%) resulted in long elution times, and in a very narrow elution window, for the majority of the CASEO components (see Fig A-1, and Table A-1, Appendix A). Increasing the amount of THF in the eluent at the start of the chromatographic separation broadened the elution window of the majority of the CASEO components and allowed the discrimination of multiple series. The selected gradient solvent system with the best performance is presented in Table 1. A flow rate of 1 mL/min was used. The appropriate salt solution (~400 μg/mL) was mixed with the HPLC effluent post-column with a Cole-Palmer syringe pump (Vernon Hills, IL) at a flow rate of 10 μL/min.

The combined column effluent and post column additive flow was introduced to a Bruker Esquire 3000^{plus} quadrupole ion trap (QIT) mass spectrometer (Bruker Daltonics, Bremen, Germany) or a Waters LCT time-of-flight (TOF) mass spectrometer (Micromass, Manchester, UK), both equipped with an electrospray ionization (ESI) source. MS^n experiments were performed in the QIT mass spectrometer. The ESI-MS, the isolation and CID conditions were optimized for each precursor ion studied aiming for a high abundance of precursor ion and effective formation of product ions. Accurate mass measurements and accurate mass tandem MS (MS/MS) experiments were performed in a LTQ Orbitrap XL (Thermo Scientific, San Jose, CA).

Table 1
Composition of the HPLC gradient elution system.

Time [min]	H_2O + 0.1% formic acid[a] [%]	THF + 0.1% formic acid[a] [%]
0	60	40
2	55	45
14	50	50
38	30	70
44	20	80
50	0	100
52	0	100
54	60	40
56	60	40

[a] The use of formic acid was shown to improve the chromatographic separation.

3. Results and discussion

3.1. LC–MS analysis of castor oil ethoxylate

Fig. 1 shows a contour plot of the mass-to-charge ratio (m/z) versus the retention time of a CASEO sample obtained by LC–ESI-TOF-MS. The long analysis time (48 min) and the optimized gradient elution conditions allowed the baseline separation of a great variety of components. For reasons of clarity and easy processing, the contour plot has been separated in sectors (labeled A to W). The identified distributions of each sector are presented in (Table 2).

In short, the main polymerization products detected are in agreement with previous studies [33–35] and Scheme 1. These are: (1) poly(ethylene glycol) (PEG), (2) glycerol PEG (G-PEG), (3) various fatty acid (*e.g.*, ricinoleic, linoleic, oleic and stearic acid) ester ethoxylate oligomers (Ric/Lin/Ole/Ste-PEG, where Ric/Lin/Ole/Ste are abbreviations of the above mentioned fatty acids, respectively), (4) G-PEG mono-, di- and tri-Ric/Lin/Ole/Ste (G-PEG-Ric_W/Lin_X/Ole_Y/Ste_Z, where W, X, Y, Z = 0, 1, 2 or 3 and $W+X+Y+Z=3$).

The PEG ester of didehydrostearic acid (DHSTE-PEG) (9,11-octadecadienoic acid), observed by Meyer et al. [35], cannot be distinguished from its isomer Lin-PEG by MS. MS/MS could potentially discriminate between these two structures based on the product ions deriving after acyl chain cleavage. Fig. 2 depicts the extracted ion chromatogram (EIC) of the ion at m/z 639. Two well-separated peaks are observed having the same exact mass. These two peaks are attributed to Lin-PEG_8 and DHSTE-PEG_8. The product ion mass spectra of these two peaks (Fig. A-2, Appendix A) did not allow the discrimination between the two structures. The characteristic product ions that provide information about the position of the double bonds in the acyl chain are of low abundance or not detected. Higher intensity of such peaks could allow the discrimination between these two structures. Based on the peak intensities, it is suggested that the second (higher intensity) peak is Lin-PEG_8, because Lin is one of the major fatty acids present in castor oil and DHSTE is a minor one.

Besides the main products multiple unknown distributions have also been detected. Some have the same m/z or nominal mass (nominal isobars) with some of the main products or with each other.

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