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Development of a Total Organic Carbon method for the quantitative determination of solubility enhancement by cyclodextrins: Application to essential oils

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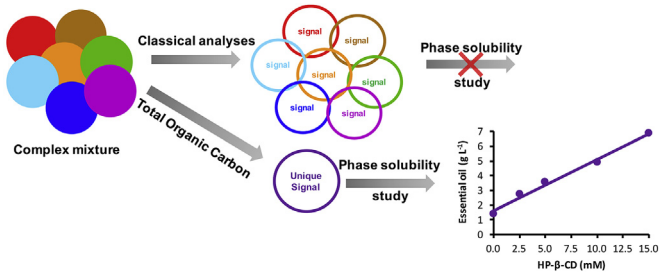
HIGHLIGHTS

- Development of a new reliable and environmentally friendly method for phase solubility studies.
- First use of Total Organic Carbon (TOC) for cyclodextrin (CD) inclusion complexes investigation.
- Validation of the method by comparison with UV–visible spectroscopy.
- Good linearity, accuracy and reproducibility were achieved.
- CD enhanced aqueous solubility of essential oils.

GRAPHICAL ABSTRACT



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ABSTRACT

Formation of inclusion complexes with cyclodextrins (CDs) is known to enhance guest solubility in aqueous medium. Different techniques allow determining the evolution in solubility of individual guest compounds. However, examination of mixtures solubility encapsulated in CDs is still a challenge. This is mainly related to the difference in the response of mixture components to the applied technique or to the fact that most of the conventional methods examine the signal of an individual constituent of the mixture. Thus, applying current techniques may not reflect the behavior of the whole mixture. Here, we used for the first time Total Organic Carbon (TOC) analysis to explore and assess the efficiency of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) to enhance the solubility of natural complex mixtures such as essential oils (EOs). Phase solubility studies were performed for eleven EOs with HP-β-CD. The TOC method has provided good validation parameters for linearity, precision and accuracy. For further validation of the method, phase solubility studies were performed with HP-β-CD for eugenol, as a model EO component. The eugenol solubility was determined by UV–Visible and TOC analyses in order to compare the results. Data obtained from both methods were similar ($p < 0.05$), thereby proving the effectiveness of the developed TOC method. Finally, the phase solubility diagrams of EOs showed that the solubilizing potential of CD increased proportionally with the decrease in EO intrinsic solubility. Results proved that TOC could be successfully applied to investigate CD/guest inclusion complexes and is expected to have a broad range of applications in the field of mixtures encapsulation.

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1. Introduction

Essential oils (EOs), synthesized by aromatic plants species, are highly complex mixtures [1]. Due to their remarkable antimicrobial and antioxidant properties, they have been proposed as alternatives to synthetic agents [2,3]. EOs have been widely used in pharmaceuticals, perfumes, cosmetics, foods as well as in edible films and packaging materials [4,5]. However, their very low aqueous solubility limits their applications. Encapsulation in cyclodextrins (CD) emerged as a potential tool to improve EOs solubility and bioavailability [6–9]. CDs are cyclic oligosaccharides obtained by enzymatic degradation of starch. They have a truncated shape with a hydrophilic surface and a hydrophobic cavity allowing them to encapsulate various guests to form non-covalent CD/guest inclusion complexes [10]. Besides native CDs (α-CD, β-CD and γ-CD), semi-synthetic derivatives have attracted much interest as they generally exhibit superior aqueous solubility and better encapsulation or solubilizing capacities toward guests [11].

Despite that CDs also improve stability, retention and biological properties of guests [6,7,12–15], the main purpose of using CDs is still to enhance the aqueous solubility of poorly soluble compounds. Phase solubility studies allow illustrating the evolution of guest solubility with CD concentration and determining the amount of CD needed to obtain desired guest solubility according to the following equation [16]:

$$S_t = S_0 + \frac{K_f S_0}{1 + K_f S_0}[CD]_t \quad (1)$$

where S_t and S_0 are the aqueous solubility of guest in CD solution or in water, respectively. K_f is the formation constant of CD/guest inclusion complex and $[CD]_t$ stands for the total concentration of CD in the aqueous medium.

Phase solubility studies require a quantitative determination of the guest solubility through precise measurements. However, EOs are complex mixtures and most of the analytical methods generally used to investigate their inclusion complexes with CDs are based on the assessment of the response of a single EO constituent [17–20]. Nevertheless, a multitude of equilibriums could take place when adding CD to EO due to the presence of various EO components [8]. Each EO constituent presents a distinct S_0 and forms inclusion complex with a specific K_f value and probably a particular stoichiometry owing to its physicochemical properties. This leads to diverse S_t values as reported in Eq. 1. Thus, the detection of the response of an individual constituent could be inaccurate because it does not reflect the behavior of the entire EO.

Furthermore, conventional techniques, i.e. fluorescence or UV–Visible spectroscopies are not appropriate in the case of mixtures. Indeed, absorbance or emission spectra of different constituents in mixtures could overlap. In addition, all components do not necessarily have a chromophore or a fluorophore moiety. Thus, the response neither is linear nor reflects the concentration of the entire EO. Moreover, the use of chromatographic methods such as HPLC-UV is time-consuming and requires large amounts of expensive solvents.

Total Organic Carbon (TOC) is a non-specific method. It is used to determine the concentration of organic carbon in aqueous samples. TOC presents several advantages over conventional methods; it is simple, economic and rapid.

TOC is key analysis in monitoring water quality [21] and evaluating the efficiency of removal of organic contaminants from wastewater [22]. Recently, TOC was also used to evaluate the ability of solid photocatalysts to adsorb CDs [23].

In the present work, phase solubility studies were carried out between hydroxypropyl-β-CD (HP-β-CD) and eleven EOs. TOC was applied for the first time in this field. The studied EOs were *Artemisia dracunculus* (tarragon), *Cinnamomum camphora CT linalool* (Ho Wood), *Citrus reticulata Blanco* (mandarin orange), *Cymbopogon nardus* (citronella grass), *Eucalyptus citriodora* (lemon eucalyptus), *Ocimum basilicum* var. *basilicum* (basil), *Origanum compactum* (oregano), *Origanum majorana CT thujanol* (marjoram), *Pimenta racemosa* (bay rum tree), *Rosmarinus officinalis cineoliferum* (rosemary) and *Satureja montana* (winter savory). The linearity, precision and accuracy of the TOC method were examined. For further validation, phase solubility studies were carried out for eugenol as a model of EO component. Eugenol solubility was determined using both TOC and UV–Visible spectroscopy analyses. Data have been statistically compared to determine the effectiveness of the TOC method.

2. Materials and methods

2.1. Materials

Essential oils were purchased from Herbes et Traditions (Comines, France). Eugenol (99%) was purchased from Acros Organics. Hydroxypropyl-β-cyclodextrin (DS = 5.6) was provided by Wacker-Chemie (Lyon, France). All products were of analytical grade and used as received. Ultrapure water was used all over the study.

2.2. Phase solubility studies

Phase solubility studies were carried out according to the method described by Higuchi and Connors [24]. Excess amount of guest (EO or eugenol) was added to HP-β-CD solutions at different concentrations ranging from 0 to 15 mM. The mixtures were shaken overnight at 25 °C and then filtered through a 0.45 μm membrane filter. At each HP-β-CD concentration, guest solubility was determined by TOC (and UV–Visible spectroscopy for eugenol). Phase solubility diagrams were obtained by plotting the apparent solubility of guests, determined either by TOC or UV–Visible analyses, as a function of HP-β-CD concentration. Experiments were done in triplicate.

2.3. TOC analyses

The amounts of EO or eugenol in the filtrates were determined by TOC using a Shimadzu TOC-V_{CSH} analyzer. This method is based on the complete oxidation of the sample to carbon dioxide (CO_2). In this study, the released CO_2 was detected by a non-dispersive infrared (NDIR) detector. Calculation of TOC value for filtrates (TOC_f) was done by subtracting the Total Inorganic Carbon (TIC_f) from the Total Carbon (TC_f) as described by the equation $TOC_f = TC_f - TIC_f$. Then, TOC for guest (EO or eugenol, TOC_G) was calculated by subtracting blank value (TOC_{CD}) form the corresponding TOC_f as follows: $TOC_G = TOC_f - TOC_{CD}$. Blank values (TOC_{CD}) were determined by measuring TOC for EO free CD solutions at the same operating conditions. Results were reported in g L^{-1} of organic carbon. Then, the solubility of EO or eugenol was determined from standard curves constructed with known EO and eugenol concentrations. The linearity of the TOC method was verified using a set of solutions containing various HP-β-CD concentrations. The