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Complexation between oleanolic and maslinic acids with native and modified cyclodextrins

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ABSTRACT

Oleanolic (OA) and maslinic (MA) acids are two natural triterpenoids with a wide range of beneficial effects for human health. However, their low solubility and permeability make their application in the food, or pharmaceutical, industry difficult. The complexation of OA and MA with α- β-, γ-, HP-α-, HP-β- and HP-γ-CDs, under different pH and temperature conditions, has been studied. Neither α- nor HP-α-CDs formed inclusion complexes, while β-, HP-β- and HP-γ-CDs provided A_L type and γ-CDs B_S phase solubility diagrams. Complexation was shown to be more stable in the case of MA but complexation efficiency was greater for OA. Increasing the pH and temperature of the complexation media tended to improve the complexation process with triterpenic acids.

1. Introduction

Oleanolic acid (OA) and maslinic acid (MA) are two natural pentacyclic triterpenoids widely distributed in nature (Figs. 1Ai and 2Ai). Many previous studies indicate that these compounds are naturally present, in both free and glycosylated forms, in hundreds of plants species (Somova, Nadar, Rammanan, & Shode, 2003; Fai & Tao, 2009; Gao, Tang, & Tong, 2012; Lin, Yan, & Yin, 2014), as well as in other organisms such as bacteria, fungi and yeasts (Parra et al., 2014). One of the plant species in which these compounds are particularly plentiful is the olive tree, and significant quantities are found in the by-products resulting from the olive oil extraction. Chouaïb et al. (2015) studied the concentration of OA and MA in olive pomace from different olive tree varieties, finding values of between 0.19 and 3.40 mg/g DW, and between 0.29 and 8.50 mg/g DW for OA and MA, respectively.

The biological and chemical properties of natural triterpenes, as well as their derivatives, have been widely studied in recent years. Around 40% of all scientific publications related to the biology and chemistry of these compounds were published between 2010 and 2015 (Sommerwerk, Heller, Kuhfs, & Csuk, 2016), with an upward trend between these dates (Tasca & Baggio, 2017). The huge interest in OA and MA lies in their broad spectrum of biological properties. Many studies highlight their role as hepatoprotectives (Chen, Liu, Yang, Zhao, & Hu, 2005; Yan, Yang, Lee, & Yin, 2014), inhibitors of rheumatoid arthritis (Choi et al., 2016), and their antimicrobial (Kurek, Nadkowska, Pliszka, & Wolska, 2012; Chouaïb et al., 2015), anticarcinogenic (Lin et al., 2014; Choulaïb et al., 2016), anti-inflammatory (Choulaïb et al., 2016), antidiabetic (Castellano, Guinda, Rada, Delgado, & Cayuela, 2013) and antiviral (anti-HIV) (Parra et al., 2014) actions.

The main disadvantage of these compounds for application in the food or pharmaceutical industry, as functional ingredients, is their low aqueous solubility and permeability. A variety of values for the water solubility of OA have been reported by different authors. Jäger, Winkler, Pfüller, and Scheffler (2007) established the water solubility of OA as 0.02 μg/ml, and Li et al. (2009) concluded that its aqueous solubility was lower than the detection limit of their methodology used (< 0.1 μg/ml). However, other authors indicated higher aqueous solubility values, including 4.61 μg/ml at 20 °C (Gao et al., 2012). No values for the aqueous solubility of MA have been found in the literature. The permeability value of OA (Papp = 1.1–1.3 × 10^{-6} cm/s in the apical-to-basolateral direction at 10 and 20 μM) has been mentioned by some authors (Jeong et al., 2007). This combination of low solubility and permeability means that these triterpenoids are of low bioavailability. Another disadvantage associated with poor aqueous solubility is the need to use organic solvents, such as cyclohexane, ethyl acetate, methanol, acetonitrile or acetone, for their extraction from plant material (Bernatoniene et al., 2016; Tasca & Baggio, 2017).

Several efforts have focused on improving the bioavailability and extractability of OA and MA by increasing their aqueous solubility. Chen, Zhong, Tan, Wang, and Wnag (2011) determined that solid-liquid nanoparticles improve the bioavailability of the OA. An increase in pH has also been proposed for increasing the solubility of these compounds. For example, Jäger et al. (2007) increased the water solubility

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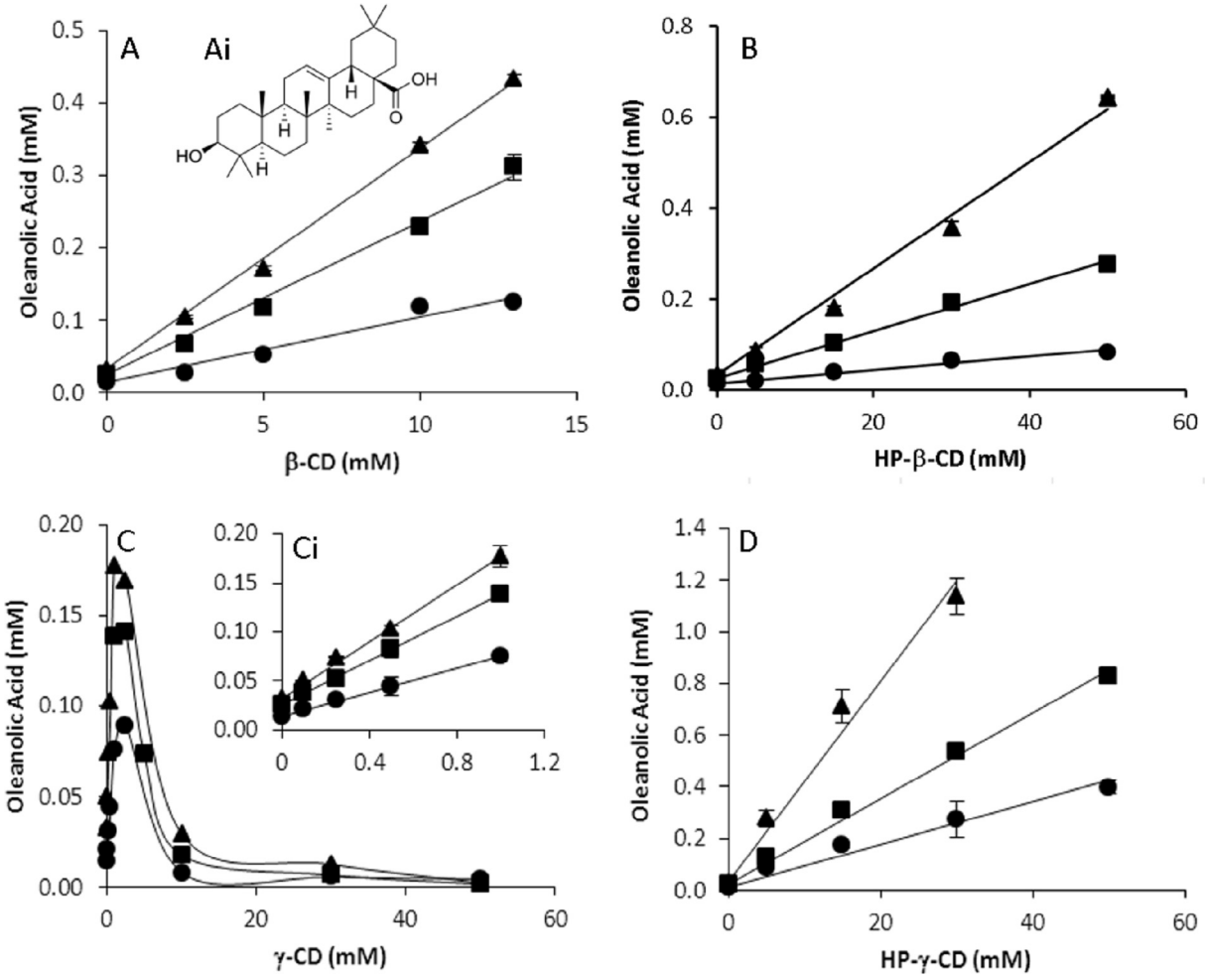

Fig. 1. Phase solubility diagrams of oleanolic acid with β-CD (A), HP-β-CD (B), γ-CD (C and Ci) and HP-γ-CD (D) in aqueous solution at 4 °C (●), 25 °C (■) and 65 °C (▲). Oleanolic acid chemical structure (Ai).

of OA to 77.2 μg/ml by increasing the water pH to 11.5. Jiang, Yang, Du, Zhang, and Zhang (2016) significantly increased the solubility of OA by the formation of solidified phospholipid complexes with hydroxyapatite. Other techniques studied to increase the aqueous solubility of these compounds have been the particle size reduction, solid dispersion, cosolvency, salt formation and the combination of any of them (Loftsson, Jarho, Másson, & Järvinen, 2005).

Complexation with cyclodextrins (CDs) has been widely used to increase the aqueous solubility of different compounds (Lucas-Abellán, Fortea, Gabaldón, & Núñez-Delicado, 2008; Mercader-Ros, Lucas-Abellán, Fortea, Gabaldón, & Núñez-Delicado, 2010; Mercader-Ros, Lucas-Abellán, & Gabaldón et al., 2010), and to improve the extraction of compounds with a poor aqueous solubility from food by-products (López-Miranda et al., 2016). Chen, Wu, Li, and Cheng (2010) improved the extraction of OA from leaves of *Chaenomeles speciosa* by using HP-β-CDs. Li et al. (2009) observed that the concentration of extracted OA increased from 0.08 mmol/l to 2.15 mmol/l when the concentration of HP-β-CDs increased from 5 mmol/l to 60 mmol/l. In a study developed by Quan et al. (2009), it was observed that the combination of HP-β-CDs with water soluble polymers (HPMC and PVP) improved the aqueous solubility of OA and its isomer ursolic acid.

CDs may be regarded as suitable tools for improving the aqueous solubility of triterpenic acids, especially OA and MA. However, previous studies have mainly focused on OA and its interaction with HP-β-CDs, and there is no information about other CDs types or different complexation conditions. For this reason, it was thought necessary to improve our knowledge on the complexation mechanism between OA and MA with different types of CDs, as well as different complexation conditions, such as pH or temperature.

The aim of this work was to study the complexation behaviour of OA and MA with natives α- β- or γ-CDs, as well as their modified HP-α-, HP-β- or HP-γ-CDs, and the effect of pH and temperature on the complexation process.

2. Material and methods

2.1. Reagents and standards

OA (94% purity) and MA (83.4% purity) were commercial extracts provided by Nutrafur S.A. (Murcia, Spain). Acetonitrile and water of HPLC grade were purchased from JT Baker (The Netherlands). The α-β-, γ-, HP-α-, HP-β- and HP-γ-CDs were purchased form Winplus International Limited (China). Reagent grade acetic and boric acids were purchase from Sharlau (Tarragona, Spain), and potassium di-hydrogen phosphate (reagent grade) were purchased from Panreac (Barcelona, Spain).

2.2. Complexation and phase solubility diagrams

The complexation process of OA and MA were evaluated by developing phase solubility diagrams, according to a modified method of that described by Higuchi and Connors (Higuchi & Connors, 1965). Excess amounts of OA and MA were added to 10 ml of aqueous solutions of increasing concentrations from 0 to 13 mM for β-CDs and 0 to 50 mM