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Solubility and solution thermodynamic properties of quercetin and quercetin dihydrate in subcritical water

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Abstract

Fundamental physicochemical data is required for the design and optimization of food engineering processes, such as extraction. Flavonoids are present in natural products such as grapes and have numerous health benefits particularly with respect to their reported antioxidant properties. Such flavonoid compounds can be extracted from these natural products using a variety of solvents, among them water. In this study, the aqueous solubilities of 3,3',4',5,7-pentahydroxyflavone (quercetin) and its dihydrate were measured at temperatures between 25 and 140 °C using a continuous flow type apparatus. The flow rate of subcritical water was studied at 0.1, 0.2 and 0.5 mL/min to study its effect on quercetin solubility and thermal degradation at temperatures greater than 100 °C. The aqueous solubility of anhydrous quercetin varied from 0.00215 g/L at 25 °C to 0.665 g/L at 140 °C and that of quercetin dihydrate varied from 0.00263 g/L at 25 °C to 1.49 g/L at 140 °C. The aqueous solubility of quercetin dihydrate was similar to that of anhydrous quercetin until 80 °C. At temperatures above or equal to 100 °C, the aqueous solubility of quercetin dihydrate was 1.5–2.5 times higher than that of anhydrous quercetin. The aqueous solubility of quercetin anhydrate and dihydrate at different temperatures was correlated using a modified Apelblat equation. The thermodynamic properties of the solution of quercetin and its dihydrate in water were than estimated from their solubility values. A flow rate effect on the aqueous solubility of quercetin and its dihydrate was not observed until above 100 °C where higher solvent (water) flow rates (>0.1 mL/min) were required to maintain a constant solubility in the saturation cell and with minimal thermal degradation of the solute (quercetin dihydrate). The study of its particle morphology under SEM indicated an aggregation of the crystals of quercetin dihydrate at subcritical water temperatures and at lower flow rates (<0.5 mL/min), thereby inhibiting stable solubility measurements and solvent flow through the saturation cell.

Introduction

For food engineering design applications, it is important to have fundamental physicochemical data, such as solute solubilities in extraction solvents, diffusivities of the solutes in like solvents, and mass transfer parameters in order to optimize the process. Our laboratory has embarked on an extensive program to experimentally determine such data and to correlate it for predictive purposes. As noted below, such fundamental physicochemical data can have applications in related fields, such as pharmaceutical technology and to the application of nutraceuticals. The molecular complexity and sensitivity of many flavonoids to environmental

factors such as light, heat, and oxygen make such measurements challenging. However, in this study we have determined the solubility of a model flavonoid, quercetin, in subcritical water using a novel experimental technique.

Flavonoids, are a diverse group of polyphenolic compounds present in plants, that provide a wide range of health benefits due to their antioxidant, anti-bacterial, anti-viral and anti-inflammatory properties (Cook and Samman, 1996). Quercetin (3,3',4',5'-7-pentahydroxy flavone) (Fig. 1) belongs to a sub-class of flavonoids known as flavonols, which find use in nutraceuticals or food supplements (Boots et al., 2008). Studies have shown that quercetin has antioxidant (Laughton et al., 1989), anti-inflammatory (Orsolic et al., 2004), anti-bacterial (Cushnie and Lamb, 2005), anti-coagulative (Bucki et al., 2003), and anti-hypertensive (Duarte et al., 2001) properties. Quercetin has also been used in gene expression modulation (Moon et al., 2006) and in the inhibition of the growth of human cancer cell lines (Larocca et al., 1990). Quercetin, existing mainly in the form of glycosides, can be found in vegetables such as onions, tomatoes, lettuce & celery (Crozier et al., 1997), fruits such as apples and berries (Bajpai et al., 2005) and tea, fruit and vegetable juices (Karakaya and El, 1999).

Quercetin is commonly extracted from the afore-mentioned sources using organic solvents (Wach et al., 2007) and microwave-assisted extraction (Huang and Zhang, 2004). Supercritical fluid extraction (Martino and Guyer, 2004, Dimitrieska-Stojkovic and Zdravkovski, 2003) and pressurized fluid extraction (Turner et al., 2006, Alonso-Salces et al., 2001) of quercetin from natural products has provided not only higher quercetin yields but also utilized a “green”, sustainable extraction technology thereby replacing toxic organic solvents. The use of pressurized fluids, such as water above their boiling points, also known as “subcritical fluids”, have shown good solvency properties in the extraction of agricultural products containing solutes of varying polarity from natural product matrices. In order to optimize the extraction of quercetin and its conjugates from natural products using subcritical water as solvent, it is important to measure their physicochemical properties, such as solubility of the quercetin compounds in water at different temperatures for process design purposes. Chebil et al. (2007) reported the aqueous solubility of quercetin at 20 °C to be less than 0.01 g/L. However, there exists no data on the actual measurement of the solubility of quercetin in water in the literature.

Studies have indicated that quercetin displays an amphipathic behavior due to phenyl rings forming the hydrophobic part of the molecule and the hydroxyl groups constituting the polar portion (Codorniu-Hernandez et al., 2003). Such compounds exhibit variable properties in terms of their aqueous solubility and resultant antioxidant capacity depending on the charge density of its hydrophilic and hydrophobic components (Mendoza-Wilson and Glossman-Mitnik, 2006). Studies have shown the antioxidant capacity of quercetin in a water-soluble phase is almost eight times greater than in a lipid-soluble phase (Usami et al., 2004). The octanol–water partition coefficient of quercetin aglycone (without a sugar group) is higher than its glucoside indicating greater solubility of the quercetin glycosides in water compared to its aglycone (Rothwell and Morgan, 2005). However, it was also indicated that, apart from the sugar groups, a greater number of hydroxyl groups also increased the octanol–water partition coefficient of quercetin. Though quercetin exists as glycosides in the natural products, studies have indicated that it is converted to aglycones upon human uptake with the help of β-glucosidase and similar enzymes (Turner et al., 2006). The nutritional supplements containing mainly quercetin aglycone and its metabolites have shown greater stability and higher half-time lives compared to its glycosides (Boots et al., 2008).

In the pharmaceutical industry, solvent-mediated polymorphic transformation is a very important process that influences the bioavailability, morphology, chemical stability and other properties of the finished product. The transformation between the anhydrate and hydrate in the pharmaceutical industries has been investigated (Gu et al., 2001, Cardew and Davey, 1985, Murphy et al., 2002). When a solvent other than water is used, polymorphs are defined as different crystal structures of the same molecular composition while hydrates are crystalline structures of the same compound differing by the water of hydration (Morris, 1999). In a solvent-mediated transformation process, the anhydrate form, also known as a metastable form, upon dissolution in water can crystallize until achieving supersaturation, i.e., forming polymorphs or hydrates (Wikstrom et al., 2008). Similar studies indicated that the anhydrous forms of caffeine, theophylline, glutethimide and cholesterol showed correspondingly higher dissolution rates than their respective hydrates (Florence and Attwood, 2006). However, these solubility studies were performed at lower temperatures (well below the boiling point of water) and it was assumed that the energy released from the crystalline form during interaction of a hydrate with water would be considerably less than for the anhydrous material.

Similar dissolution studies performed on cefdinir (an antimicrobial therapeutic drug) indicated an increase in the aqueous solubility of the monohydrate at subcritical temperatures when compared to the anhydrous form (Cabri et al., 2006). This increase in the solubility of the monohydrate over the anhydrous form was primarily related to the microstructural properties of the compound at the experimental temperatures. Another important property affecting the dissolution properties of the hydrated form over the anhydrous form is the water activity. Studies have indicated that a greater deviation from the equilibrium water activity value for each specific compound would result in a significant difference between the exhibited aqueous solubilities of the anhydrous and the hydrated forms (Li et al., 2008).

As indicated previously in this section, there exists no data for the aqueous solubility of quercetin in the literature. It is also proven difficult to measure the aqueous solubility of flavonoid compounds above the boiling point of water using a static apparatus. The anthocyanins extracted from red onions using pressurized hot water in a static batch extractor showed thermal degradation at 110 °C and residence time as low as 8 min (Petersson et al., 2010). Similar studies were also performed on the subcritical water extraction of silymarin compounds from milk thistle which showed thermal degradation at temperatures greater than 100 °C (Duan et al., 2009). This study reports on the measurement of the solubility of quercetin and its dihydrate in subcritical water using a continuous flow apparatus. The effect of the operating conditions such as solvent flow rate and temperature on the measurement of aqueous solubility of quercetin dihydrate was studied supplemented by microstructural studies using scanning electron microscopy (SEM).