PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
ESCUELA DE INGENIERÍA

MEASUREMENT AND PC-SAFT MODELING OF THE SOLUBILITY OF GALLIC ACID AND PHLOROGLUCINOL IN AQUEOUS MIXTURES OF DEEP EUTECTIC SOLVENTS

BRUNO ALEJANDRO SEPÚLVEDA ORELLANA

Thesis submitted to the Office of Research and Graduate Studies
in partial fulfillment of the requirements for the degree of
Master of Science in Engineering

Advisor:
ROBERTO IVÁN CANALES MUÑOZ
JOSÉ RICARDO PÉREZ CORREA

Santiago de Chile, August 2020

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Members of the Committee:
ROBERTO IVÁN CANALES MUÑOZ
JOSÉ RICARDO PÉREZ CORREA
NESTOR ESCALONA BURGOS
JUAN DE LA FUENTE BADILLA
CRISTIÁN SANDOVAL MANDUJANO

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For my family and friends who never stopped believing and trusting me. For the end of a stage and the beginning of an endless journey.

ACKNOWLEDGEMENTS

I never imagined how much I would grow pursuing this master's, and I am not only referring to knowledge, but to professional and personal growth, learning to be self-sufficient, disciplined, persevering and organized. Therefore, I would like to dedicate the following paragraphs to all the people who, in one way or another, have been involved in this process that has been so important to me.

First of all, I would like to thank my principal investigators. Thank you to Roberto Canales for the confidence placed in me from the beginning of this project, for supporting me in each important decision about this thesis, for his patience, encouragement, guidance, open debates and friendship. I also appreciate him giving me the possibility of fulfilling an internship abroad, which gave me many personal growth experiences and the ability to perform an excellent quality job. Second, I would like to express my gratitude to Professor Ricardo Pérez, who facilitated the resources for my internship in Germany, in addition to the use of his own laboratory. I also appreciate his time used to answer all my questions regarding planning and experiments that arose during the course of the master's. He supported me in the most important decisions of my thesis with his wisdom, knowledge and patience. I cannot fail to also thank the professors of the Technical University of Dortmund (Germany), especially my supervisors Do Hoang Tam and Christoph Held, who were fully available to teach me and transmit all their knowledge during my stay there, creating bonds and connections that last until today. Also, thank you all for your participation in the research, analysis and especially modeling of the data of this research.

On the other hand, I would like to thank my laboratory partners, mainly Vincenzo Cotroneo, Matías Campos and Sebastián Ormazábal. Only they really know all the sacrifice involved in carrying out experiments every day, arriving at dawn and leaving when only the guard is left. Thanks for those moments of karaoke, laughter and of course open debates about any concerns that arose. Although the workspace was always a bit noisy,

knowledge and learning abounded and that is what was most important. Also, I would like to highlight the help of my undergraduate research students Valeria Fröhlich and Monserrat Núñez, who were always willing to learn and collaborate in everything necessary for the development of this research. In addition, I would like to make an honorable mention to Nicolás Gajardo, a friend and unconditional colleague who accompanied me on my internship abroad and was a great support in my growth as a student and in all the decisions regarding my master's.

It is impossible not mention my family: mainly, mom, dad and sister. Although, they could not help me in academics, they always found a way to help me with their unconditional support. They were there for me when I arrived home late not wanting to study, when I slept 2 hours daily, when I had to get up at 6 AM to get to the university and endless other small details that make a difference in a routine as exhausting as the university is. This work is dedicated especially for you, my unconditional support system.

Likewise, I'd like to thank my university volleyball teammates, especially to Joaquín Ossandón for all his help and support. Also, thank you to all my friends, those from school and university, who constantly cared about my physical and mental health, being 100% willing to help me. I would also like to thank María José Barra for her constant support and for the help with the grammar correction of this document. Without your support, attention and words of encouragement, it would have been impossible to complete this work.

Finally, I wanted to thank God for guiding me correctly and to my institution, the Pontifical Catholic University of Chile for providing me with the necessary resources for the development of my bachelor's and master's degree. Thank you from the bottom of my heart to everyone who, in one way or another, helped me in my professional growth during this beautiful process contributing to form the person I am today.

Gracias totales.

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ABSTRACT

Many natural compounds present in fruits and vegetables have received increasing attention due to their expanding technological applications. The most interesting applications are found in the food, nutraceutical and pharmaceutical industries, since many of these compounds have been associated with health benefits including reduced levels of cholesterol and hypertension, as well as protection against cardiovascular diseases and cancer, among others. Some of these natural compounds are polyphenols. These are one of the major families of phytochemicals with a wide spectrum of bioactivities, given their ability to interact strongly with enzymes. They are industrially extracted from several sources, in most cases using organic solvent which are inefficient, expensive and non environmentally friendly. The extraction process can be improved significantly using deep eutectic solvents (DES). These mixtures are non-toxic, biodegradable and low cost. However, to design a DES extraction process properly, the solubility of the target molecules in the respective DES should be determined.

Gallic acid (GA) and phloroglucinol (PH) are two abundant phenolic compounds present in fruits and brown seaweeds. They are used as typical polyphenol standards when extracting vegetable or algal matrices. This work focuses on measuring the solubility of these phenolic compounds in aqueous solvent mixtures at 293.15, 303.15 and 313.15 K. The co-solvents included in this study comprises traditional solvents such as ethanol, levulinic acid, glycerol and ethylene glycol. In addition, this study includes some DES; those formed with choline chloride as HBA and ethylene glycol (DES 1), levulinic acid (DES 2) and glycerol (DES 3) as HBD in 1:2 molar ratio at 101.3 kPa. The experimental data was used to fit PC-SAFT parameters and to provide estimations of solubility at different temperatures for a further understanding of the extraction of these polyphenols from food matrices. Furthermore, the studied systems were analysed using PXRD to detect polymorphism in the solid/liquid equilibrium process.

As expected, our results indicate that DES are better solvents compared with ethanol. This behavior was explained due to the intermolecular interactions and the solvatochromic parameters, where the value of the hydrogen bond acceptor parameter presented a direct relationship with the solubility. Specifically, GA was more soluble in DES 2 while PH dissolves better in DES 1. This was explained due to the particular interaction of their functional groups with both solvents. In addition, PH was more soluble than GA in all the aqueous systems tested. The molecular structure and arrangement of hydroxyl groups of PH reduce its steric hindrance and strengthen its hydrogen bonds, favoring its interactions with aqueous mixtures.

Solid-liquid equilibrium (SLE) modeling was successfully achieved with PC-SAFT for GA in pure and aqueous systems. However, SLE of phloroglucinol was not modeled due to the change in the crystalline structure of this polyphenol, requiring further analysis and considerations in the equation of state. This is observed in the PXRD analysis that showed a change in the diffraction planes of PH, therefore, these systems present polymorphism and cannot be modeled with the same PC-SAFT conditions as GA.

Keywords: solubility, gallic acid, phloroglucinol, deep eutectic solvents, PC-SAFT.

RESUMEN

Muchos compuestos naturales presentes en frutas y verduras han recibido una creciente atención debido a la expansión de sus aplicaciones tecnológicas. Las aplicaciones más interesantes se encuentran en las industrias alimentarias, nutracéuticas y farmacéuticsa, ya que muchos de estos compuestos se han asociado con beneficios para la salud, como por ejemplo la reducción de los niveles de colesterol e hipertensión, la protección contra enfermedades cardiovasculares y cáncer, entre otros. Algunos de estos compuestos naturales de interés son los polifenoles. Estos son una de las principales familias de fitoquímicos con un amplio espectro de bioactividades, dada su capacidad de interactuar fuertemente con las enzimas. Se extraen industrialmente de varias fuentes, en la mayoría de los casos utilizando solventes orgánicos que son ineficientes, caros y poco amigables con el medio ambiente. El proceso de extracción se puede mejorar significativamente utilizando solventes de punto eutéctico profundo (DES). Estas mezclas son no tóxicas, biodegradables y de bajo costo. Sin embargo, para diseñar correctamente un proceso de extracción con DES, se debe determinar la solubilidad de las moléculas escogidas en el DES respectivo.

El ácido gálico (GA) y el floroglucinol (PH) son dos compuestos fenólicos abundantes presentes en frutas y algas pardas principalmente. Se usan como estándares típicos de polifenoles cuando se extraen matrices vegetales o de algas. Este trabajo se centra en medir la solubilidad de estos compuestos fenólicos en mezclas de solventes acuosos a 293.15, 303.15 y 313.15 K. Los co-disolventes incluidos en este estudio comprenden solventes tradicionales como etanol, ácido levulínico, glicerol y etilenglicol. Además, se incluye el estudio de mezclas acuosas de algunos DES, los cuales están formados con cloruro de colina como HBA y etilenglicol (DES 1), ácido levulínico (DES 2) y glicerol (DES 3) como HBD, sintetizados en relación molar 1:2 a presión atmosférica. Los datos experimentales se utilizaron para ajustar los parámetros PC-SAFT de los polifenoles, con el objetivo de

poder proporcionar estimaciones de solubilidad a diferentes temperaturas para una mejor comprensión de la extracción de estos polifenoles de las matrices alimentarias. Además, los sistemas estudiados se analizaron utilizando PXRD para detectar el polimorfismo en el proceso de equilibrio sólido-líquido.

Como se esperaba, nuestros resultados indican que los DES son mejores solventes que los tradicionales, exceptuando el caso del etanol. Este comportamiento se explicó debido a las interacciones intermoleculares y los parámetros solvatocrómicos, donde el valor del parámetro *aceptor de enlace de hidrógeno* presentaba una relación directa con la solubilidad. Específicamente, GA fue más soluble en DES 2 mientras que para el PH se obtuvo una mejor solubilidad en DES 1. Esto se explicó debido a la interacción particular de sus grupos funcionales con ambos solventes. Además, el PH fue más soluble que el GA en todos los sistemas acuosos probados. La estructura molecular y la disposición de los grupos hidroxilo del PH generan un bajo impedimento estérico y fuertes interacciones de puentes de hidrógeno, lo que favorece su interacción con las mezclas acuosas.

El modelado de la ecuación sólido-líquido (SLE) se logró con éxito mediante PC-SAFT para GA en sistemas acuosos. Sin embargo, el SLE para el floroglucinol no se pudo modelar debido al cambio en la estructura cristalina de este polifenol, lo que requiere un análisis y consideraciones adicionales en la ecuación de estado. Esto se observa en el análisis PXRD que mostró un cambio en los planos de difracción de PH, por lo tanto, estos sistemas presentan polimorfismo y no pueden modelarse en las mismas condiciones de PC-SAFT que GA.

Palabras Claves: solubilidad, ácido gálico, floroglucinol, *Deep eutectic solvents*, PC-SAFT.

1. INTRODUCTION

The natural compounds contained in fruits and vegetables such as vitamins, phenolic compounds and micronutrients, have received considerable attention due to their widely studied health benefits. In particular, polyphenols can protect against an important number of chronic disease given their ability to interact strongly with enzymes (Ozcan, Akpinar-Bayizit, Yilmaz-Ersan, & Delikanli, 2014). Phenolics are organic compounds that include at least one phenol group, i.e., and an aromatic ring attached to a hydroxyl group (Sroka & Cisowski, 2003). Some well documented health benefits associated to the consumption of phenolic compounds include reduced levels of cholesterol and hypertension, as well as protection against cardiovascular diseases (Zuo, Chen, & Deng, 2002; Huang & Ferraro, 1992) and cancer (Wang & Bachrach, 2002). Moreover, polyphenols are antifungal (Shukla, Srivastava, Kumar, & Kumar, 1999), antimicrobial (Gunckel et al., 1998; Kubo, Xiao, & Fujita, 2001), anti-inflammatory (Kroes, Van Den Berg, Quarles Van Ufford, Van Dijk, & Labadie, 1992; Cháfer, Fornari, Stateva, Berna, & García-Reverter, 2007; N. Li, Khan, Qiu, & Li, 2018) and antioxidant agents (Sroka & Cisowski, 2003; Aruoma et al., 1998; Cháfer et al., 2007; Fernandes & Salgado, 2015).

The benefits offered by phenolic compounds can be applied in a wide range of industries. For example, new foods, nutraceuticals or pharmaceutical products with specific health promoting properties can be designed by incorporating these bioactive compounds (N. Li et al., 2018; Kusumaningsih et al., 2016). To prepare these products, isolated polyphenols or rich polyphenol extracts are required; hence, efficient extractions processes must be designed. Some well studied and widely applied polyphenols extraction methods at laboratory scale or at industrial level are conventional extraction with organic solvents at atmospheric pressure, soxhlet, pressurized hot water extraction, ultrasound extraction and microwave extraction (Diaconu, Nechifor, Nechifor, Ruse, & Totu, 2009; Rojas Molina, Castro-López, Sánchez-Alejo, Niño-Medina, & Martinez, 2016), among others. The most adequate method to be used will depend on the properties of the raw material, the intended use and the specific polyphenols to be recovered, nevertheless, all extraction methods need

solvents. Therefore, knowing the solubility of the target polyphenols in the chosen solvent is a first step in the design of the extraction process (Ran, He, Yang, Johnson, & Yalkowsky, 2002).

At industrial scale, conventional extraction with organic solvents such as ethanol, glycerol, methanol and ethylene glycol, among others, is commonly used (Carasek, Bernardi, do Carmo, & Vieira, 2019; Cunha & Fernandes, 2018) for extracting polyphenols like tannins and anthocyanins from grape. However, this method is inefficient (low yields, slow, large volumes of solvent are needed), expensive, and not environmentally friendly. Deep eutectic solvents (DES) are an emerging and attractive alternative to conventional organic solvents, which combine the best properties of ionic liquids (Maugeri & Domínguez De María, 2012) along with being safer for the environment, biodegradable and low cost (Zhang, De Oliveira Vigier, Royer, & Jérôme, 2012; Carasek et al., 2019; Cunha & Fernandes, 2018). DES are prepared by mixing a hydrogen bond acceptor (HBA) with a hydrogen bond donor (HBD), where the eutectic mixture has a melting temperature lower than that of each individual compound, due to the formation of intermolecular hydrogen bonds (Zhang et al., 2012).

This work focuses on measuring the solubility of two phenolic compounds, gallic acid and phloroglucinol in different aqueous mixtures. Conventional organic solvents were used (pure ethanol and aqueous mixtures of: levulinic acid, glycerol and ethylene glycol), as well as 3 DES formed by the HBA choline chloride and the conventional solvents above as HBDs (ethylene glycol (DES 1), levulinic acid (DES 2) and glycerol (DES 3)); all in a molar ratio 1:2. The solubilities of the aqueous mixtures of HBDs were compared with that of their respective aqueous DES mixtures. A variation of the flask-shake method was used to determine the experimental solubilities. In addition, to detect polyphormism after adding a solvent to a given polyphenol standard, X-ray powder diffraction (PXRD) analysis was carried out. Experimental solubilities were used to calibrate a solid-liquid equilibrium (SLE) model using the PC-SAFT approach, which will be useful for the design of the extraction process.

1.1. Hypothesis and objectives

Previous studies involving extraction of natural compounds with DES have shown excellent results. Hence, the hypothesis of this work is that gallic acid and phloroglucinol (phenolic compounds) are more soluble in water/DES mixtures than in traditional aqueous solvent mixtures (ethanol, ethylene glycol, levulinic acid and glycerol).

In accordance with the proposed hypothesis, the general objective of this thesis is to verify if indeed gallic acid and phloroglucinol (polyphenols) are more soluble in aqueous mixtures of DES than in aqueous mixtures with traditional solvents at 293, 303 and 313 K. In addition, we expect to find the best solvent for each phenolic compound. The specific objectives are: i) implement an experimental methodology to measure the solubility at different temperatures, ii) compare the solubility data obtained with the implemented methodology with values from the literature, iii) powder X-ray diffraction analysis (PXRD) to detect polyphormism (multiple crystalline forms) in the studied SLE systems, iv) use PC-SAFT for modeling the SLE results.

1.2. Contents

Chapter 2 summarizes an extensive bibliographic research regarding the most relevant topics of this thesis. First, the importance of solubility and the main measuring techniques is discussed. Then, the phenolic compounds considered in this study are described and their importance, origin and main characteristics are discussed. Next, deep eutectic solvents are described and discussed. PC-SAFT modeling is briefly presented, and finally, the powder X-ray diffraction technique and its importance in changing the diffraction planes and unit cell structure is explained.

Chapter 3 presents the experimental methodology that was used to prepare the samples and calculate the solubility, considering the materials and equipment used.

Chapter 4 includes the experimental results of solubility, as well the results of PC-SAFT modeling with the different tables and figures that support the information.

Finally, Chapter 5 contains the conclusions of this investigation, where it is verified if the hypothesis and objectives were fulfilled.

2. LITERATURE REVIEW

The following section is a bibliographical review of the most relevant topics of this research, structured as follows. Subsection 2.1 introduces the concept of solubility, its experimental methodology, analytical technique and its importance. Subsection 2.2 summarizes the importance of the phenolic compounds used (gallic acid and phloroglucinol) and the main raw materials where these polyphenols are obtained from. Subsection 2.3 introduces the reader to eutectic mixtures, their constitutive components, classification and properties. Subsection 2.4 covers information about the PC-SAFT model and their origin. Finally, subsection 2.5 introduces PXRD analysis, its use and importance for the detection of polymorphism in the crystallization of molecules.

2.1. Solubility measurement

Solubility can be described as the property that measures the ability of a substance in a solid, liquid or gaseous state to dissolve within another (solvent) reaching chemical equilibrium and resulting in a homogeneous system (Martins, Lopes, & De Andrade, 2013; Alexandru, n.d.). As an outcome of the measurement of solubility, the maximum concentration reached by a compound in the equilibrium between two phases is obtained. However, the different compounds vary widely in their solubilities due to differences in their structures and properties. A clear example is the variation of the solubility according to different conditions of the solution such as pH, co-solvents, temperature, among others (Di & Kerns, 2016).

Solubility values are needed for formulating new products in the food, pharmaceutical and nutraceutical industries. In addition, it is useful to evaluate biological activities, to optimize chemical structures, and to carried out pharmacokinetic analysis (Di & Kerns, 2016). However, measuring solubilities is difficult. The physical state of the compound and the physical and chemical conditions of the solution may affect the concentration of the compound dissolved and the precipitate generated; in addition, metastable states

can be reached during the experimental procedure. Hence, well developed and carefully performed methods are required to reduce the experimental error and the formation of metastable states.

In an organic compound, the solubility is directly related to the polarity of the molecular bonds and molecular structure between solute and solvent. In general, nonpolar or weakly polar substances are more likely to dissolve better in less polar systems, while polar solutes tend to dissolve better in polar solvents. This means that the solubility of solids or liquids in another liquid will only occur if the interaction between solute and solvent is high enough to disrupt the solute-solute and solvent-solvent interactions. In addition, the change in entropy is related to the temperature of the system and it is a factor that must be considered to assess whether a substance dissolves easily or not in a given solvent (Martins et al., 2013).

The aqueous solubility of different compounds, organic or inorganic, plays an important role in the chemical, pharmaceutical, food and cosmetic industries. The solubility data provides essential information for the design of separation processes, such as precipitation, crystallization and extraction of fluids (Q. Li et al., 2013; Letcher & Macedo, 2007; Noubigh, Aydi, Mgaidi, & Abderrabba, 2013). The solubility allows the prediction of how a substance may behave under different circumstances, which is key for process design and product development.

2.1.1. Experimental methods

As mentioned before, solubility measurements require well-developed and carefully performed experimental methods. The two most commonly used in the literature are the direct and indirect methods. In the direct method, chemical analysis or property measurement is carried out in the liquid phase, once the solid/liquid system reaches equilibrium. In turn, the indirect method first determines the solubility product constant (Ksp) from which the solubility is deduced. They are used extensively for the solubility determination of slightly soluble compounds (Hefter & Tomkins, 2003).

The direct method can be either analytical or synthetic. The analytical method requires the chemical analysis of several solid and liquid phases in equilibrium to determine the solubility of the solid. On the other hand, the synthetic method does not require a chemical analysis since the solubility is calculated by varying parameters pertinent to a specific thermodynamic property of the system. These parameters can be temperature, pressure, composition, among others (Hefter & Tomkins, 2003).

In this study we used the direct analytical method in saturated shake-flasks to measure solubilities, proposed more than 50 years ago and is still commonly used since it is simple and provides reliable measurements. This method consists in adding an excess amount of solute into a mixture, under controlled isothermal and isobaric conditions, in order to saturate the liquid and observe a solid precipitate (Hefter & Tomkins, 2003; Baka, Comer, & Takács-Novák, 2007; Shefter & Higuchi, 1963). The time to reach equilibrium can vary between 12 h and 7 d, depending on the solute, the solvent, the agitation and the amount of material used (Apley et al., 2015). After equilibrium, the solution is separated from the decanted solid and the concentration of solute is measured in the liquid phase. Although this method is one of the simplest to measure solubilities, it is slow and consists of several manipulation steps. The results depend on a rigorous control of external variables, such as temperature, pressure, agitation time and sedimentation time, as well as a careful separation of the saturated solution (Baka et al., 2007). In this study, we used small Eppendorf tubes and a thermoregulated agitated system (thermomixer) (Wysoczanska, MacEdo, Sadowski, & Held, 2019), as shown in Figure 2.1.

The gravimetric analysis method can take a long time (Hefter & Tomkins, 2003). In this method, a stock solution is prepared in vials of glass or plastic. The vials are placed in a rotary kiln, or in a thermoregulated stirrer, and then allowed to equilibrate for 48 hours. A sample of solution is extracted from the vials with a preheated syringe with a filter. This sample is weighed and then taken to an evaporation chamber in order to evaporate the solvent. After this, the sample is re-massed (now without the solvent). The solubility is obtained from the difference between the initial and the post-dried samples. To

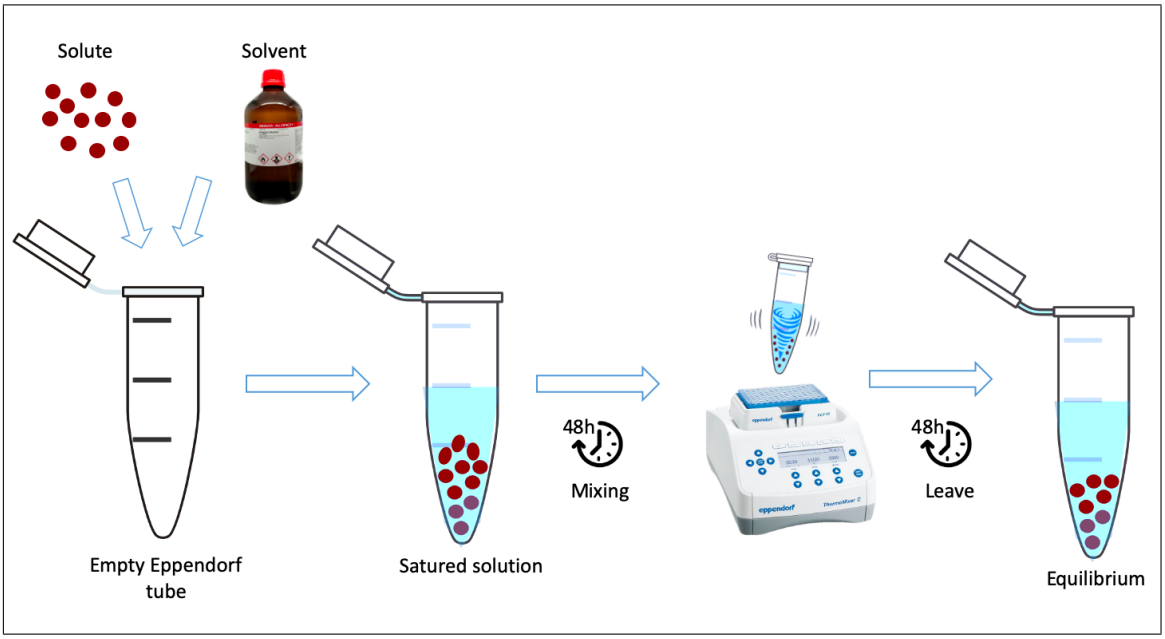

Figure 2.1. Shake-flask methodology used to find the solid-liquid balance of the samples.

ensure a total evaporation of the solvent, the sample is placed in a vacuum drying chamber and remastered after 24 hours (Daldrup, Held, Ruether, Schembecker, & Sadowski, 2010). However, this method is no longer widely accepted since sometimes there are solid residues that do not evaporate, and in general the data is overestimated.

2.1.2. Analytical techniques

Several techniques can be used to quantify solubility, whether chemical (UV-Vis, HPLC, GC) or physical (density, refractive index), being UV-Vis and HPLC the most reported analytical methods in the literature nowadays for measuring the solubility of phenolic compounds (Hefter & Tomkins, 2003), given their reliability and accuracy.

2.2. Phenolic Compounds

Phenolic compounds are organic molecules composed of at least one hydroxyl group attached to an aromatic ring. These are reactive secondary metabolites found in a wide

range of plant-derived foods, occurring in all vegetative organs, as well as in flowers and fruits, vegetables, cereals, grains, seeds and drinks derived from the above. These are mainly classified as flavonoids, stilbenes, tannins and phenolic acids. Despite the fact that their structure can be very complex and varied, they are generally called polyphenols (Ozcan et al., 2014). Polyphenols are the main component that contribute color (such as blue, red, orange and purple pigments), taste and flavor to food. Furthermore, one of their main characteristics is their ability to react with one-electron oxidants preventing free radical formation in biological systems, which is related to its antioxidant and protein interaction properties.

In general, polyphenols have shown beneficial health effects, including control of cholesterol levels, depression and hypertension, as well as protection against cardiovascular diseases (Zuo et al., 2002; Huang & Ferraro, 1992) and cancer (Wang & Bachrach, 2002). They also have antifungal (Shukla et al., 1999), antimicrobial (Gunckel et al., 1998; Kubo et al., 2001), anti-inflammatory (Kroes et al., 1992; Cháfer et al., 2007; N. Li et al., 2018) and antioxidant properties (Sroka & Cisowski, 2003; Aruoma et al., 1998; Cháfer et al., 2007; Fernandes & Salgado, 2015). The benefits offered by phenolic compounds can be applied in a wide range of industries such as food, pharmaceutical, cosmetics, textiles, paint and dyes (N. Li et al., 2018; Kusumaningsih et al., 2016). They can improve the stability of products containing lipids or fats, avoiding rancidity (Gunckel et al., 1998; Ran et al., 2002; Cháfer et al., 2007).

There is a subset of phenolic compounds called tannins which are soluble in water and have a high molecular weight (between 500 and 3000 Da) (Chung, Wei, & Johnson, 1998). These form complexes with alkaloids, polysaccharides and proteins. The main source of tannins is a variety of plants utilized as food and feed including food grains. Some examples are sorghum, millet, barley, grape (dark/light) seed/skin, apple juice, strawberries, raspberries, blackberries, cranberries, pomegranate, walnuts, peach, blackberry, olive, plum, chick pea, black-eyed peas, lentils, haricot beans, faba beans, winged beans

red/white wine, cocoa, chocolate, tea, cider, coffee, immature fruits. (Ozcan et al., 2014; Chung et al., 1998)

Tannins may be subdivided into hydrolysable, non-hydrolysable or condensed and phlorotannins. Hydrolysable tannins are esters of gallic acid (gallo- and ellagi-tannins) with a central carbohydrate core. Condensed tannins (also known as proanthocyanidins) are polymers of polyhydroxyflavan-3-ol monomers structurally related to flavonoids. Lastly, phlorotannins or seaweed polyphenols consist entirely on combinations of phloroglucinol units and have been isolated from various genera of brown algae (Phaeophyceae). (Ozcan et al., 2014; Chung et al., 1998; Mämmelä, Savolainen, Lindroos, Kangas, & Vartiainen, 2000; Lorenzo et al., 2019; Pal Singh & Bharate, 2006; Quéguineur et al., 2012).

This research was focused on two types of polyphenols: gallic acid and phloroglucinol. They were chosen mainly because they are the base of vegetable and algae polyphenols, in which they are found in high concentrations. Also, they serve as typical polyphenol standards which are low cost and used for analysis of total polyphenols content (TPC) when extracting vegetable or algal matrices.

2.2.1. Gallic acid

Gallic acid or 3,4,5-trihydroxybenzoic acid ($C_7H_6O_5$) is one of the most abundant phenolic compounds in nature; it consists of an aromatic ring with 3 hydroxyl groups and a carboxylic acid group (Cháfer et al., 2007) as seen in Figure 2.2 (a). This compound was first identified in plants by Carl Wilhelm Scheele in 1786 (Fernandes & Salgado, 2015). Gallic acid is a crystalline and slightly colorless or yellow solid, which has a molecular weight of 170.12 g/mol. Its main physicochemical characteristics are: melting point of 210 ^{o}C with decomposition between 235 to 240 ^{o}C; density of 1.69 kg/L and a pKa of 4.40 (both at 20 ^{o}C) (Fernandes & Salgado, 2015).

Gallic acid together with other phenolic compounds is found as a biologically active component in oil mill wastewater (Cabrera, López, Martinez-Bordiú, De Dupuy Lome,

& Murillo, 1996; Obied et al., 2005; Hamdi, 1993; Visioli et al., 1999); in food grains such as: seeds (Yilmaz & Toledo, 2004), barley, millet, beans, peas, carobs (Chung et al., 1998); in plants, fruits and vegetables (Yeh & Yen, 2003) such as: olives (Visioli et al., 1999), apples, bananas, blackberries, blueberries, dates, grapes, hawthorn berries, peaches, pears, persimmons, plums, raspberries and strawberries (Chung et al., 1998); in liquids such as: red wine (Murase et al., 1999), tea (Cháfer et al., 2007; Wang & Bachrach, 2002), olive oil (Obied et al., 2005; Visioli et al., 1999); among others. It currently has many industrial applications, such as anticancer and antimicrobial agents for the pharmaceutical industry, antioxidants in food and petroleum companies, source material for ink and color manufacturing, and raw material for the chemical synthesis of propyl gallate and trimethropim (Mota, Queimada, Pinho, & Macedo, 2008; Fernandes & Salgado, 2015).

2.2.2. Phloroglucinol

In general, seaweeds are considered a source rich on bioactive compounds (such as, polyunsaturated fatty acids, vitamins, polysaccharides, minerals, and phenolic compounds). Seaweeds can produce a many secondary metabolites that can perform a wide spectrum of biological activities. According to their pigments, algae are mainly classified among three groups: Chlorophyta (green algae), Rhodophyta (red algae) and Phaeophyta (brown algae). Brown algae contain the highest amounts of phytochemicals such as terpenes, carotenoids, phenolic compounds, soluble fiber and iodine (Pádua, Rocha, Gargiulo, & Ramos, 2015; Gupta & Abu-Ghannam, 2011). Specifically, brown algae contain a wide variety of phlorotannins or phlorogancinol-based polyphenols, formed from the polymerization of phloroglucinol monomer units (1,3,5-trihydroxybenzene). This chemical structure is given by an aromatic ring with three hydroxyl groups as seen in Figure 2.2(b). As previously mentioned, phlorotannins are present in many marine organisms, especially in brown algae, where the concentration is highly variable depending on the species and geographic area (Pádua et al., 2015; Gupta & Abu-Ghannam, 2011).

Phloroglucinol, as well as other phenolic compounds mentioned above, has shown a variety of biological activities such as antioxidant, anti-inflammatory, antimicrobial, anti-diabetic, anti-allergic and anti-HIV (Pádua et al., 2015). For this reason, these compounds are currently being studied in the pharmaceutical industry to improve the bioactivity of drugs. Also, these have a particular application in the textile industry as a dye (Kusumaningsih et al., 2016).

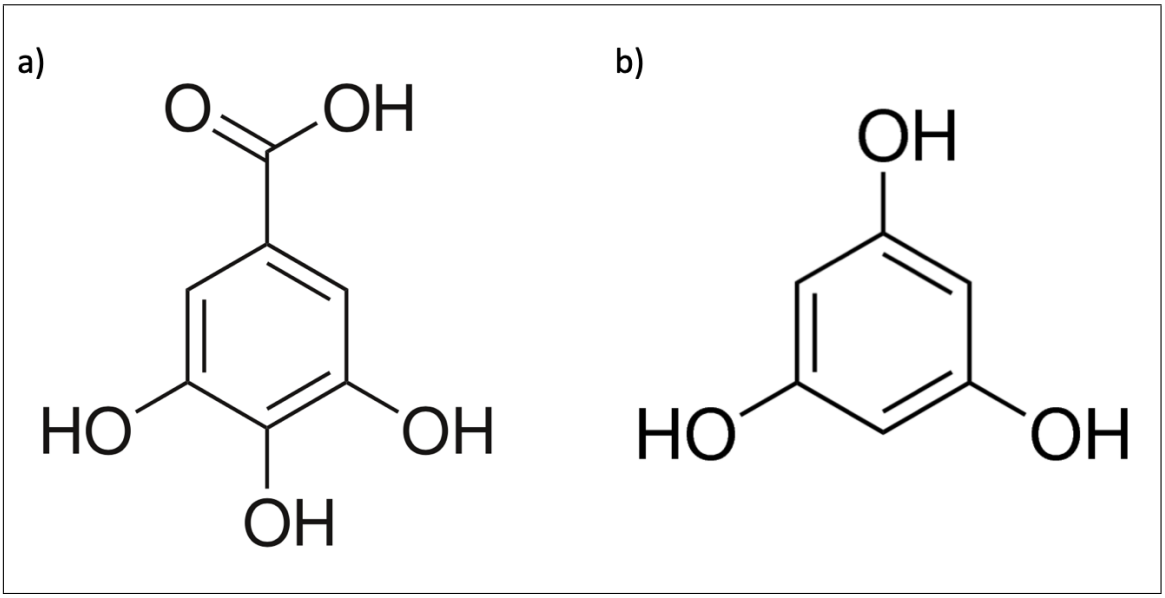

Figure 2.2. Chemical structure of **(a)** Gallic Acid and **(b)** Phloroglucinol.

2.3. Deep Eutectic Solvents (DES)

2.3.1. History

A Deep Eutectic Solvent (DES) is a mixture of chemical compounds or elements generally composed of two or three components that interact through hydrogen bonds, to form a eutectic mixture with a melting point lower than each individual component. In most cases, a quaternary ammonium salt is mixed, acting as a hydrogen bond acceptor (HBA) with metal salts or a hydrogen bond donor (HBD) that has the ability to complex with the halide anion of quaternary ammonium salt (Zhang et al., 2012). The name "DES"

derives from the eutectic point seen when a HBA and a HBD are mixed in a specific molar ratio.

A classic example of this anomaly is the 1:2 molar mixture of choline chloride with urea, where the freezing point of each is 575.15 K and 407.15 K, respectively, while freezing point of the mixture is 285.15 K (Abbott, Capper, Davies, Rasheed, & Tambyrajah, 2002). This is shown in Figure 2.3.

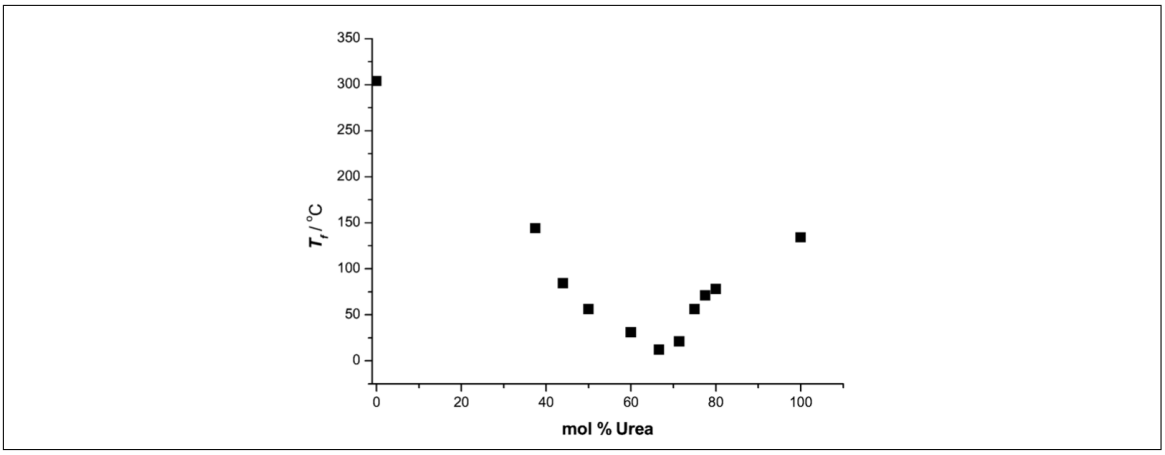

Figure 2.3. Freezing point of choline chloride/urea mixtures as a function of composition (Abbott et al., 2002).

This concept was first introduced by Abbott et al. in 2001 (Abbott et al., 2001). DESs are currently attracting widespread scientific and technological interest as a low cost alternatives to conventional solvents, and possess many advantages such as: (1) they are simple to synthesize since the components salt (HBA) and hydrogen bond donor (HBD)/complexing agent can be easily mixed and converted to DES without need for further purification; (2) they have low production cost due to the low cost of raw materials; and (3) DES are expected to have good biocompatibility when quaternary ammonium salts such as choline chloride (ChCl) are used. (Hayyan et al., 2012; Singh, Lobo, & Shankarling, 2012).

As mentioned above, due to its low cost, biodegradability and low toxicity, ChCl was widely used as an organic salt. For instance, some HBDs are glycerol, urea, carbohydrate-derived polyols or renewably sourced carboxylic acids. These DESs can be used in many applications because they exhibit similar physico-chemical properties. Compared to traditional organic solvents, DESs are not considered flammable or volatile organic solvents, hence, they can be stored for long times (Zhang et al., 2012).

Deep eutectic solvents can be described by the general formula:

$$Cat^{+}X^{-}zY$$

where Cat^{+} can be any ammonium, phosphonium, or sulfonium cation, and X is a Lewis base, generally a halide anion. The complex anionic species are formed between X and either a Lewis or Bronsted acid Y (z refers to the number of Y molecules that interact with the anion). Most of the studies have focused on quaternary ammonium and imidazolium cations with particular emphasis being placed on more practical systems using choline chloride, [$ChCl$, $HOC_2H_4N^{+}(CH_3)_3Cl^{-}$] (Smith, Abbott, & Ryder, 2014).

DESs are mainly classified according to the nature of the complexing agent used. Possible types and classification of DESs are shown in Figure 2.1.

Table 2.1. Types of DESs, their general formula and terms. (Smith et al., 2014).

Type	**General formula**	**Terms**
type I	$Cat^{+}X^{-}zMCl_x$	M = Zn, Sn, Fe, Al, Ga, In
type II	$Cat^{+}X^{-}zMCl_x \cdot yH_20$	M = Cr, Co, Cu, Ni, Fe
type III	$Cat^{+}X^{-}zRZ$	Z = $CONH_2$, COOH, OH
type IV	$MCl_x + RZ = MCl^{+}_{x-1} \cdot RZ + MCl^{-}_{x+1}$	M = Al, Zn and Z = $CONH_2$, OH

2.3.2. DES Preparation

The two most used methods for preparing DESs are the heating method and the grinding method. The heating method (the most commonly used in literature) is based on

mixing the two components, HBA and HBD, which are then heated at 373K under constant stirring until a homogeneous liquid is formed. The grinding method, which has been largely explored in the preparation of DESs, for pharmaceutical purposes, consists in mixing HBA and HBD and then grinding them in a mortar with a pestle at room temperature until a homogeneous liquid is formed (Florindo, Oliveira, Rebelo, Fernandes, & Marrucho, 2014).

2.3.3. Applications

The first applications of eutectic compounds were implemented before the recognition of DES by Abbott, such as in the separation and purification of molecular mixtures (Davey, Garside, Hilton, McEwan, & Morrison, 1995), pharmaceutical processes (Stott, Williams, & Barry, 1998), enzymatic catalysis (Gill & Vulfson, 1994) and synthesis (Erbeldinger, Ni, & Halling, 1998).

Figure 2.4 shows in simple terms a chronology of the applications of the eutectic mixture in the last years, from enzymatic catalysis to current use of natural DESs. Upcoming developments on DESs and natural DESs will rely on the behavior of the components, the description of the properties and the interactions established between the pairs that constitute the eutectic mixture (Paiva et al., 2014). Some of these applications are shown in Figure 2.5.

2.3.4. Properties

2.3.4.1. Freezing point

As mentioned in the previous section, DESs are formed by one HBA and one HBD which can be solid or liquid, capable of generating a new liquid phase by mainly hydrogen bonds cross-association. This new phase is generally characterized by a lower freezing point than individual constituents. Table 2.2 shows some examples of lower freezing points in DESs than pure hydrogen bond donors (HBD) (Zhang et al., 2012).

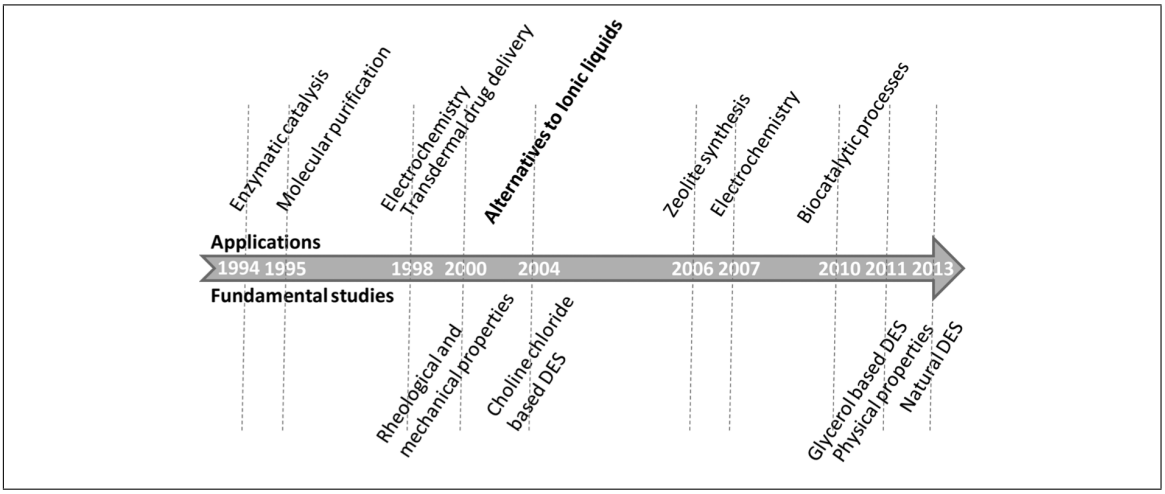

Figure 2.4. Timeline of reported developments, both on applications and fundamental studies on deep eutectic solvents (Paiva et al., 2014).

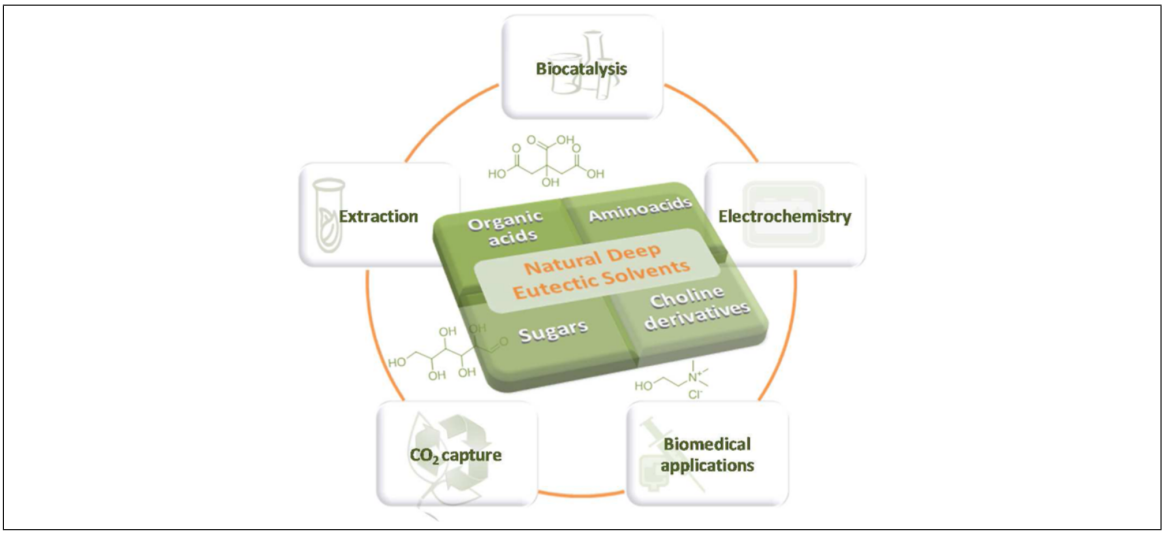

Figure 2.5. Application of DES (Paiva et al., 2014).

2.3.4.2. Density

The density is an important physical property for a solvent (Zhang et al., 2012). This property varies according to the functional groups, structure of HBA and HBD along with the chain length of the compound. In general, DESs are more dense than water and their ability to dissolve in a solvent depends on the nature of the anions and the cations that

Table 2.2. Freezing point (T_f) of the reported DESs. $T_m^\circ/^\circ C$: melting point of pure HBD (Zhang et al., 2012).

HBD	**ChCl : HBD (molar ratio)**	$T_m^\circ/^\circ C$	$T_f^\circ/^\circ C$
Urea	1 : 2	134	12
Thiourea	1 : 2	175	69
Acetamide	1 : 2	80	51
Imidazole	3 : 7	89	56

form them. The density of DESs is higher than that of water which vary between 1100 $kg{\cdot}m^3$ and 2400 $kg{\cdot}m^3$ (Wasserscheid & Welton, 2008).

Table 2.3 shows some densities of common DESs at 298.15 K, that were also used throughout the experiments of this paper. There have also been studies on the effects of density with respect to the molar fraction of the DES precursors (Abbott et al., 2011). The relationship between the molar ratio and the density in Figure 2.6 can be observed, in general, the density decreases when the percentage of salt increases in the DES, in general this trend is maintained among several DES generated.

Table 2.3. Densities of common DESs at 298.15 K (Zhang et al., 2012).

Salts	**HBD**	**Salt: HBD** (mol:mol)	**Density** (ρ, gcm^{-3})
ChCl	EG	1 : 3	1.12
ChCl	Glycerol	1 : 2	1.18
ChCl	Urea	1 : 2	1.25
ChCl	Malonic acid	1 : 2	1.12

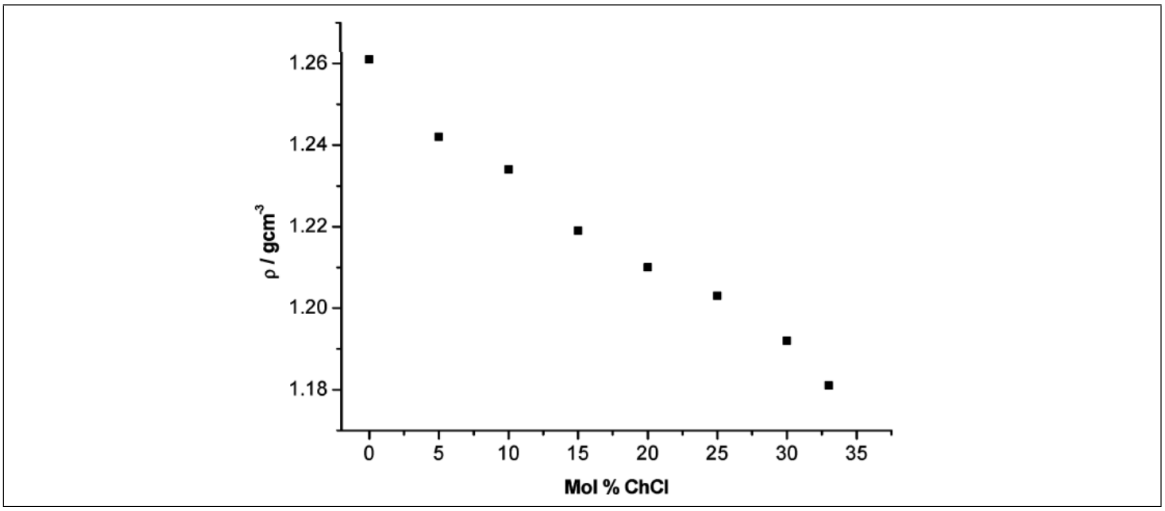

Figure 2.6. Density molar ratio dependence of DESs (Abbott et al., 2011).

2.3.4.3. Viscosity

Viscosity influences the mass transport phenomena and the conductivity for ionic fluids, thereby affecting their suitability for particular applications (Florindo et al., 2014).

Most DESs exhibit relatively high viscosities (>100 cP) at room temperature. An extensive hydrogen bond network between each component produced by a high viscosity results in a lower mobility of free species within the DES (Zhang et al., 2012; Abbott, Capper, & Gray, 2006). For instance, in the case of a ChCl/glycerol DES, an increase of the ChCl/glycerol molar ratio results in a decrease of the DES viscosity (Figure 2.7). Also, viscosity decreases by adding small amounts of water or cosolvent.

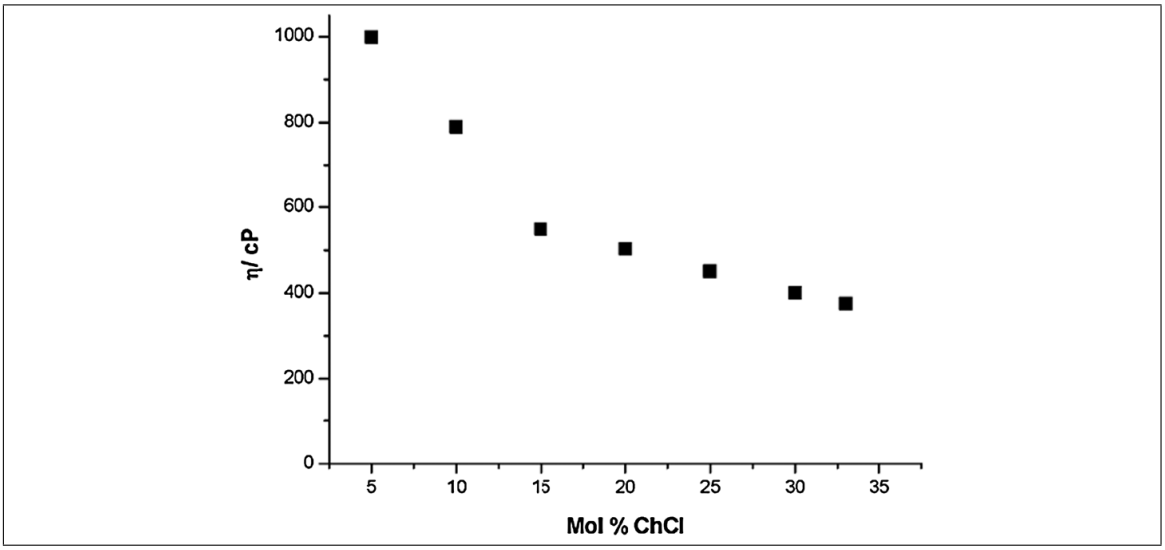

Figure 2.7. Correlation of viscosity and molar % of ChCl in DES with glycerol. Retrieved from (Abbott et al., 2011).

2.3.4.4. Thermal decomposition

Decomposition temperature is an important property, especially for their applications as alternative solvents. The range of temperature and application at which a deep eutectic solvent can maintain its liquid form is determined by this property. (Florindo et al., 2014). This temperature is determined by the mass loss of the sample. Literature is not very extensive regarding this topic but it is possible to find data on some of the traditional compounds and their decomposition (Florindo et al., 2014; Zhang et al., 2012; Ullah et al., 2015; Gajardo-Parra et al., 2019; Delgado-Mellado et al., 2018) which are made mainly by thermogravimetric analysis (TGA). Furthermore, the thermal stability of DES is known to improve compared to pure HBD and worsen compared to HBA.

2.4. PC-SAFT modeling

The perturbed chain SAFT equation of state (EOS) or PC-SAFT was first proposed and developed by Gross and Sadowski in 2001 (Gross & Sadowski, 2001) as an alternative to the original version of SAFT derived by Chapman et al. (Chapman, Jackson, & Gubbins, 1988; Chapman, Gubbins, Jackson, & Radosz, 1989). The latter is a thermodynamic approach derived from Wertheim's first order thermodynamic perturbation theory (Wertheim, 1984b, 1984a, 1986b, 1986a; Pontes et al., 2017). This approach was based on principles of statistical mechanics. These principles allow for the identification and quantification of structure and molecular interaction effects on properties and phase behavior of a fluid. An example of these effects are the size and shape of the molecule as well as intermolecular forces and degree of molecular association.

The PC-SAFT model has been successful in a large number of diverse systems, demonstrating improvements over previous results with SAFT on long chain molecules, such as polymers or ionic liquids, and even low molecular weight substances. Given this, it has been widely applied to model thermodynamic properties, specially phase equilibria (Pontes et al., 2017; Gross & Sadowski, 2001, 2002a; Zubeir, Held, Sadowski, & Kroon, 2016).

2.4.1. The Model

One of the objectives of this thesis is to model the solubility of polyphenols in aqueous mixtures of DES. PC-SAFT is an appropriate method for modeling solid-liquid equilibria of complex mixtures (Held, Cameretti, & Sadowski, 2011). It has demonstrated excellent performance and great flexibility in the modeling of complex systems containing polar compounds (Tumakaka & Sadowski, 2004; Kleiner & Gross, 2006), polymers (Gross & Sadowski, 2002b; Tumakaka, Gross, & Sadowski, 2002; Gross, Spuhl, Tumakaka, & Sadowski, 2003), associated compounds (Gross & Sadowski, 2002a), pharmaceuticals

(Ruether & Sadowski, 2009), electrolytes (Cameretti & Sadowski, 2005; Held, Cameretti, & Sadowski, 2008; Held & Sadowski, 2009), among others.

PC-SAFT uses a hard-chain fluid as the reference system, where fluid molecules are represented as same sized hard chains, composed of smaller bound segments. This is based on the development of a new dispersion term that explicitly explains the attractive interaction between hard chains and the non-spherical shape of molecules (Canales, Held, Lubben, Brennecke, & Sadowski, 2017).

Molecules from different compounds differ in the number of segments and their size. A dispersive potential is included to account for attraction and repulsion forces and an associating potential is added to allow for special interaction between chains, such as hydrogen bonds. Each of these constitute an explicit contribution to the residual molar Helmholtz free energy of the fluid a^{res}.

The residual Helmholtz energy (a^{res}) is defined as the sum of contributions of different molecular forces and also as the difference between the total free energy of molar Helmholtz and free energy of an ideal gas under the same conditions. To obtain a^{res} , all the energies that are deviated from the reference system are treated as unique contributions that can be considered independently (for example, the attractive forces of van der Waals, among others), as follows:

$$a^{\text{res}} = a - a^{\text{ideal}} = a^{\text{hc}} + a^{\text{disp}} + a^{\text{assoc}} \tag{2.1}$$

Where a^{hc} represents the hard chain repulsion of the reference system. On the other hand, a^{disp} explains Helmholtz's energy contributions due repulsive and attractive interaction between hard chains and the non-spherical shape of the molecules. Finally, a^{assoc} reflects the special self-association interactions (Held, Neuhaus, & Sadowski, 2010; Held et al., 2011) that are used in the original PC-SAFT model (Gross & Sadowski, 2001).

A more rigorous definition of each of these contributions for mixtures can be found in the original literature of (Chapman et al., 1988; Gross & Sadowski, 2001, 2002a). However, it is presented below in general terms.

2.4.1.1. Hard-chain contribution (a^{hc})

The hard chain contribution (a^{hc}) to Helmholtz's residual molar free energy is defined as

$$\frac{a^{hc}}{RT} = \bar{m}\frac{a^{hs}}{RT} - \sum_i x_i \left(m_i - 1\right) \ln g_{ii}^{hs} \tag{2.2}$$

$$\bar{m} = \sum_i x_i m_i \tag{2.3}$$

where R is the universal gas constant, T is the system temperature, a^{hs} is Helmholtz's molar free energy of the hard sphere fluid, x_i is the molar fraction of component i, m_i is the number of segments of component i, and g_{ii}^{hs} is the hard-sphere radial pair distribution function for component segments.

2.4.1.2. Dispersion contribution (a^{disp})

The dispersion contribution (a^{disp}) of residual molecular free energy of Helmholtz is given by

$$\frac{a^{disp}}{RT} = -2\pi\rho I_1 \overline{m^2\epsilon\sigma^3} - \pi\rho\bar{m}C_1 I_2 \overline{m^2\epsilon^2\sigma^3} \tag{2.4}$$

where,

$$\overline{m^2\epsilon\sigma^3} = \sum_i \sum_j x_i x_j m_i m_j \left(\frac{\epsilon_{ij}}{kT}\right) \sigma_{ij}^3 \tag{2.5}$$

$$\overline{m^2\epsilon^2\sigma^3} = \sum_i \sum_j x_i x_j m_i m_j \left(\frac{\epsilon_{ij}}{kT}\right)^2 \sigma_{ij}^3 \tag{2.6}$$

$$C_1 = \left(1 + \bar{m}\frac{8\eta - 2\eta^2}{(1-\eta)^4} + (1-\bar{m})\frac{20\eta - 27\eta^2 + 12\eta^3 - 2\eta^4}{[(1-\eta)(2-\eta)]^2}\right)^{-1} \tag{2.7}$$

where η is the reduced density of the system.

There are the Berthelot-Lorenz mixing rules which are used for the interactions of mixed solutions between two components i and j (for example, water and gallic acid), which are described below:

$$\sigma_{ij} = \frac{1}{2}\left(\sigma_i + \sigma_j\right) \tag{2.8}$$

$$u_{ij} = \sqrt{u_i u_j}\left(1 - k_{ij}\right) \tag{2.9}$$

where k_{ij} in the previous equation is a binary interaction parameter that can be used to correct the deviations of the geometric mixing rule of dispersion energy. This parameter (if necessary) is determined by adjusting the binary data, for example activity coefficients or solubilities (Held et al., 2010); in this case they were adjusted for solubilities for all cases.

2.4.1.3. Association contribution (a^{assoc})

The association contribution (a^{assoc}) to the free energy of residual molar Helmholtz is defined as:

$$\frac{a^{assoc}}{RT} = \sum_i x_i \left[\sum_{A_i}\left[\left(\ln X^{A_i} - \frac{X^{A_i}}{2}\right) + \frac{M_i}{2}\right]\right] \tag{2.10}$$

where M_i is the number of associating sites on each compound i, and X^{A_i} is the mole fraction of the molecules i not bonded at site A, given by,

$$X^{A_i} = \left[1 + N_{Av} \sum_j \sum_{B_j} x_j \rho X^{B_j} \Delta^{A_i B_j} \right]^{-1} \tag{2.11}$$

over all sites on molecules $j : A_j, B_j, C_j \ldots$ and over all components. Where N_{Av} is the Avogadro constant and $\Delta^{A_i B_j}$ is the associating strength given by,

$$\Delta^{A_i B_j} = \left(\frac{d_i + d_j}{2} \right)^3 g_{ij}^{hs} \kappa^{A_i B_j} \left[\exp\left(\frac{\epsilon^{A_i B_j}}{kT} - 1 \right) \right] \tag{2.12}$$

where $\kappa^{A_i B_j}$ and $\epsilon^{A_i B_j}$ are the cross-associating volume and energy respectively.

In a mixture containing two associating compounds, the cross-associating interactions are obtained with the equations proposed by Wolbach and Sandler (Wolbach & Sandler, 1998), that are shown in equations 2.13 and 2.14:

$$\epsilon^{A_i B_j} = \frac{\epsilon^{A_i B_i} + \epsilon^{A_j B_j}}{2} \tag{2.13}$$

$$\kappa^{A_i B_j} = \sqrt{\kappa^{A_i B_i} \kappa^{A_j B_j}} \left(\frac{\sqrt{\sigma_{ii} \sigma_{jj}}}{\frac{1}{2}\left(\sigma_{ii} + \sigma_{jj} \right)} \right)^3 \tag{2.14}$$

In summary, for non-associative molecules, three parameters of pure components are required: the segment diameter (σ_i), the number of segments per chain (m_i) and the dispersion energy parameter (u_i/k). Also, two additional parameters are required for the mixtures; these are segment diameter (σ_{ij}) and segment energy (u_{ij}) which are estimated using the rules mentioned above. In this way, molecular chains are physically characterized by the number of segments σ_i and their diameter m_i, while the interaction between segments is represented by the segment energy ϵ/k. Hydrogen bond type interactions are

taken into account by the incorporation of associating sites in the chain. These sites are described by the associating energy $\epsilon^{A_i B_i}$ and the effective associating volume $\kappa^{A_i B_i}$.

2.4.2. Solid-liquid equilibrium modeling

For the calculation of solubility, an equilibrium condition between the liquid and the solid phase is required as explained earlier in the experimental section. Assuming a pure solid phase and neglecting the influence of the different heat capacities of the solid and the liquid, it is possible to calculate the molar fraction of the solute in the liquid phase, that is, its solubility, as follows:

$$x_i^{\mathrm{L}} = \frac{\varphi_{0i}^{\mathrm{L}}}{\varphi_i^{\mathrm{L}}} \exp\left\{ -\frac{\Delta h_{0i}^{\mathrm{SL}}}{RT}\left(1 - \frac{T}{T_{0i}^{\mathrm{SL}}}\right)\right\} \tag{2.15}$$

where $\varphi_{0i}^{\mathrm{L}}/\varphi_i^{\mathrm{L}}$ is the ratio of the fugacity coefficients of component i (polyphenol) as a pure substance and in the mixture, respectively. $\Delta h_{0i}^{\mathrm{SL}}$ is the enthalpy of fusion, and T_{0i}^{SL} is the fusion temperature of pure polyphenol (gallic acid and phloroglucinol) (Held et al., 2010).

2.4.3. PC-SAFT pure component parameter estimation

As previously mentioned, there are five pure component parameters that describe the associated substances. Three of them are the non-associative parameters which are related to the shape and size of the molecules, while the remaining two, called associative parameters, are related to the forces of interaction between the molecules. In general, all these parameters are fit to experimental data. It can be by osmotic pressure, vapor pressure or the equilibrium liquid densities. The parameters obtained through this classic method have been able to model many compounds.

There are various approaches to know how the parameters are used. One that has been successfully applied to 1-alkanols according to Grenner et al. is using generalized

pure compound parameters for all substances of the same family (Grenner, Kontogeorgis, von Solms, & Michelsen, 2007). This consists of optimizing the five parameters of pure compounds with vapor pressure and liquid density data in order to calculate the geometric mean of the two associated parameters. Finally, the three unassociated parameters are readjusted keeping the association parameters constant (Grenner et al., 2007). Through this, the association parameters are closely related to the functional groups found in the molecules and their position.

Another approach of the parameters is to apply them to a group contribution method (GC). This process takes advantage of the correlation between functional groups and SAFT parameters. GC consists of applying a contribution group scheme directly to the calculation of EoS parameters, improving its predictive capacity (Tamouza, Passarello, Pascal, & Hemptinne, 2005). The main advantage of this type of method is the reduction in the number of parameters that must be adjusted, which significantly simplifies the optimization problem. However, there are difficulties when experimental data on the thermodynamic properties of a sample of compounds are not readily available. It is also problematic when it is considered that some families of compounds have different functional groups or positions within a molecule. This varies the interaction between its molecules and does not allow the assumption that the association parameters are constant.

On the other hand, the calculation of the parameters can be very complex and varies greatly depending on the method used. A recent review (Borgonovo & Plischke, 2015) refers to the importance of conducting a sensitivity analysis to obtain information on the behavior of the model, its structure and its response to changes in inputs. Various methods of sensitivity analysis have been developed, leading to a wide and growing output of literature on this topic.

Currently some methods have been proposed to improve the estimation of pure composite parameters for SAFT EoS and to be applied to PC SAFT. Sensitivity analyzes have been carried out to adjust parameters of the same family, for example, alcohols of different chain length, obtaining PC-SAFT parameters as a function of chain length or molecular

weight. In Fuenzalida et al. a method is proposed in which information from a sensitivity analysis is used to define an improved weight-variable cost function depending on temperature and fix the least sensitive parameter (Fuenzalida, Cuevas-Valenzuela, & Pérez-Correa, 2016). In this way it is possible to determine the most sensitive application ranges in the equation.

For this specific work, the parameters of the pure PC-SAFT component for solvents were taken from the literature (Gross & Sadowski, 2002a; Zubeir et al., 2016; Cameretti & Sadowski, 2008; Haghbakhsh, Parvaneh, Raeissi, & Shariati, 2017; Karakatsani, Spyriouni, & Economou, 2005; Held & Sadowski, 2016; Altuntepe et al., 2017). The parameters of gallic acid and phloroglucinol were adjusted by experimental solubility data. Also a binary interaction parameter was applied according to equation 2.9, where k_{ij} values were obtained from literature or fitted to experimental solubility data of gallic acid and phloroglucinol.

2.5. Power X-Ray Difraction (PXRD)

X-ray crystallography involves passing an X-ray beam through a crystal. These rays are diffracted which allows obtaining a pattern of intensities that provides important information about the sample being studied, managing to characterize it. This technique can be performed on a single crystal of the material of interest, which is called single-crystal X-Ray Diffraction (XRD). On the other hand, crystalline powder can also be used as a sample, which is known as Powder X-Ray Diffraction (PXRD) (Smyth & Martin, 2000).

XRD is a non-destructive technique that provides interesting information on the structure of the crystal under analysis. The peaks obtained from the diffraction of the X-ray beam allow one to obtain a diagram that manages to characterize the atoms of the compound under study. However, the main limitation of this technique is that the sample corresponds to a single crystal of the material. Therefore, the results may not match the exact composition of the original crystal.

On the other hand, PXRD is characterized by being a rapid technique for the identification of compounds in crystals and has relevant applications in scenarios in which chemical methods cannot be used. An example of one of these cases is when quasi-isochemical or polymorphic compounds are present (Artioli, 2017). The main difference of PXRD compared to XRD is that in the former, the sample corresponds to microcrystals of the material, which allows studying a greater part of the material. Therefore, it is considered a bulk characterization technique.

2.5.1. Importance

Many crystalline materials cannot be fractionated into individual particles of the size or quality necessary to use single crystal diffraction techniques, such as XRD. It is for this reason that the existence of the PXRD is important. This method does not limit the type of material or the system that can be studied. It permits the understanding of the structure and properties of compounds of interest that cannot be treated with single crystal diffraction techniques (Harris, Tremayne, & Kariuki, 2001).

PXRD is a non-destructive technique that is capable of determining various characteristics of both organic and inorganic compounds (Das, Ali, & Hamid, 2014). It provides information on the structure, phases, texture, average grain size, crystallinity, strain and defects of the crystal. On the other hand, it stands out for being a quick method to identify unknown compounds in a sample, where sample preparation is simple and the information obtained can be interpreted in a relatively simple way (Bunaciu, Udriştioiu, & Aboul-Enein, 2015).

This method has many applications which are important for making scientific advances in various areas. In the pharmaceutical industry, PXRD is used for the design of drugs, allowing a formulation to be established by discovering the morphology and degree of crystallization, in addition to identifying polymorphic compounds (Bunaciu et al., 2015). On the other hand, it allows to measure the final dose of the active ingredients in drugs,

monitors structural changes that have been generated during the formulation and determines if the sample is present in liquid, gas or solid phase (Das et al., 2014).

In forensic science it is mainly used in laboratories for the identification of qualitative phases (Eckardt, Krupicka, & Hofmeister, 2012). In the analysis of criminal evidence it is considered that this method is usually easy and fast, which is why it is commonly used for the analysis of powder samples. Furthermore, it is versatile and non-destructive, so it is used to analyze organic, inorganic and metallic specimens, qualitatively or quantitatively (Bunaciu et al., 2015).

2.5.2. Methodology

Thanks to scientific advances, the range of size and quality of crystals that can be studied with techniques such as XRD has increased. However, there is a large group of compounds that do not meet the necessary requirements but that can be treated with PXRD. Fortunately, many advances have been made in methodologies to determine the structure of crystalline materials using this technique (Harris et al., 2001).

The Bragg-Brentano parafocusing system is commonly used, which is characterized by having a divergent beam from a line source. This beam falls on the species being studied and then passes through a receiving slot. Here a detector is in charge of converting the X-ray photons that have been diffracted to voltage pulses, which are finally integrated into a speed meter. In this way, the diffractogram is obtained, which is a diagram of the intensity as a function of the diffraction angle (Bunaciu et al., 2015).

Figure 2.8 shows an example of a diffractogram, in which the structure under analysis corresponds to aluminum oxide. The diffraction phenomenon can be described with Bragg's law, managing to predict the direction of interference of the X-rays that are scattered in the crystalline sample. The diffractogram is a graph that uses the intensity data, which are obtained from the diffraction angle. In a diffraction diagram it is important to consider the position of the peaks (which correspond to the angle at which the beam is

diffracted) and their respective intensities (which correspond to the height of the peak). The diffraction directions that are obtained depend on the system being studied and therefore vary according to the shape and size of the sample. On the other hand, the intensity of each peak is specific to each material.

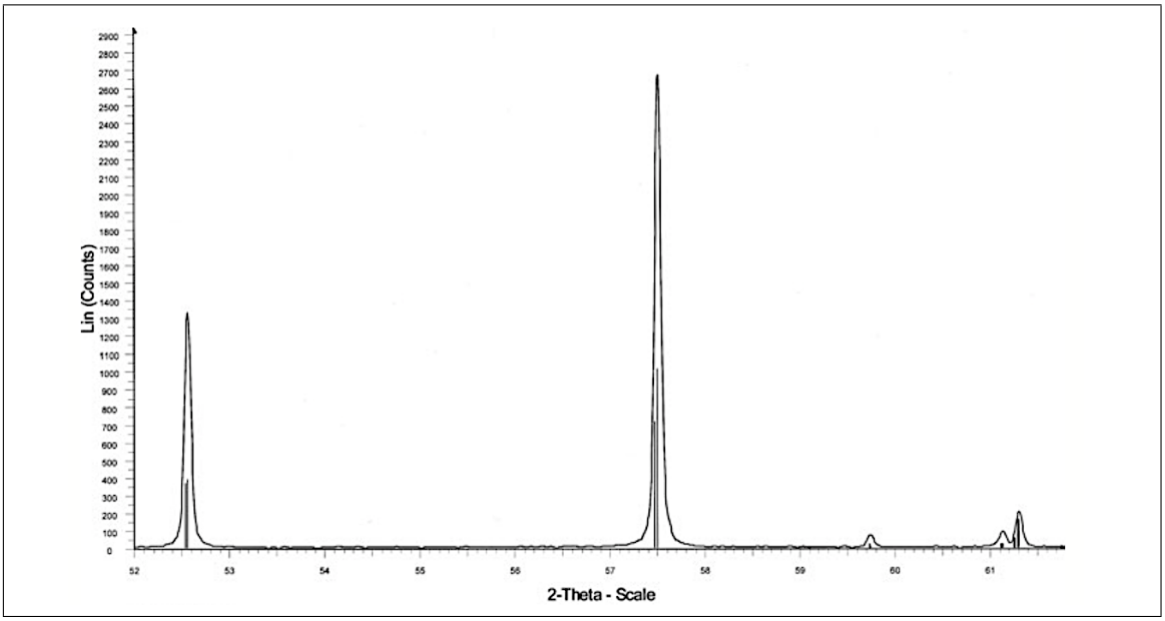

Figure 2.8. Aluminum oxide diffractogram (Eckardt et al., 2012).

Also through the use of PXRD it is possible to identify the different crystalline phases present in a sample due to the diffraction pattern that uniquely characterizes them. However, sometimes the available knowledge about these crystalline phases is limited and due to low concentrations it is difficult to determine the presence of a polymorphic substance. Figure 2.9 shows a case study for the compound tiotropium bromide, in which its different polymorphic forms were analyzed with PXRD. In the diffractogram it can be verified that, despite being the same compound, the peaks presented by each sample with the different solvents are different. Therefore, the diffraction planes change, presenting different crystals. Due to this structural difference, polymorphic forms of the same compound, for example, may generate different bioavailability or change the shelf life of the drug (Egusa, Okazaki, Schiewe, Werthmann, & Wolkenhauer, 2017).

Preparing the sample for the PXRD is simple and is also one of the critical steps in making the correct analysis. It is necessary that the compound does not present impurities, which must be removed since they can produce low X-ray reflection. The analysis requires that the sample be finely granulated, which ensures the participation of a sufficient number of particles for diffraction to occur. It should also be considered that the particles must not have an arbitrary texture and that the properties of the sample can distort the intensities (Bunaciu et al., 2015).

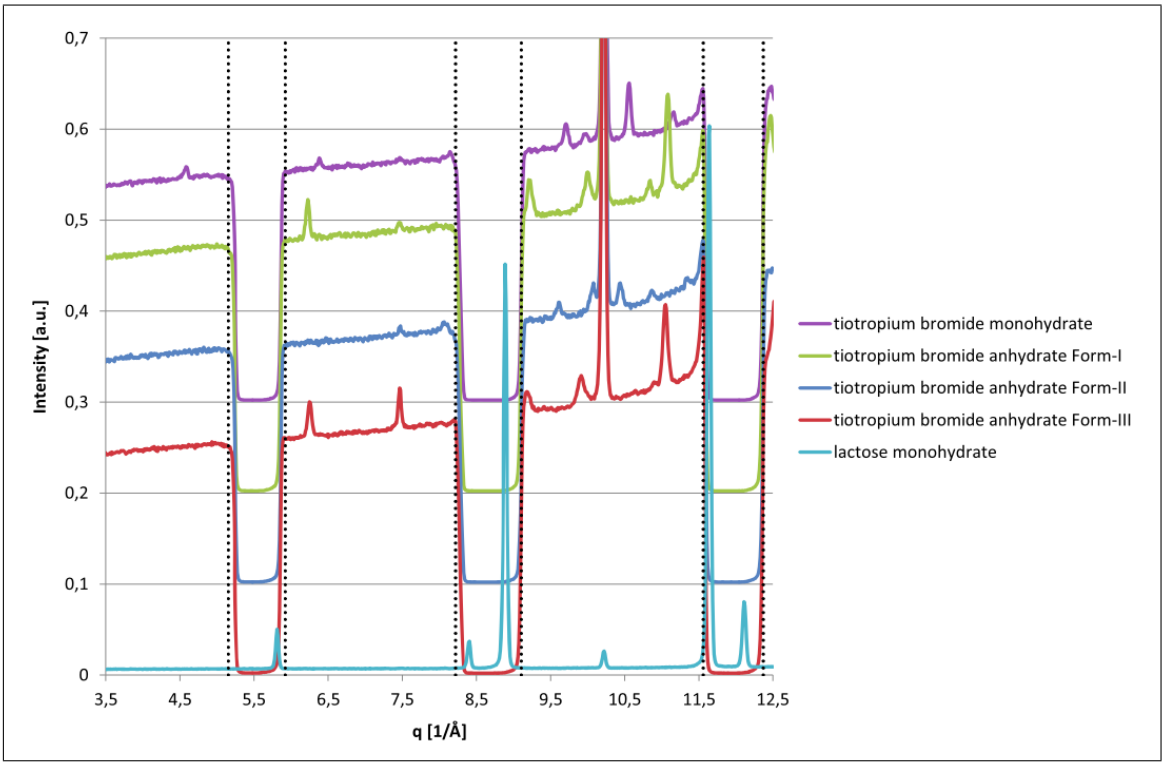

Figure 2.9. Diffractogram of different polymorphic structures of the tiotropium bromide compound. Dotted lines delimit masked areas (Egusa et al., 2017).

3. MATERIAL AND METHODS

3.1. Materials

Gallic acid ($C_7H_6O_5$, MW = 170.12; ≥97.5% purity; CAS No. 149-91-7) and phloroglucinol ($C_6H_6O_3$, MW=126.11; ≥99.0% (HPLC) purity; CAS No. 108-73-6) were the phenolic compounds used in this study. Milli-Q water (water purification system Milli-Q Reference Merck) (conductivity approximately <100 µS / cm) (Figure 3.1) was used to prepare all solvent mixtures. In addition, choline chloride ($((CH_3)_3N(Cl)CH_2CH_2OH$, MW = 139.62; ≥98.0% purity; CAS No. 67-48-1), levulinic acid ($CH_3COCH_2CH_2COOH$, MW = 116.12; ≥98.0% purity; CAS No. 123-76-2), ethanol (CH_3CH_2OH, MW = 46.07; ≥99.5% (anhydrous) of purity; CAS No. 64-17-5), ethylene glycol ($HOCH_2CH_2OH$, MW = 62.07; ≥99.8% (anhydrous) of purity; CAS No. 107-21-1) and glycerol ($HOCH_2CH$ (OH) CH_2OH, MW = 92.09; ≥99.5% purity; CAS No. 56-81-5) were purchased from Sigma-Aldrich and used as received. A summary of the compounds is represented in table 3.1.

Table 3.1. Summary of the compounds used

Solutes					
Chemical	**Abbreviation**	**Mw [g/mol]**	**CAS**	**Supplier**	**Purity**
Gallic Acid	GA	170.120	149-91-7	Sigma-Aldrich	0.975
Phloroglucinol	PH	126.110	108-73-6	Sigma-Aldrich	0.990

Solvents					
Chemical	**Abbreviation**	**Mw [g/mol]**	**CAS**	**Supplier**	**Purity**
Water	H_2O	18.015	7732-18-5	Sigma-Aldrich	-
Ethanol	EtOH	46.069	64-17-5	Sigma-Aldrich	0.995
Choline chloride	ChCl	139.620	67-48-1	Sigma-Aldrich	0.980
Ethylene Glycol	EG	62.068	107-21-1	Sigma-Aldrich	0.998
Levulinic Acid	Lev	116.115	123-76-2	Sigma-Aldrich	0.980
Glycerol	Gly	92.0938	56-81-5	Sigma-Aldrich	0.995

Figure 3.1. Water purification system Milli-Q Reference Merck.

3.2. Preparation of aqueous solvent mixtures

The traditional solvents used to calculate the solubility in gallic acid and phloroglucinol were ethanol, ethylene glycol, glycerol, levulinic acid and glycerol, which were described in the previous section. All these solvents were used as aqueous mixtures as a 1:1 mass ratio with water, except ethanol which was used purely. The aqueous mixtures were prepared using an analytical balance (Mettler Toledo Excellence Model XS205DU, 0.0001 g uncertainty) (Figure 3.2). The volume of solvent mixture used to determine the solubility was approximately 25 mL. All aqueous solvent mixtures were prepared in covered glass jars to avoid volatilization.

Figure 3.2. Analytical balance Mettler Toledo Excellence Model XS205DU.

3.3. Preparation of deep eutectic solvents

The DES were prepared gravimetrically using the same analytical balance mentioned above. Initially, the hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) were placed in a flask, heating them to 353.15 K forming a homogeneous liquid. The amount of water contained in each DES was measured using a Volumetric Karl Fischer (Metrohm, Switzerland) (Figure 3.3). The samples prepared were HBA + HBD (1: 2 mole ratio), where the HBA was always choline chloride, while the HBD used were: ethylene glycol (DES 1), levulinic acid (DES 2) and glycerol (DES 3). Afterwards, mixtures of DES + water in 50% weight fraction were prepared to decrease the viscosity for the solubility measurements. A summary of the composition of DES is shown in Table 3.2.

Table 3.2. Summary of the DES used

Deep Eutectic Solvents			
Abreviation	**HBA**	**HBD**	**Mole ratio**
DES 1	Choline chloride	Ethylene glycol	1:2
DES 2	Choline chloride	Levulinic acid	1:2
DES 3	Choline chloride	Glycerol	1:2

Figure 3.3. Volumetric Karl Fischer Metrohm.

3.4. Solubility measurements

Solubilities were measured using the saturated shake-flask method. First, the aqueous solvent mixture was introduced into 2 mL volume Eppendorf tubes by adding an excess amount of polyphenol standard to the liquid phase (Figure 3.4). This solution was continuously stirred (Noubigh, Abderrabba, & Provost, 2007) at 1000 rpm on a thermal regulator (Eppendorf ThermoMixer C, $\pm$ 0.1 °C) (Figure 3.5). Composition was verified at several times and it was determined that the samples should be kept 48 h under stirring and 48 h in rest to ensure equilibrium (X. Li et al., 2018); both procedures were carried out under

thermal regulation (Noubigh et al., 2013). After resting, a 10 μL sample was taken with an Eppendorf micropipette from the liquid phase (Figure 3.7). Each sample was diluted to a specific dilution factor determined previously for each solvent. Then the absorbance was measured by UV-vis spectrophotometry in the range 190-300 nm (Spectrophotometer Analytik JenaSpecord 210 Plus) (Figure 3.8), since in all the tested mixtures gallic acid and phloroglucinol presented absorbance peaks at wavelengths 213 and 205 ($\pm$ 1 nm), respectively.

Based on the absorbance data obtained and the previously defined dilution, it was possible to calculate the concentration of the respective polyphenol in the different solvent mixtures. Thus, solubilities were calculated directly using external calibration curves for each system (gallic acid or phloroglucinol + aqueous solvent mixture). The linearity of the curve was evaluated through a linear regression analysis (Mota et al., 2008). Calibration curves made with absorbance values were used in all systems except those with ethanol, where calibration curves were calculated using density. These curves, measured with an Anton Paar 4500 DMA Densimeter (Graz, Austria) (Figure 3.6). Can be found all calibration curves in supporting information (Figures A3 to A10).

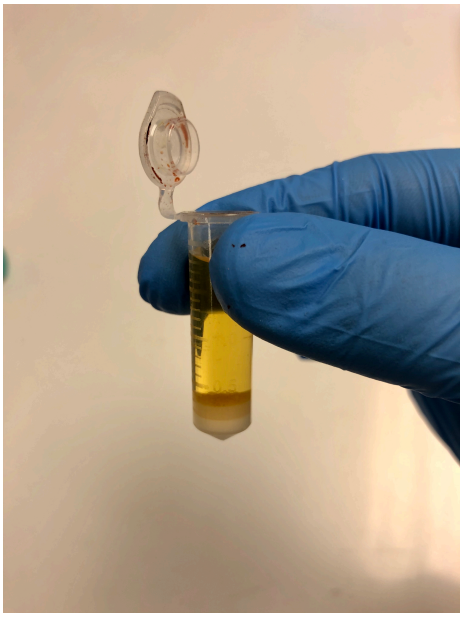

Figure 3.4. 2mL Eppendorf tube in solid-liquid equilibrium.

Figure 3.5. Eppendorf ThermoMixer C with thermal regulator.

Each solubility experiment was performed three times per system; the average solubility value plus the corresponding standard deviation were reported. Solubilities were

Figure 3.6. Anton Paar 4500 DMA Densimeter.

expressed as percentage of mass fraction (solute mass over solution mass) (Daneshfar, Ghaziaskar, & Homayoun, 2008),

$$\%w_1 = \frac{m_1}{m_1 + m_2} \cdot 100 = \frac{m_1}{m_3} \cdot 100 \tag{3.1}$$

Where the solute is represented as 1, the solvent as 2 and the solution as 3 for all cases.

Figure 3.7. Eppendorf micropipette 10 μL for sample extraction in solid-liquid equilibrium.

3.5. X-ray powder diffraction measurements

In addition to temperature and pH values (Voges et al., 2019), the solubility is affected by the formation of new compounds during the interaction of the solute with the solvent. Therefore, it is important to know the diffraction planes of pure gallic acid and to see the changes in the crystal structure, unit cell structure and polymorphisms that could occur when adding the different solvent mixtures. For this, the solid precipitated in the saturated mixture was subjected to X-ray powder diffraction (XPRD) made by MiniFlex PXRD (Rigaku, Tokyo, Japan). Measurements were carried out at ambient temperature (298 K) and ambient pressure (101.3 kPa), scanning between 2° and 60° at a speed of 5° per minute, with a step size of 0.02°. A $CuKa$ radiation was applied (k=1.54184 nm c) with a tube voltage and current set at 40 kV and 15 mA, respectively (Voges et al., 2019; X. Li et al., 2018).

Figure 3.8. UV-vis Spectrophotometer Analytik JenaSpecord 210 Plus.

Figure 3.9. X-ray powder diffraction (XPRD) made by MiniFlex.

4. RESULTS AND DISCUSSION

4.1. PXRD analysis

PXRD analysis was performed for the remaining solid solute after the equilibration with its respective liquid solution in order to assess any change in the crystal structure of gallic acid or phloroglucinol. Figure 4.1 shows the diffractogram of pure **(a)** gallic acid and **(b)** phloroglucinol in water and all the aqueous solvent solutions composed by ethylene glycol, levulinic acid, glycerol, DES 1, DES 2 and DES 3. These results show that gallic acid has the main peaks at 16º, 19º, 25º and 26º 2θ. These peaks are comparable as those reported by Kaur et al. (2016) (Kaur, Cherukuvada, Managutti, & Row, 2016), showing that our results are well reproduced. Also, it can be seen that for almost all of the other solvent mixtures the peaks are the same in every case. That is, the solvents behave as an amorphous structure, presenting the same peaks as in the pure state. This means that no change is generated in the structure of the polyphenol unit cell and therefore, there are not polymorphous or new formations of solvates during the experiment. The only exception is observed when the solute is mixed with ethanol where its diffraction curve shows a decrease and a slight displacement in the main peak by 2θ-16. Also 2 new peaks appear in approximately 2θ-25 and 2θ-28. This could be explained by the strong interaction that occurs between gallic acid and pure ethanol, which causes that the crystalline structure changes and the diffraction planes are modified compared with the pure solute. This mainly causes distortion in the unit cell of gallic acid structure in this case.

Otherwise, the diffractogram for pure phloroglucinol is very similar to that reported by Kumar et al. in 2014, with the main peaks at approximately 22º, 23º and 27º 2θ (Kumar, Senthamilselvi, & Govindaraju, 2014) showing that our results are well reproduced for the pure state. However, it can be seen that the other solvent mixtures do not follow the same pattern as in the case of gallic acid. Only in the systems with water and ethylene glycol, the same diffraction curve behavior as in pure state are observed, but for the other

systems, there is a change in the intensity and position of the peaks, which means that the diffraction planes of this mixture have changed. Consequently, the structure of the unit cell also changes and the formation of polymorphisms is evident. It has been seen that for several systems the change in structure or polymorphism of the solute (in general for those that are sparingly soluble solids) give defective values of solubility with respect to the real one, therefore it is necessary to ensure that the desired crystal structure in the solid is acquired (Königsberger, 2019).

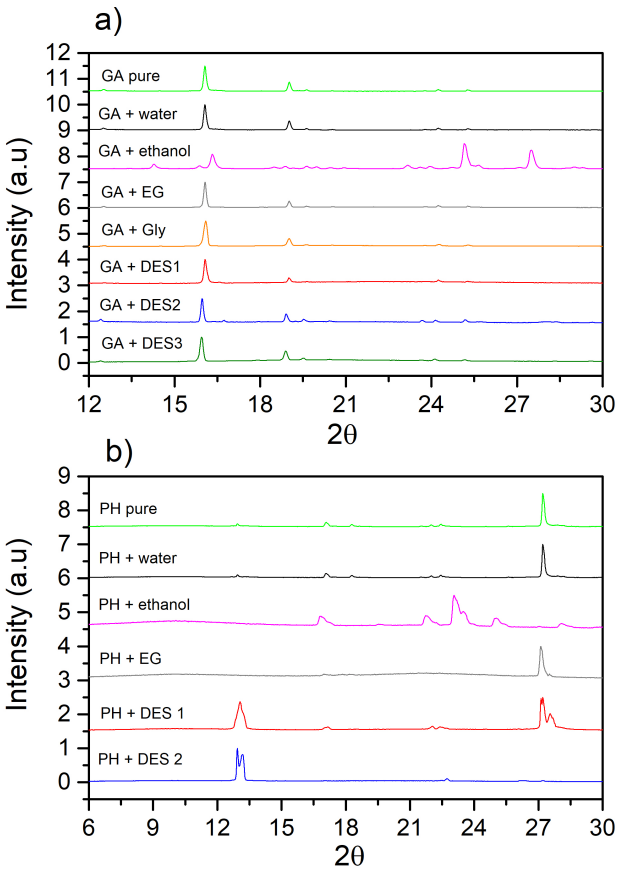

Figure 4.1. PXRD of pure **(a)** gallic acid and **(b)** phloroglucinol (–) after the solid-liquid equilibrium in: water (–), ethanol (–) and in 50 wt%. aqueous solutions of: ethylene glycol (–), glycerol (–), DES 1 (–), DES 2 (–) and DES 3 (–).

4.2. Experimental solubility

Solubility measurements for gallic acid and phloroglucinol were carried out for different solvents (water, ethanol and 50 wt.% of aqueous mixtures of ethylene glycol, levulinic acid, glycerol, DES 1, DES 2 and DES 3) at different temperatures between 293.15 K and 313.15 K at 101.3 kPa with pH values of mixtures reported in Table 4.1 for all systems. The solubility data is shown in Table 4.2 for gallic acid along with the PC-SAFT modeling results and Table 4.3 for phloroglucinol.

Table 4.1. pH values for gallic acid and phloroglucinol dissolved in an aqueous systems of solvents.

Gallic acid		
Solvent	**Average**	**SD**
Water	2.91	0.006
Ethanol	3.83	0.021
Ethylene glycol [a]	2.57	0.042
Glycerol [a]	2.76	0.020
DES1 [a]	2.27	0.038
DES2 [a]	1.78	0.055
DES3 [a]	2.13	0.041
Phloroglucinol		
Solvent	**Average**	**SD**
Water	4.12	0.031
Ethanol	5.45	0.030
Ethylene glycol [a]	4.71	0.010
DES1 [a]	3.30	0.016
DES2 [a]	1.76	0.015

[a] Mixtures in 50 wt%. aqueous solutions.

The experimental method was validated by measuring the solubility of gallic acid in two common solvents used in the separation industry, i.e., water and ethanol. These solvents were measured and compared with reported literature data (Daneshfar et al., 2008; Srinivas, King, Howard, & Monrad, 2010; Mota et al., 2008; Noubigh et al., 2013; Lu &

Lu, 2007; Q. Li et al., 2013), which can be seen in the Figure 4.2 for water and Figure A1 for ethanol. $ARD(\%)$ were calculated for single points of solubility for each system obtained in this work compared with those selected at the same temperature and pressure from literature as Equation 4.1,

$$ARD(\%) = 100 \cdot \frac{N_{\text{exp}} - N_{\text{lit}}}{N_{\text{exp}}} \tag{4.1}$$

where N_{exp} and N_{lit} are solubility of each system at a specific temperature from this work and from literature, respectively.

The experimental data shows a good agreement with the reported data for water (Daneshfar et al., 2008; Srinivas et al., 2010; Mota et al., 2008; Noubigh et al., 2013; Lu & Lu, 2007; Q. Li et al., 2013) and ethanol (Daneshfar et al., 2008). Also Figure A2 shows the absolute relative deviations (ARD) for gallic acid + water system, whose values are below 29.8%. It can be noted that in Figure A2 the values obtained experimentally are in an acceptable range in comparision with the literature, considering all the experimental differences (equipment, solvents, human error). Otherwise, the ARD value for the gallic acid + ethanol system is below 5.2%. In particular, this maximum ARD value of 29.8% is compared to the article by Mota et al. in 2008 at 303.15 K, which shows high solubility difference compared to the rest of the literature, as can be seen in Figure 4.2.

As expected, the solubility of gallic acid and phloroglucinol in ethanol is an order of magnitude greater than the solubility in water for all the temperatures. This is mainly due to the polarity of the compounds, in this case, ethanol has less polarity than water. The maximum solubility for all the systems was observed in the system using pure ethanol as solvent in both cases, as shown Table 4.2 and 4.3. Particularly, the effect on solubility of gallic acid with the addition of ethanol to a water mixture has been already reported.(Huaman-Castilla et al., 2019) On the other hand, the ability to form hydrogen bonds with gallic acid is another property to take into account.

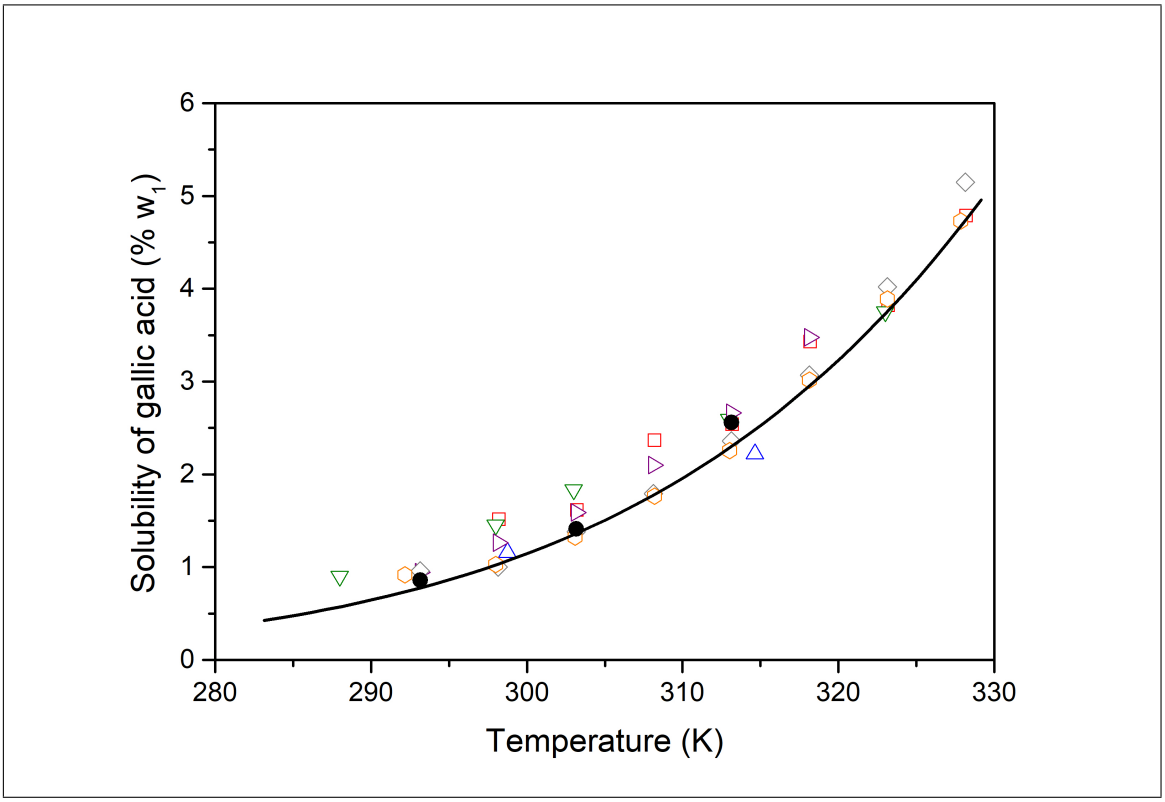

Figure 4.2. Solubility of gallic acid in water at different temperatures. This work (●).(Daneshfar et al., 2008)(□), (Srinivas et al., 2010)(△), (Mota et al., 2008)(▽), (Noubigh et al., 2013)(▷), (Lu & Lu, 2007)(◇), (Q. Li et al., 2013)(⬡). Continuous line represents the PC-SAFT model with parameters reported in this work in Table 4.4.

Table 4.2. Solubility measurements of gallic acid in different aqueous mixtures at temperatures between 293.15 K and 313.15 K at 101.3 kPa.

T (K)	Solubility ($\%w_1$)			
	exp	SD	PC-SAFT	Deviation
Water				
293.15	0.861	0.009	0.776	9.914
303.15	1.413	0.033	1.361	3.688
313.15	2.558	0.097	2.301	10.038
Ethanol				
293.15	18.814	0.267	19.222	-2.171
303.15	19.469	0.105	19.514	-0.231
313.15	20.211	0.238	20.001	1.041
Ethylene glycol [a]				
293.15	6.567	0.111	5.873	10.573
303.15	10.325	0.266	8.986	4.294
313.15	11.974	0.164	13.113	-9.506
DES 1 [a]				
293.15	7.198	0.336	7.241	-5.653
303.15	11.106	0.385	10.862	-0.404
313.15	15.875	0.194	15.494	-0.748
DES 2 [a]				
293.15	8.997	0.052	8.668	3.655
303.15	12.833	0.437	12.979	-1.138
313.15	18.031	0.260	18.442	-2.282
Glycerol [a]				
293.15	3.287	0.130	3.132	4.708
303.15	4.691	0.202	5.130	-9.342
313.15	8.075	0.515	8.062	0.161
DES 3 [a]				
293.15	5.839	0.123	5.611	3.914
303.15	8.564	0.272	8.614	-0.584
313.15	12.224	0.231	12.606	-3.125

[a] Mixtures in 50 wt%. aqueous solutions.

Standard uncertainties u are u(T) = 0.1 K and u(P) = 0.1 KPa. The relative standard uncertainties u_r is $u_r(w) = 5$, where w represents the % mass fraction.

Deviation = $100 \cdot \left(\frac{S_{\text{PC-SAFT}} - S_{\text{exp}}}{S_{\text{exp}}} \right)$

Table 4.3. Solubility measurements of phloroglucinol in different aqueous mixtures at temperatures between 293.15 K and 313.15 K at 101.3 kPa.

T (K)	**Solubility ($\%w_1$)**	
	exp	**SD**
	Water	
293.15	1.285	0.015
303.15	2.102	0.046
313.15	3.763	0.048
	Ethanol	
293.15	36.542	0.170
303.15	37.823	0.247
313.15	39.908	0.189
	Ethylene glycol [a]	
293.15	8.303	0.156
303.15	11.220	0.354
313.15	16.110	0.842
	DES 1 [a]	
293.15	13.450	0.444
303.15	16.849	0.319
313.15	21.681	0.493
	DES 2 [a]	
293.15	12.745	0.171
303.15	15.670	0.051
313.15	20.970	0.350
	Glycerol [a]	
293.15	3.690	0.051
303.15	5.475	0.197
313.15	8.503	0.396
	DES 3 [a]	
293.15	7.127	0.076
303.15	10.485	0.475
313.15	14.851	0.342

[a] Mixtures in 50 wt%. aqueous solutions.

Standard uncertainties u are u(T) = 0.1 K and u(P) = 0.1 KPa. The relative standard uncertainties u_r is $u_r(w) = 5$, where w represents the % mass fraction.

4.3. Solubility of gallic acid in aqueous solutions of HBD or DES

The dissolution of both, gallic acid and phloroglucinol, caused a distortion in the UV-vis spectrum when mixed with an aqueous solution of levulinic acid. This is probably due to an esterification reaction of the carbonyl group of levulinic acid and the hydroxyl groups of polyphenols. This reaction has been extensively studied in the literature and it is influenced by water, temperature and pH of the mixture (Altuntepe et al., 2017). For this reason, only ethylene glycol and glycerol were used as HBD precursors. However, DES 2 formed using levulinic acid as HBD did not present polymorphism, so it is assumed that levulinic acid in presence of choline chloride in the aqueous solution did not react with the polyphenols.

The solubility of gallic acid and phloroglucinol in aqueous mixtures of ethylene glycol and glycerol, was compared with the results using aqueous mixtures of DES 1, DES 2 and DES 3. Thus, it was compared the HBD with its respective DES and their effectiveness to be used as an extracting solvent. Firstly, Figure 4.3 shows the solubility of (a) gallic acid and (b) phloroglucinol in aqueous HBD mixtures. As seen in the results, both, gallic acid and phloroglucinol, show a higher solubility in the aqueous solution with ethylene glycol compared with the other mixture composed by glycerol. This behavior can be explained due to the symmetry of ethylene glycol and its lower volume, which allows less steric hindrance and therefore a higher affinity for polyphenols.

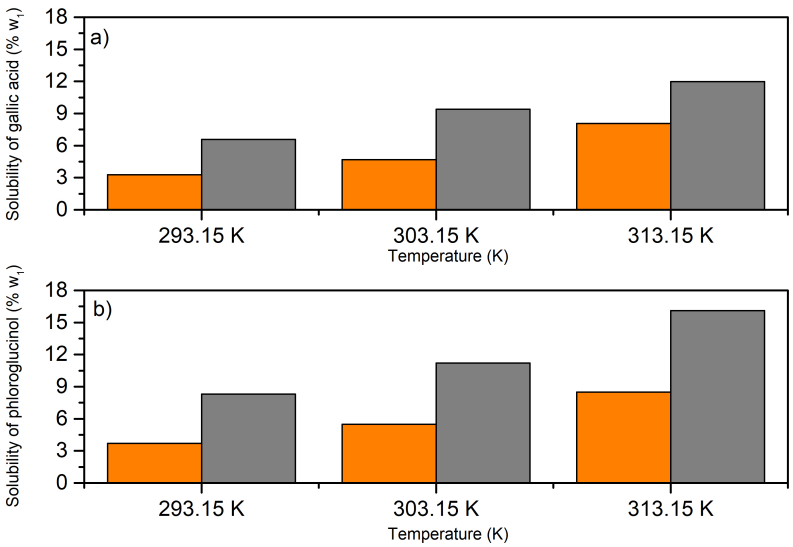

Figure 4.3. Solubility of **(a)** gallic acid and **(b)** phloroglucinol in 50 wt%. aqueous solutions of ethylene glycol ( ) and glycerol ( ) at 293.15 K, 303.15 K and 313.15 K.

On the other hand, Figure 4.4 shows the solubility of gallic acid and phloroglucinol in aqueous mixtures of DES. Firstly, Figure 4.4 (a) shows the comparison of solubility between the aqueous mixtures of DES 1, DES 2 and DES 3 for gallic acid. DES 2 based on levulinic acid shows the best results for the 3 measured temperatures, with a maximum solubility value of 18.03 % by weight at 313.15 K followed by DES 1 based on ethylene glycol which has a lower but very similar result. Otherwise, (b) shows the same comparison for phloroglucinol. In this case, DES 1 based on ethylene glycol shows the best results for the 3 measured temperatures, with a maximum solubility value of 21.68 % at 313.15 K; followed by DES 2 based on levulinic acid which also has a lower but very similar result. There is a clear tendency to increase solubility for both DES systems with increasing temperature, however the molecular structure of polyphenols can strongly influence solubility. The solubility behavior in Figure 4.4 can be explained due to the functional groups that gallic acid and phloroglucinol has in its molecular structure. Gallic acid has a great

capacity form dimers and bonds (mainly hydrogen bonds) with another carboxyl group. This groups can be found in the aqueous mixture of DES 2 (based on levulinic acid), thus explaining that the solubility of GA is higher in DES 2 than in DES 1 due to the high affinity of the carboxyl groups. However, this behavior does not occur for phloroglucinol, since it does not have a carboxyl group in its molecular structure. PH only has hydroxyl groups, those that have an affinity with the aqueous mixture of DES 1 (based on ethylene glycol) due to the OH groups that its HBD has. Despite these results, the solubility of phloroglucinol was higher than the solubility of gallic acid in pure water, ethanol and all aqueous solvents. This is mainly due to the fact that gallic acid has a tendency to carry out multiple interactions between its molecules (Braun, Bhardwaj, Florence, Tocher, & Price, 2013), generating a greater steric effect. GA has intramolecular interactions of hydrogen bonds between GA molecules due to the arrangement of their hydroxyl groups. Furthermore, gallic acid (GA) can form non-polar dimers with the carboxyl group of another GA molecule, which makes it less available to bind with solvents, generating a greater steric effect than phloroglucinol. On the other hand, phloroglucinol has a greater availability of hydrogen bonds to donate and interact with solvents since it has a very symmetrical structure, which makes it less likely to interact with another PH molecule.

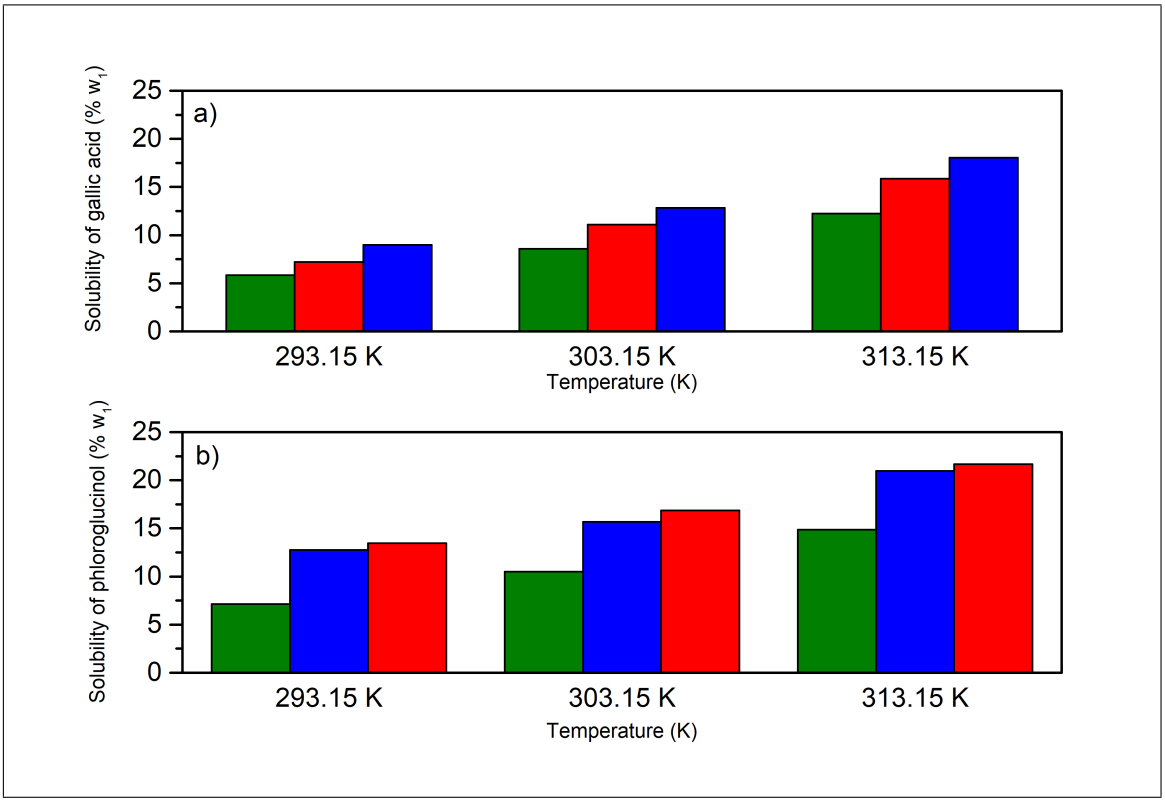

Figure 4.4. Solubility of **(a)** gallic acid and **(b)** phloroglucinol in 50 wt%. aqueous solutions of DES1 (■), DES2 (■) and DES3 (■) at 293.15 K, 303.15 K and 313.15 K.

Figure 4.5 shows the comparison of solubility of the aqueous mixtures of DES and their respective aqueous HBD carried out in (a) - (c) gallic acid and (b) - (d) phloroglucinol. As a result, the aqueous DES mixture produces a higher solubility of both solutes compared with the aqueous HBD solution for all temperatures. This behavior can be due to the addition of HBA or due to the intrinsic properties of DES. However, looking at the previous figures, it can be seen that phloroglucinol presented higher solubility for all aqueous systems compared to gallic acid as discussed before.

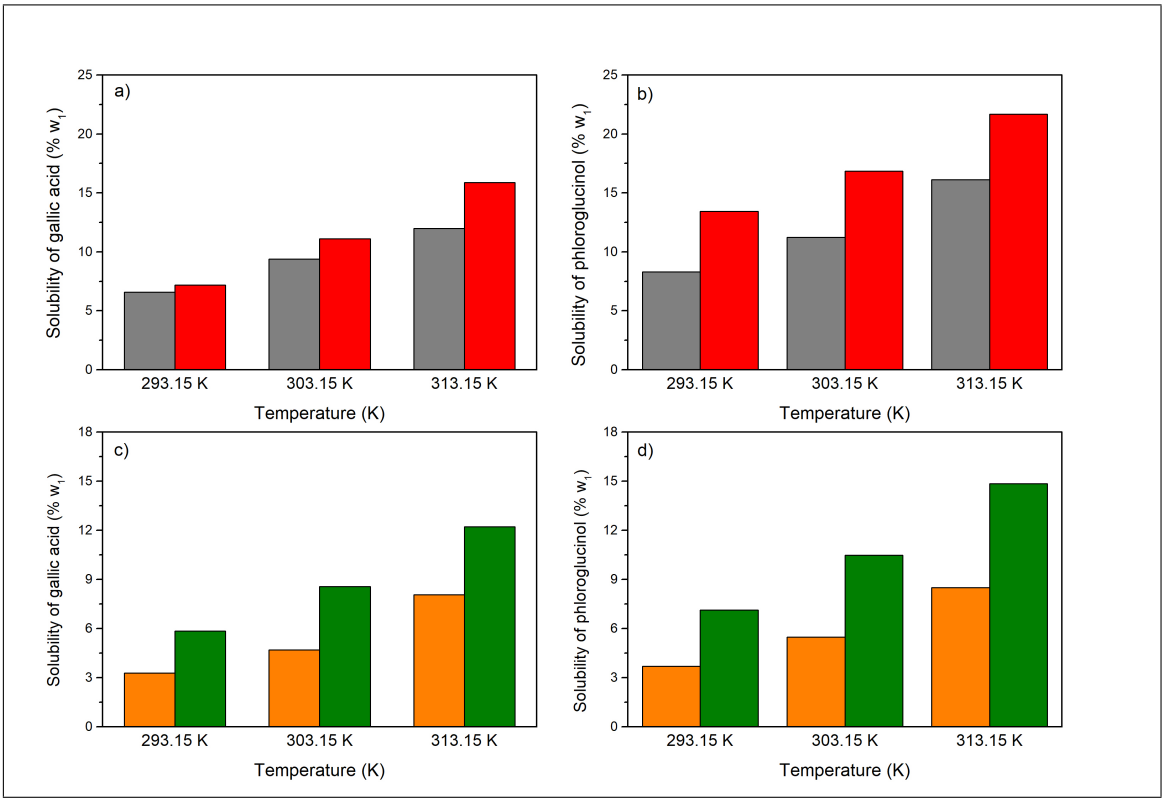

Figure 4.5. Solubility of **(a)** Gallic acid in ethylene glycol^a and DES1^a, **(b)** Phloroglucinol in ethylene glycol^a and DES1^a, **(c)** Gallic Acid in glycerol^a and DES3^a and **(d)** Phloroglucinol in glycerol^a and DES3^a at 293.15 K, 303.15 K and 313.15 K. The bars represent solubility for ethylene glycol^a (■), DES1^a (■), glycerol^a (■) and DES3^a (■), where (^{a}) represents aqueous solutions of 50 wt%.

To assess the behavior of the solubility curves in the different systems outlined above, an analysis will be carried out with the parameters of the Kamlet-Taft solvatochromic relationship. These represent the most complete and frequently used quantitative measures of the properties of the solvent (Jessop, Jessop, Fu, & Phan, 2012) to investigate the polarity of ionic liquids and DES (Florindo, McIntosh, Welton, Branco, & Marrucho, 2017). The Kamlet-Taft parameters are 3 which represent: hydrogen bond donor capacity (α), hydrogen bond acceptor capacity (β) and the polarity / polarizability (π^*) properties of solvents as contributors to the overall polarity of the solvent. For this analysis, the parameters (π^* vs β) and (α vs β) are correlated and shown in Figure 4.6 and Figure A11

respectively, with data from the literature (Jessop et al., 2012; Kamlet, Abboud, Abraham, & R.W, 1983; Senol, 2005; Florindo et al., 2017; Marcus, 1993) as indicated in the Table A.1. In these figures it can be clearly seen that the order of the solubility values of the two polyphenols in aqueous mixtures shows the same trend as the values of the hydrogen bond acceptor capacity parameter (β) of the solvents in pure state. On the other hand, the polyphenols (gallic acid and phloroglucinol) presented an acid pH in all aqueous mixture systems (values reported in Table 4.3) with a maximum pH value of 3.83 and 5.45 for gallic acid and phloroglucinol respectively. These pH values are lower than the pKa value of the most acidic functional group in each polyphenol (pKa = 4.25 for the carboxyl group of GA (Erdemgil et al., 2007) and pKa = 8.8 for the hydroxyl group of PH (Lohrie & Knoche, 1993)), therefore, the formation of the species in equilibrium is favored in polyphenols, acting as a donor of hydrogen bonds. Consequently, solvents behave as hydrogen bond acceptors, therefore, the best acceptors with a higher value of β, should have a higher solubility, which is what occurs and is presented in the trend of Figures 4.6 and A11.

Analyzing the next parameter (π^*), it does not have an apparent significant effect on the solubility since in Figure 4.6 and Figure A11. There is no correlation between the solvents and the experimental solubility with a variation of (π^*), however, this correlation is presented with the variation of β as mentioned above. This can be explained because the ability to polarize a molecule (π^*) that has all solvents will not predict the behavior of donating or accepting hydrogen bonds. Furthermore, it is possible that the effect of intermolecular interaction of the solutes with the aqueous solution is more relevant than the ability of the molecule to polarize.

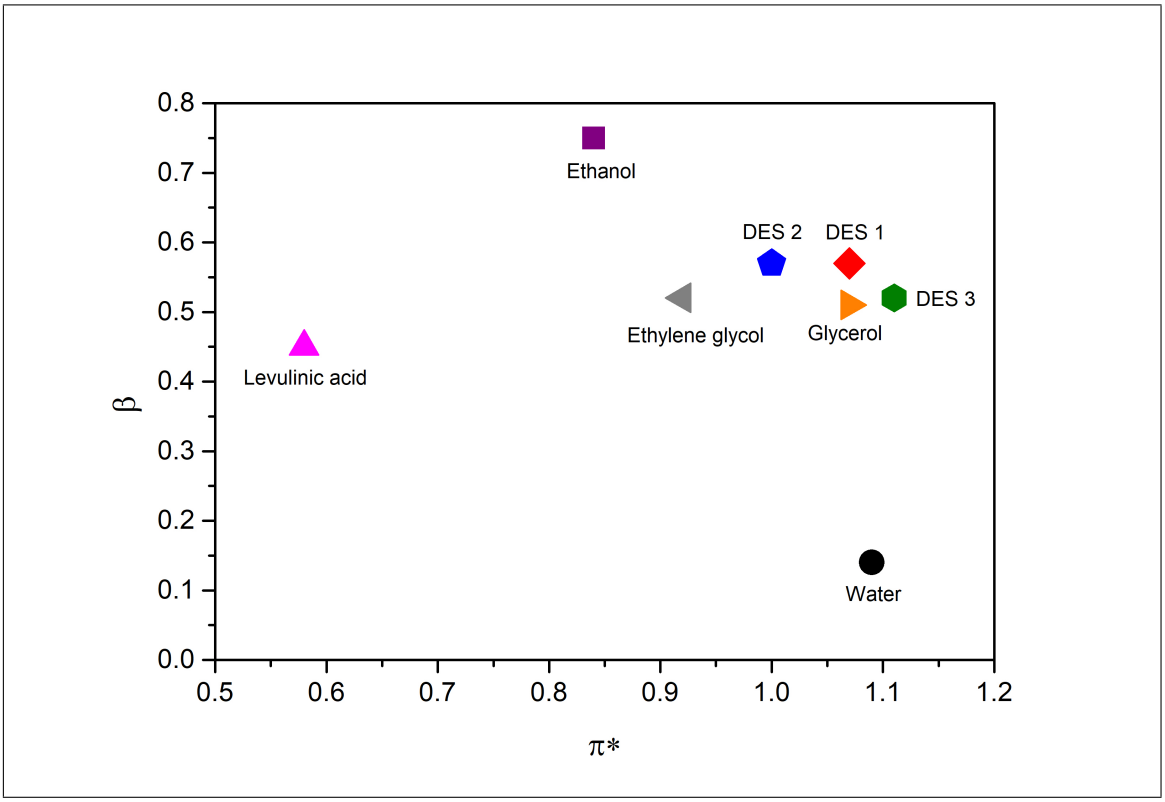

Figure 4.6. Solvatochromic parameters (π^* vs β) for molecular solvents. Where: water (●), ethanol (■), DES1 (◆), DES2 (⬟), DES3 (⬢), ethylene glycol (◀), glycerol (▶) and levulinic acid (▲).

Finally, the solubility data apparently does not correlate with the parameter α, since polyphenols behave like hydrogen bond donors. Consequently, the solubility data should be related to the opposite parameter which is to accept hydrogen bonds, which is what occur and is shown in Figure 4.6. This apparent null relation with the parameter α can be seen graphically in Figure 4.6 where DES 1 and DES 2 have the same value of β and a very different α, however , its solubility in each polyphenol is very similar both for the case with gallic acid and with phloroglucinol.

4.4. PC-SAFT solubility and parameters

The PC-SAFT calculated values for all the mixtures are reported in Figure 4.7, where the solubility of (a) gallic acid and (b) phloroglucinol is shown. This modeling was only performed for gallic acid. Phloroglucinol was not modeled due to its change in its crystal structure, affecting solubility predictions. This is because in order to apply the SLE equation 2.15, no changes in the heat capacities and the diffraction planes should occur when the solute mixes with the respective solvent. As discussed above, this happens for gallic acid (with the exception of ethanol mentioned above), but not for phloroglucinol. Also, for gallic acid modeling it was obtained an average absolute deviation (AAD) of 4.15 % was obtained. $AAD(\%)$ is represented in Equation 4.2, where n is the number of data considered in the calculation:

$$AAD(\%) = \frac{100}{n} \sum_{i=1}^{n} \left| \frac{N_{\text{exp}} - N_{\text{lit}}}{N_{\text{exp}}} \right| \tag{4.2}$$

The solubility of gallic acid in all the pure liquids and aqueous mixtures was modeled using PC-SAFT by calculating the fugacity coefficients for Eq. 2.15. Pure-component parameters for gallic acid were fit to its experimental solubility in water obtained in this work. Gallic acid was modeled as a self-associating molecule by assuming each three association donor and acceptor sites. Pure-component parameters for the other compounds used in this study (water, ethylene glycol, levulinic acid, glycerol, DES1, DES2 and DES3) were retrieved from literature (Cameretti & Sadowski, 2008; Gross & Sadowski, 2002a; Haghbakhsh et al., 2017; Karakatsani et al., 2005; Altuntepe et al., 2017; Zubeir et al., 2016; Held & Sadowski, 2016). The solubility of gallic acid in ethanol was not modeled because of the changes in the PXRD diffractogram of gallic acid after its mixing in ethanol, it was decided not to present the data in the Figure 4.7, since it is necessary to investigate more about this interaction, since the modeling parameters change. However, the data fit quite well and is presented in Table 4.2. All the PC-SAFT pure-component parameters are reported in Table **??**. Most of the binary interaction parameters (k_{ij}) were fit in this work from solid-liquid equilibrium, and some values, for instance, water + choline chloride or

water + levulinic acid were taken from literature.(Zubeir et al., 2016; Altuntepe et al., 2017) All the k_{ij} values are reported in Table 4.5, where they are represented by Eq. 4.3 with the constants a_{ij} and b_{ij} as:

$$k_{ij} = a_{ij} + b_{ij} \cdot (T - 298.15\ K) \tag{4.3}$$

Only the binary systems composed by water + choline chloride needed a temperature-dependent k_{ij}.

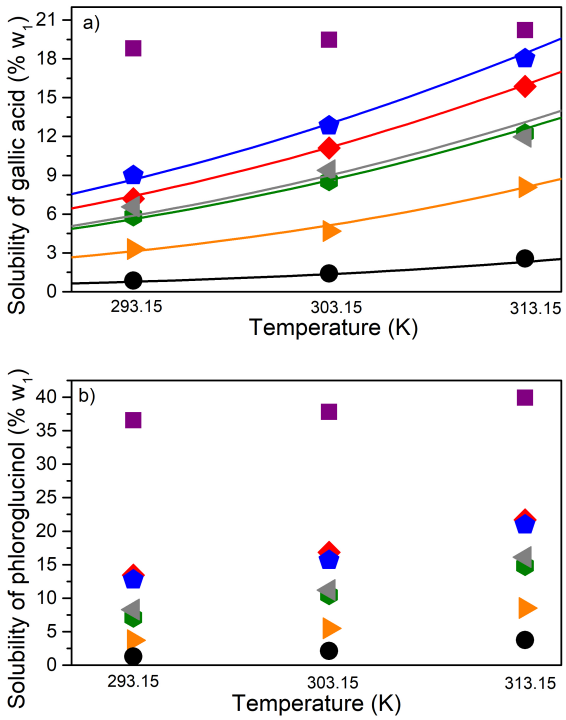

Figure 4.7. Solubility of **(a)** Gallic Acid and **(b)** Phloroglucinol in water (●), ethanol (■), DES1[a] (◆), DES2[a] (⬟), DES3[a] (⬢), ethylene glycol[a] (◀) and glycerol[a] (▶) at 293.15 K, 303.15 K and 313.15 K. Continuous line represents the PC-SAFT model with parameters reported in Table 4.4.([a]) represents mixtures of 50 wt%. aqueous solutions.

Table 4.4. PC-SAFT parameters.

PC-SAFT parameters						
Abreviation	m_i [-]	σ_i [$\dot{A}$]	ϵ/k [K]	$\kappa^{A_iB_i}$ [-]	$\epsilon^{A_iB_i}/\kappa$ [K]	Scheme
GA [a]	3.1897	2.2409	185.9531	0.0110	1722.8110	3B (3-3)
H_2O [b]	1.2047	2.7927	353.9449	0.0451	2425.6710	2B (1-1)
EtOH [c]	2.3827	3.1771	198.2400	0.0324	2653.4000	2B (1-1)
ChCl [d]	13.0200	2.3680	228.0700	0.2000	8000.0000	2B (1-1)
EG [e]	3.3940	2.8052	319.9200	0.0228	1889.8600	4C (2-2)
Lev [e]	2.0311	4.1241	266.4953	0.0171	4578.3660	2B (1-1)
Gly [f]	2.0070	3.8150	430.8200	0.0019	4633.4700	2B (1-1)
DES1 [g]	3.5408	3.2782	465.0741	0.0021	4971.9890	2B (1-1)
DES2 [g]	3.4672	3.6847	477.7234	0.0030	4601.3090	2B (1-1)
DES3 [h]	7.7594	2.5699	275.0000	0.1000	5000.0000	2B (1-1)

[a] This work. [b] (Cameretti & Sadowski, 2008). [c] (Gross & Sadowski, 2002a). [d] (Zubeir et al., 2016).

[e] (Karakatsani et al., 2005). [f] (Held & Sadowski, 2016). [g] (Haghbakhsh et al., 2017). [h] (Verevkin et al., 2015).

The PC-SAFT modeling was performed with two different approaches: (a) modeling the DES as a pseudo-pure compound, and (b) modeling with the individual components of the DES. Since some interaction parameters between the individual components themselves were not available in the literature, the missing k_{ij} were fitted in this work. The k_{ij} were not changed through the different DES systems. Both approaches show reliable results, which are in good agreement with the experimental data. For reasons of presentation only, the results for the PC-SAFT modeling with the pseudo-pure component parameters are shown in this work.

Table 4.5. PC-SAFT binary interaction parameters k_{ij} fit to experimental data obtained in this work.

System	a_{ij}^{*}	b_{ij}^{**}
GA/H_2O [a]	-0.0095	-
GA/EtOH [a]	-0.3519	0.0020
GA/ChCl [a]	-0.2500	-
GA/EG [a]	-0.2300	-
GA/Lev [a]	-0.2900	-
GA/Gly [a]	-0.1500	-
GA/DES1 [a]	-0.190	-
GA/DES2 [a]	-0.2120	-
GA/DES3 [a]	-0.2000	-
H_2O/EtOH [a]	-0.0310	-
H_2O/ChCl [b]	-0.0285	0.0001
H_2O/EG [a]	-0.0300	-
H_2O/Lev [c]	0.0600	-
H_2O/Gly [a]	-0.0050	-

[a] Type of data used for fitting:solid-liquid (this work). [b] Type of data used for fitting:liquid-liquid (this work).

[c] (Zubeir et al., 2016). [d] (Altuntepe et al., 2017).

* and ** represent the parameters of the equation $k_{ij} = a + b \cdot T$

The PC-SAFT modeling results are compared with the experimental values of the solubility of gallic acid in the different liquid phases as shown in Figure 4.7. The deviation ($100 \cdot (S_{PC-SAFT} - S_{exp})/S_{exp}$) of the solubility calculated with PC-SAFT ($S_{PC-SAFT}$) compared with all the experimental points (S_{exp}) are reported Table 4.2 obtaining values within 10.6%, showing that PC-SAFT present a reasonable representation of the experimental data within the experimental error observed for data from this work compared with literature.

5. CONCLUSIONS AND PERSPECTIVES

Solubility measurements for gallic acid (GA) and phloroglucinol (PH) were carried out in water, ethanol, aqueous mixtures of HBDs and aqueous mixtures of DES at different temperatures between 293.15 K and 313.15 K at 101,3 kPa. All the systems were measured with the shake-flash method at controlled temperature and analyzing the samples through absorbance and density calibration curves. The experimental technique used was validated by comparing the values with the literature, where ARD values below 14.3 % and 5.2 % were obtained for GA-water and GA-ethanol systems respectively.

Pure polyphenols and the solid remaining after the equilibrium in each solubility experiment were analyzed through PXRD analysis to see the influence of the solvent on the diffraction planes. Pure gallic acid presented the same diffraction curve for all the systems, maintaining the peaks in all cases, indicating that there was no change in the diffraction planes or in the structure of the polyphenol unit cell, even after the presence of the different solvents during the solubility experiment. However, diffraction planes of the pure compound are different with those of the compound in presence of ethanol in the solubility experiments. Ethanol behaved as an exception, showing the appearance of new diffraction planes. Otherwise, pure phloroglucinol presented a different diffraction curve for most solvent mixtures with displacement and the appearance of new peaks.

PC-SAFT was applied to the systems that do not present changes in its crystalline structure, i.e. only gallic acid. Modeling was performed using the solid-liquid equation assuming no effects of the heat capacities. The results of the gallic acid solubility modeling in aqueous solvent mixtures obtained ARD values below 10.04 % water and ethanol mixtures, 10.57 % in HBDs aqueous mixtures and -5.65 % in DES aqueous mixtures.

It is shown that for all systems the solubility increased with increasing temperature, as expected. The solvent that produced a higher solubility in gallic acid and phloroglucinol was ethanol for both polyphenols, followed by DES 2 and DES 1 for GA and PH, respectively, however, PH had higher solubility in water, ethanol and the aqueous systems

compared to GA. This is mainly due to the fact that gallic acid has a tendency to carry out multiple interactions between its molecules, generating greater steric hindrance. On the other hand, phloroglucinol has a greater availability of hydrogen bridges to donate and interact with solvents, since it has a very symmetrical structure.

To assess the behavior of the solubility curves in the different systems an analysis was performed with the solvatochromic Kamlet-Taft parameters. Analyzing the graphs of parameters π^* vs β and α vs β, it can be clearly seen that a higher solubility is correlated with an increasing β parameter. This is because polyphenols have a pKa values lower than the pH values of the medium, therefore, the formation of the species in equilibrium is favored acting as a donor of hydrogen bonds. Consequently, solvents behaved as hydrogen bond acceptors, therefore, this means that solvents with higher β will act as a higher acceptor of hydrogen bonds and therefore, will cause a greater interaction between solute-solvent and solubility.

As future work it would be interesting to assess the change of the structure of phloroglucinol in the presence of the different solvents and model its solubility results in PC-SAFT. In addition, it would be interesting to test other polyphenol standards and use other DES types to see their behavior, since the more extensive the literature regarding the solubility of polyphenols, the better computational modeling of these data can be performed, opening the opportunity for future conceptual separation design using process simulation.

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APPENDIX

A. SUPPORTING INFORMATION

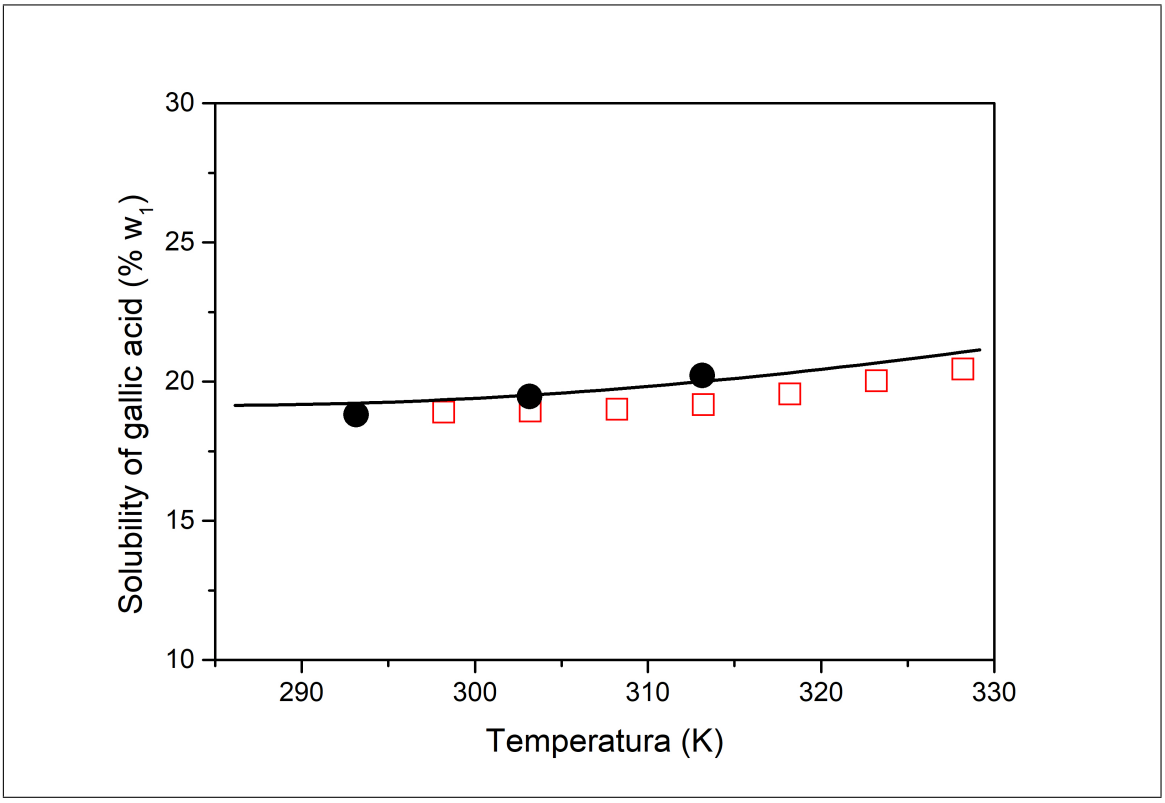

Figure A.1. Solubility of Gallic acid in ethanol at different temperatures. This work it is represent by (●). Literature data is reported by (Daneshfar et al., 2008)(□) Continous line represents the PC-SAFT model with parameters reported in Tables 4.4 and 4.5.

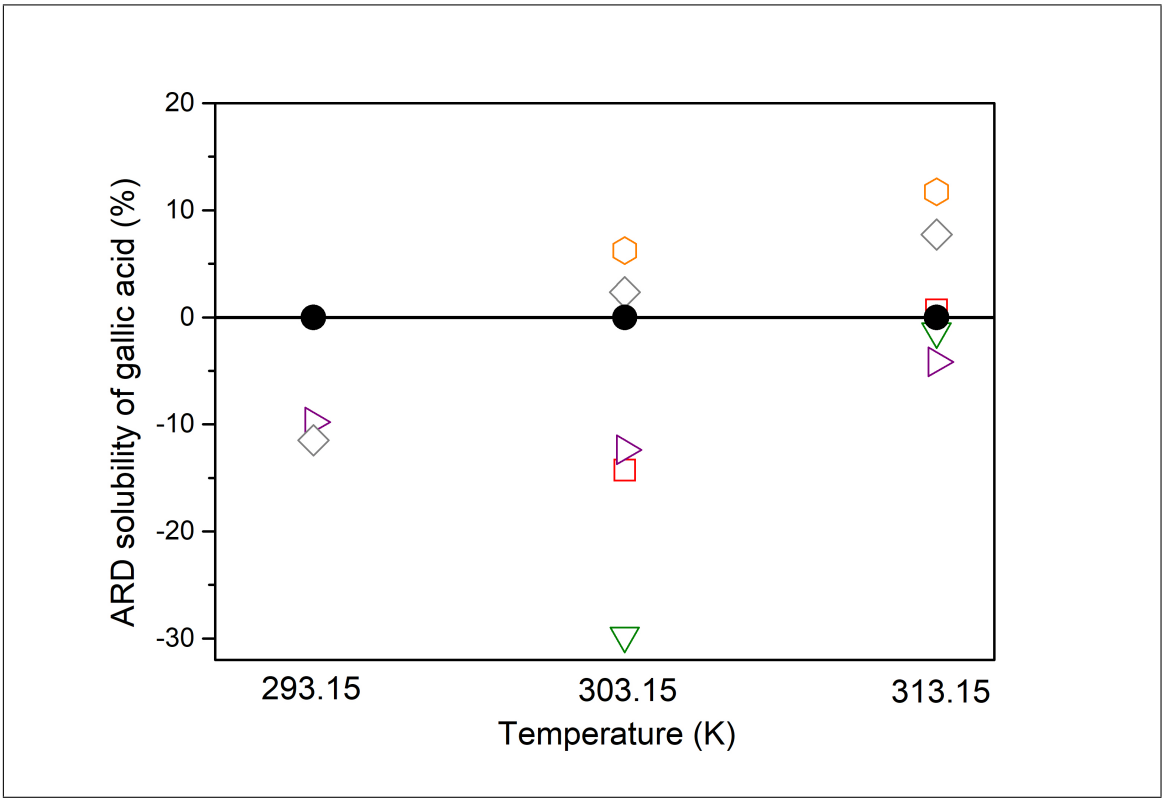

Figure A.2. ARD (%) for water comparing: this work (●), (Daneshfar et al., 2008)(□), (Mota et al., 2008)(▽), (Noubigh et al., 2013)(▷), (Lu & Lu, 2007)(◇), (Q. Li et al., 2013)(⬡).

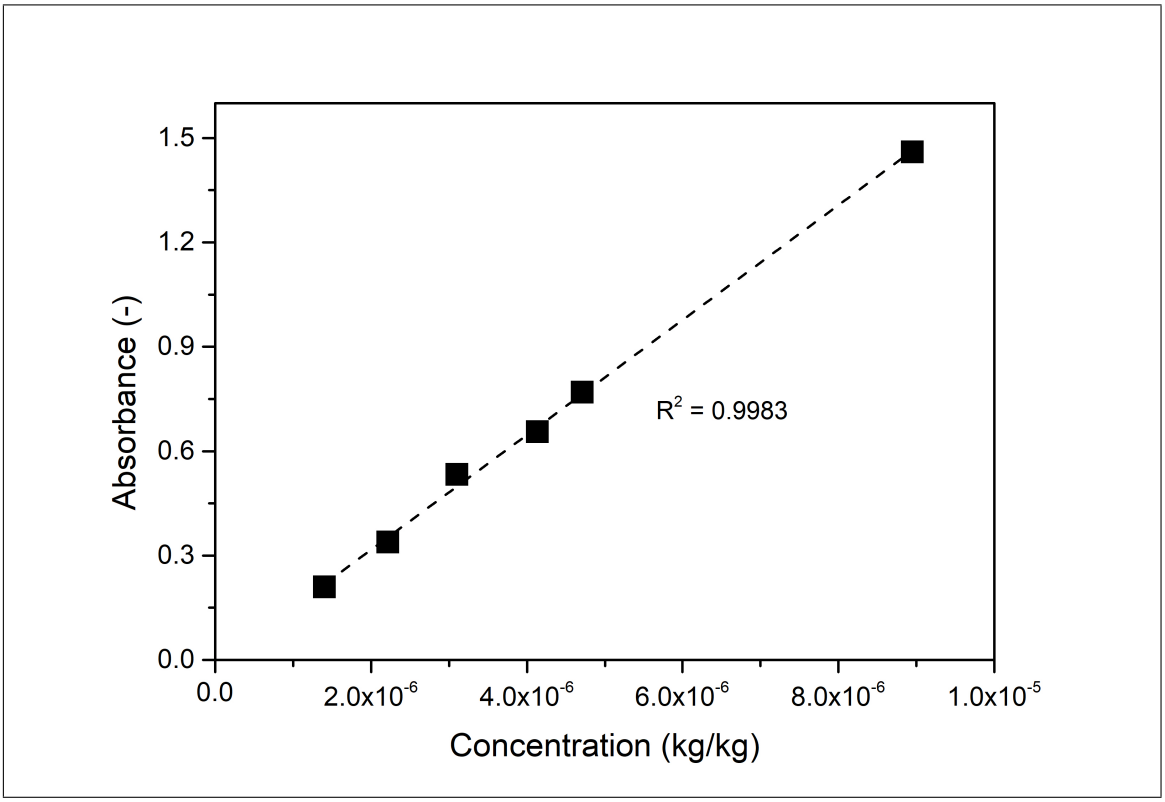

Figure A.3. Calibration curve of [gallic acid + water] system at 293.15, 303.15 and 313.15 K with a dilution factor of 2500.

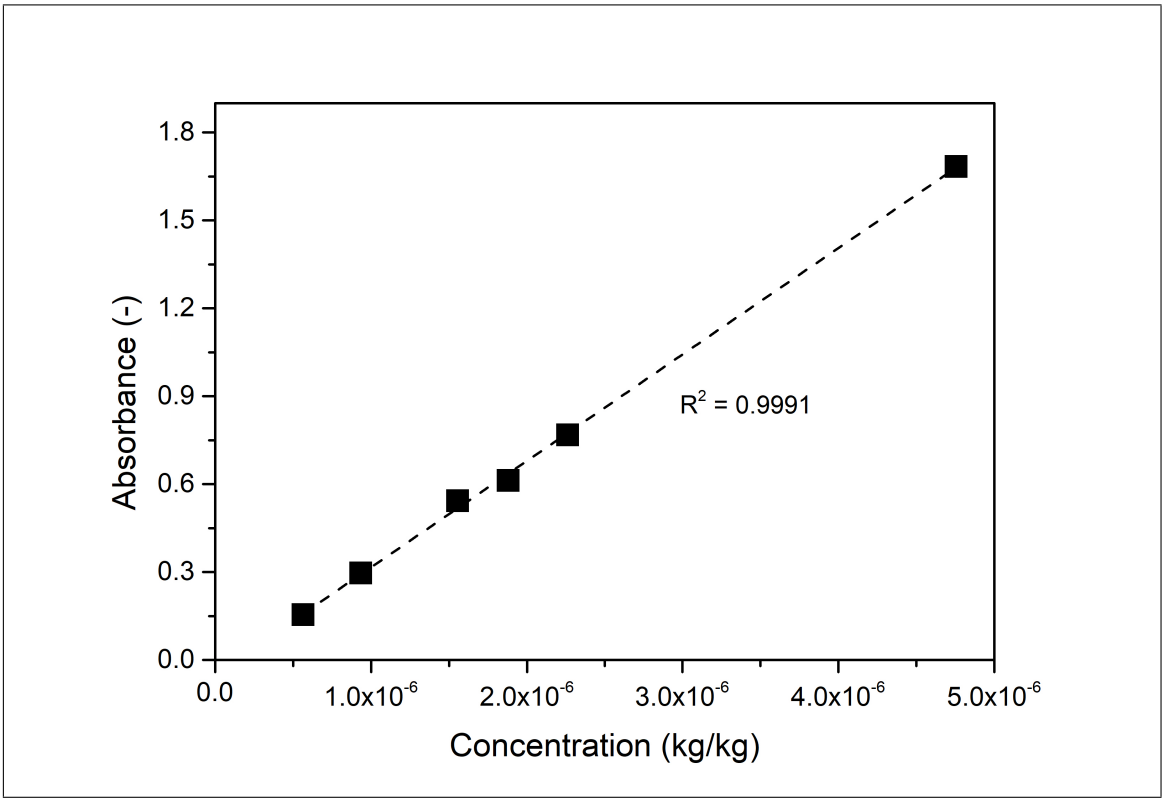

Figure A.4. Calibration curve of [phloroglucinol + water] system at 293.15, 303.15 and 313.15 K with a dilution factor of 5500.

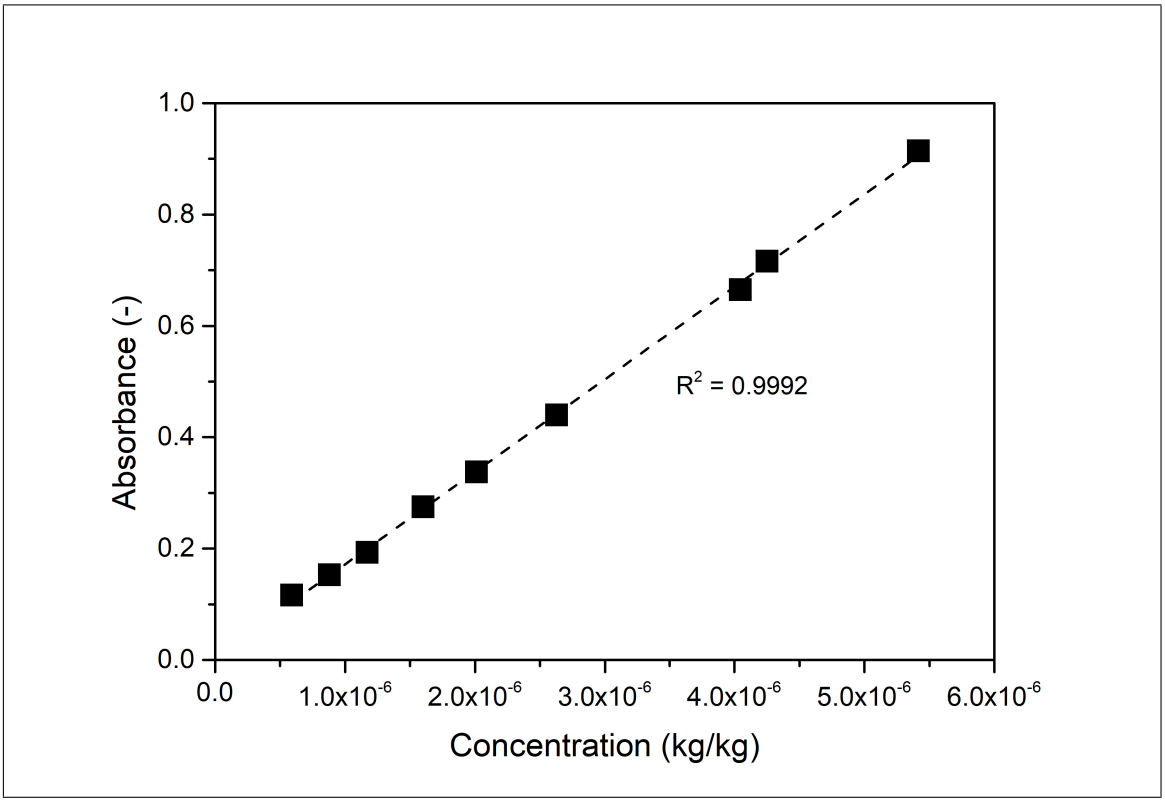

Figure A.5. Calibration curve of [gallic acid + DES1*] system at 293.15, 303.15 and 313.15 K, [gallic acid + DES2*] system at 293.15 K and [gallic acid + ethylene glycol*] system at 293.15 and 313.15 K with a dilution factor of 30000. Where (*) represents mixtures with water 1:1 in mass ratio.

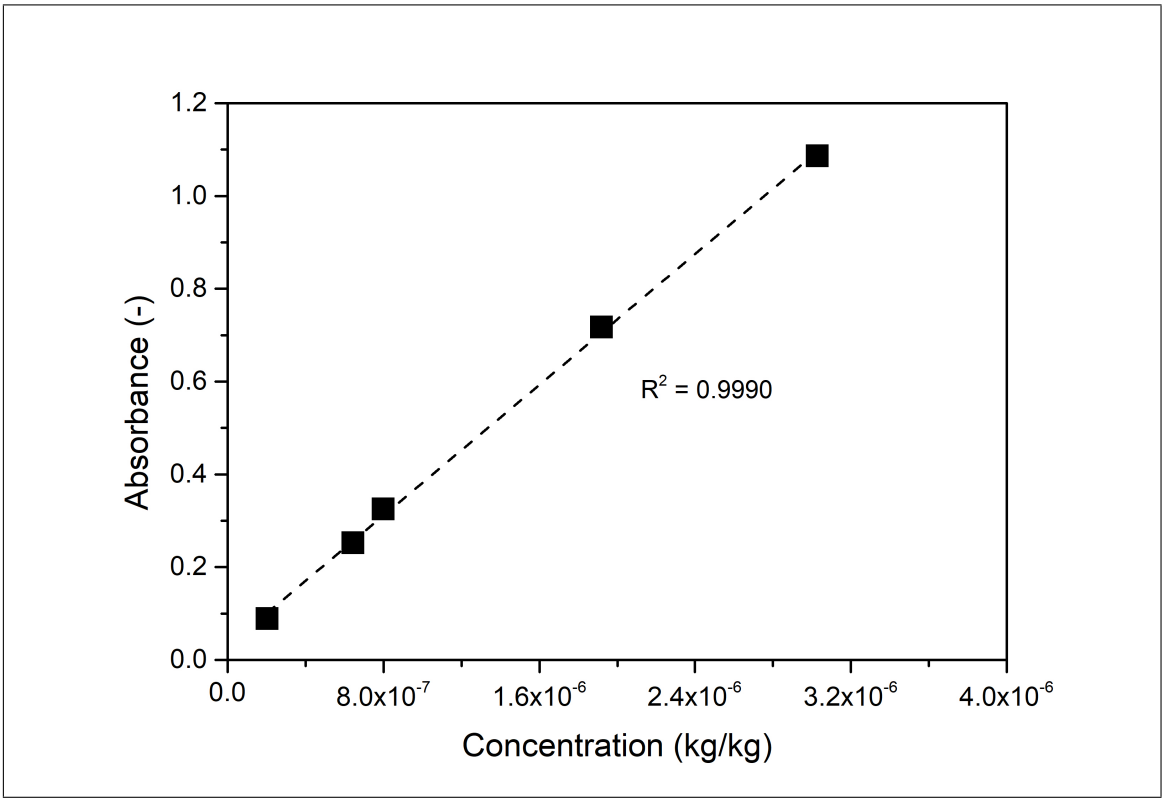

Figure A.6. Calibration curve of [phloroglucinol + DES1*] system at 293.15, 303.15 and 313.15 K, [phloroglucinol + DES2*] system at 293.15, 303.15 and 313.15 K and [phloroglucinol + ethylene glycol*] system at 293.15, 303.15 and 313.15 K with a dilution factor of 60000. Where (*) represents mixtures with water 1:1 in mass ratio.

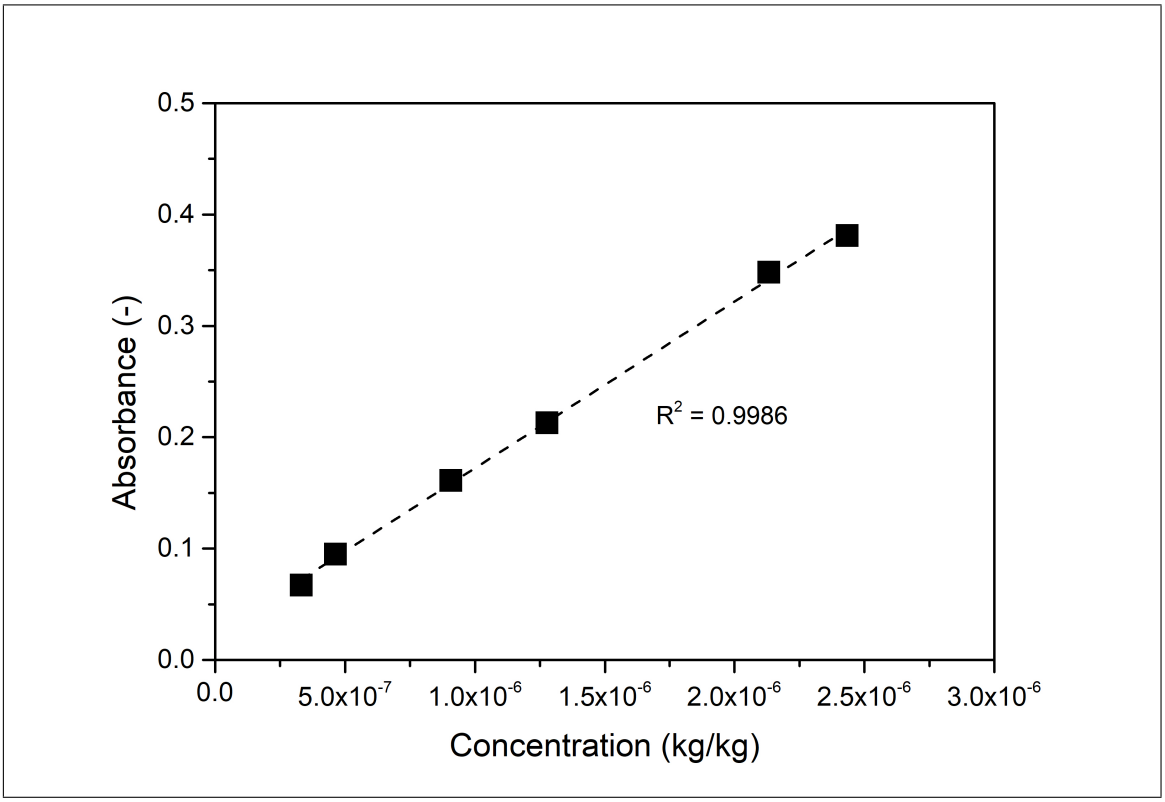

Figure A.7. Calibration curve of [gallic acid + DES2*] system at 303.15 and 313.15 K, [gallic acid + ethylene glycol*] system at 303.15 K, [gallic acid + DES3*] system at 293.15, 303.15 and 313.15 K and [gallic acid + glycerol*] system at 293.15, 303.15 and 313.15 K with a dilution factor of 30000. Where (*) represents mixtures with water 1:1 in mass ratio.

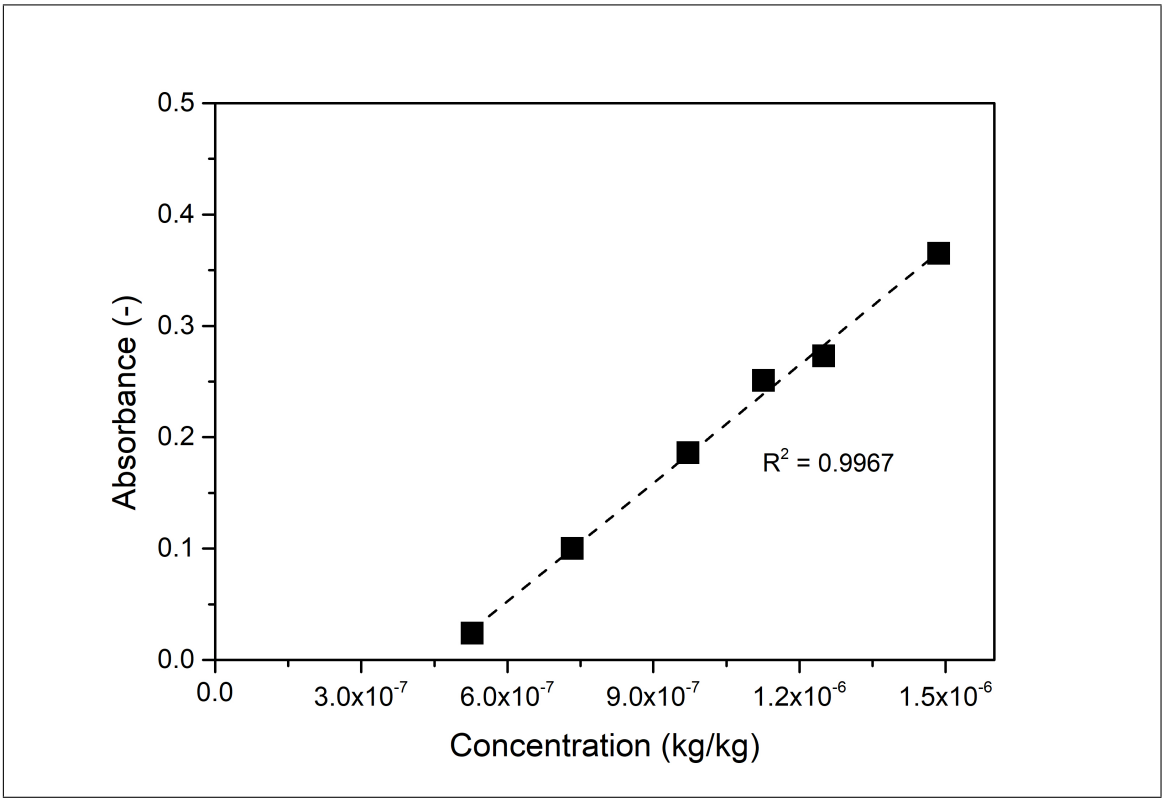

Figure A.8. Calibration curve of [phloroglucinol + DES3*] system at 293.15, 303.15 and 313.15 K and [phloroglucinol + glycerol*] system at 293.15, 303.15 and 313.15 K with a dilution factor of 60000. Where (*) represents mixtures with water 1:1 in mass ratio.

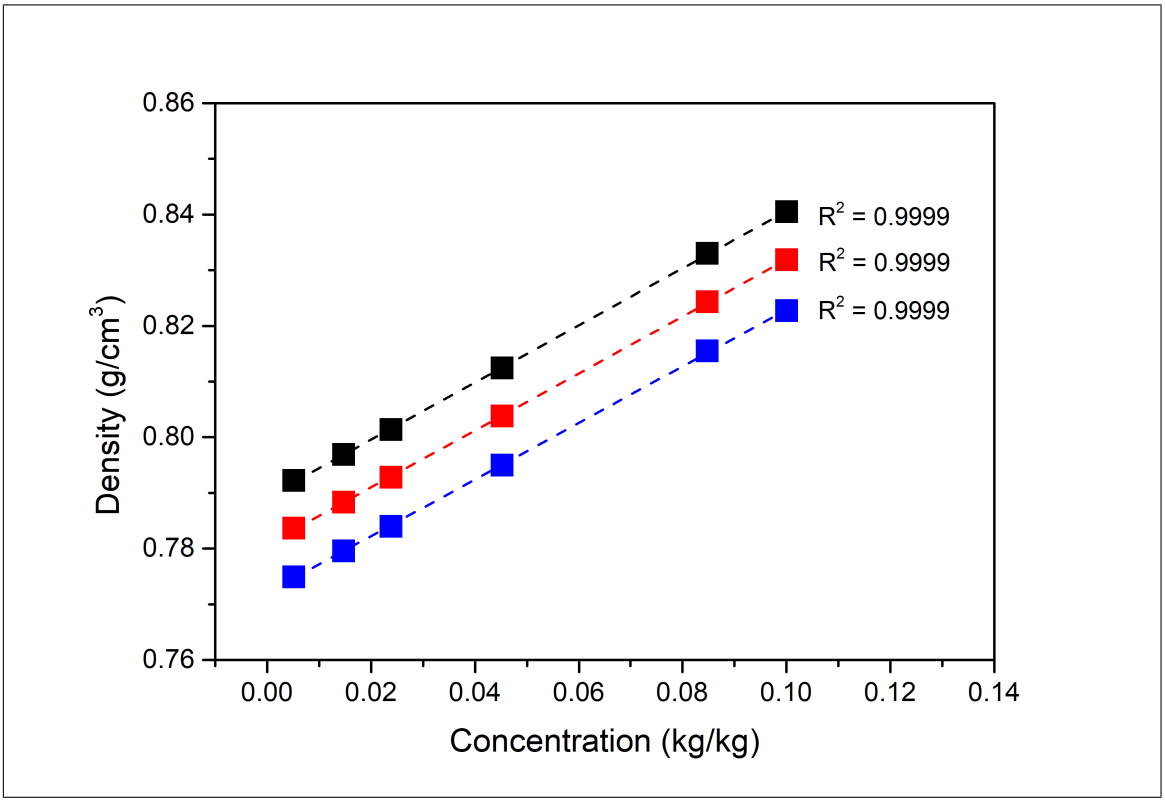

Figure A.9. Calibration curve of [gallic acid + ethanol] system at 293.15 K (■), 303.15 K (■) and 313.15 K (■) with a dilution factor of 2.

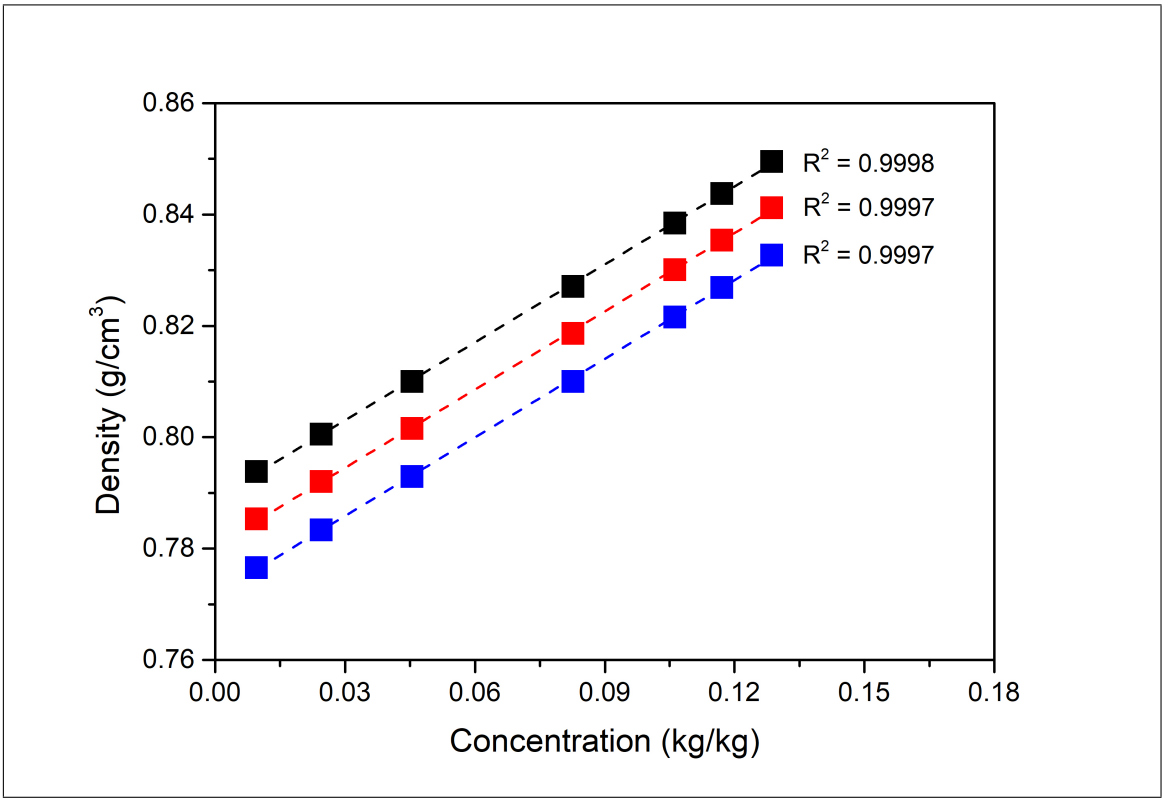

Figure A.10. Calibration curve of [phloroglucinol + ethanol] system at 293.15 K (■), 303.15 K (■) and 313.15 K (■) with a dilution factor of 2.

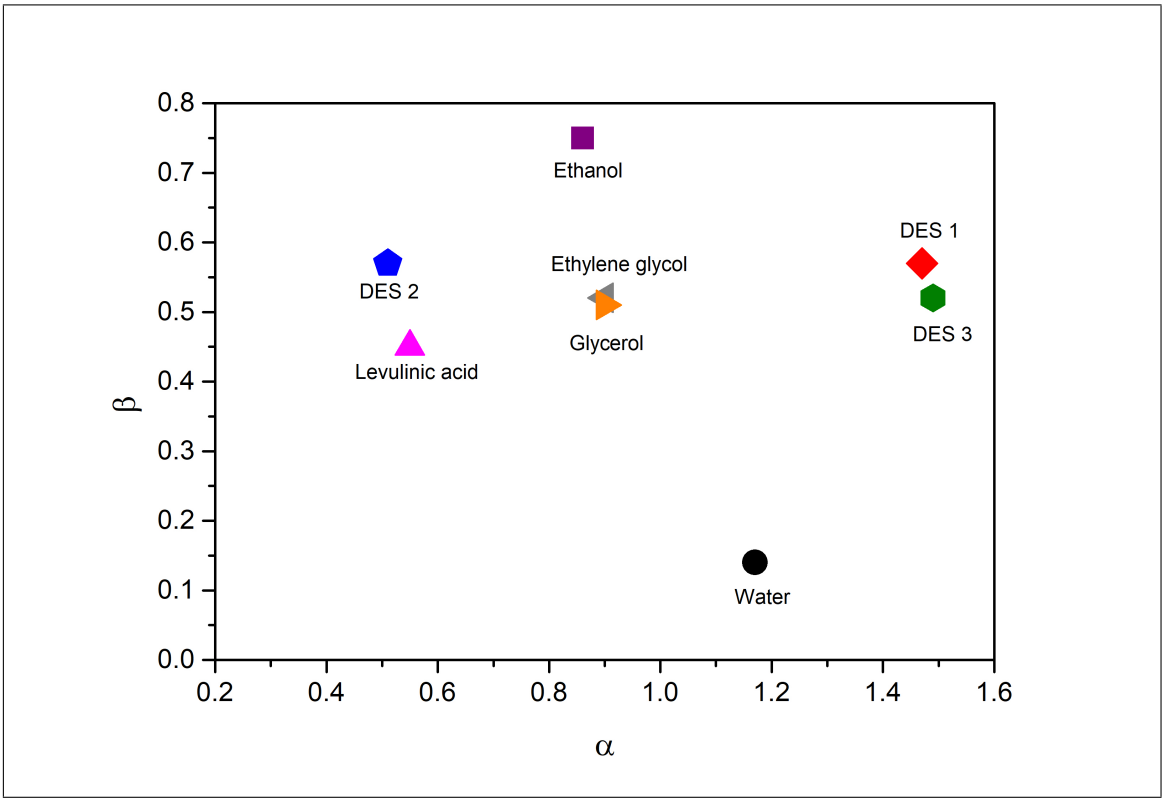

Figure A.11. Solvatochromic parameters (α vs β) for molecular solvents. Where: water (●), ethanol (■), DES1 (◆), DES2 (⬟), DES3 (⬢), ethylene glycol (◀), glycerol (▶) and levulinic acid (▲).

Table A.1. Solvatochromic parameters for molecular solvents

Solvent	α	β	π^*
Water (Jessop et al., 2012)	1.17	0.14	1.09
Ethanol (Jessop et al., 2012)	0.86	0.75	0.84
Ethylene glycol (Kamlet et al., 1983)	0.90	0.52	0.92
Levulinic acid (Senol, 2005)	0.55	0.45	0.58
Glycerol (Jessop et al., 2012; Marcus, 1993)	0.90	0.51	1.07
DES1 (Florindo et al., 2017)	1.47	0.57	1.07
DES2 (Florindo et al., 2017)	0.51	0.57	1.00
DES3 (Florindo et al., 2017)	1.49	0.52	1.11