



Extraction of pharmaceuticals from hospital wastewater with eutectic solvents and terpenoids: Computational, experimental, and simulation studies

Diego Rodríguez-Llorente^a, Elisa Hernández^b, Pablo Gutiérrez-Sánchez^a, Pablo Navarro^b, V. Ismael Águeda^a, Silvia Álvarez-Torrellas^a, Juan García^a, Marcos Larriba^{a,*}

^a Catalysis and Separation Processes Research Group (CyPS), Department of Chemical Engineering and Materials, Complutense University of Madrid, Avda. Complutense s/n, 28040 Madrid, Spain

^b Department of Chemical Engineering, Autonomous University of Madrid, C/Francisco Tomás y Valiente 7, 28049 Madrid, Spain

ARTICLE INFO

Keywords:

Terpenoids
Eutectic solvents
Pharmaceuticals
Hospital wastewater
Liquid–liquid extraction
COSMO-RS

ABSTRACT

The presence of pharmaceuticals in wastewater, mainly in hospital wastewater, is a serious environmental concern, as they are not removed by conventional processes in wastewater treatment plants and are discharged into the natural environment. This work proposes extracting drugs from hospital wastewater using natural, renewable, and non-toxic solvents such as terpenes and eutectic solvents. First, molecular simulation has been used with the COSMO-RS method performing a massive screening of 43 terpenes, 11 eutectic solvents, and 5 conventional solvents with 31 common pharmaceuticals. The most promising solvents in the screening have been chosen to extract 11 pharmaceuticals simultaneously. Experimental tests with ultrapure water and real hospital wastewater matrices showed a strong influence of pH and matrix on extraction. Under the optimal conditions, global pharmaceutical extraction yields with carvacrol of 94.16 % and the eutectic solvent thymol + dodecanoic acid of 96.86 % were obtained. The regeneration and reuse of both solvents were studied in 5 consecutive stages, showing the carvacrol's high stability and regenerability. Using carvacrol, countercurrent extraction tests showed a fast mass transfer of pharmaceuticals and high extraction yields using low solvent-to-feed (S/F) ratios. The predictions obtained with COSMO-RS were similar to the experimental results, confirming the reliability of this method for selecting alternative solvents for the extraction of pharmaceuticals. Finally, the drug removal process was simulated in a countercurrent extraction. The complete removal of pharmaceuticals from hospital wastewater could be achieved using carvacrol with an S/F of 2.00 at pH 4.00 in an extractor with six equilibrium stages.

1. Introduction

Research on wastewater has grown exponentially over the years [1]. Pharmaceuticals are among the potential micropollutants that have been measured in wastewater and the environment. Concentrations present in the environment can already affect biota [2]. In conventional wastewater treatment plants, part of their removal is achieved in the biological reactors of the secondary treatment. However, they are discharged into the natural environment due to their wide variety, low concentration, and refractory behaviour [3]. Hospital wastewater can contribute more than half of the discharge contribution of pharmaceuticals to domestic wastewater, and concentrations in hospital

wastewater can be 4 to 150 times higher [4].

Since conventional water treatment is not adapted for their removal, specific treatments for hospital wastewaters should be developed, focusing efforts on eliminating pharmaceuticals, viruses, and antibiotic-resistant microorganisms. This way, specific treatments could be applied, and the dilution of pharmaceuticals could be avoided [5,6]. Numerous techniques are currently being studied to eliminate pharmaceuticals from wastewater. Improved biological processes have been proposed [7,8], also using microalgae [9]. Also, oxidation processes such as ozonation [10], persulfate oxidation [11], photocatalysis [12–14], membrane processes [15], and other advanced oxidation processes [16–20]. In addition, separation processes such as adsorption

* Corresponding author.

E-mail address: marcoslarriba@ucm.es (M. Larriba).

<https://doi.org/10.1016/j.cej.2022.138544>

Received 27 May 2022; Received in revised form 11 July 2022; Accepted 5 August 2022

Available online 8 August 2022

1385-8947/© 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

[21–23] or filtration [4,24] have also been developed. On the other hand, liquid–liquid extraction is a widely established operation in the pharmaceutical industry to separate pharmaceuticals [25]. The major problem with this technique is using some hazardous conventional solvents, which are toxic, dangerous and environmentally unfriendly. Therefore, a search for alternative solvents has been undertaken. These include the use of ionic liquids [26–28], and more recently, the application of eutectic solvents [29–34]. As the release of pharmaceuticals into the environment can cause risks to human health and aquatic environments [35], this work has sought to develop a technology to remove drugs from hospital water by liquid–liquid extraction. Hydrophobic solvents of natural origin, such as terpenoids and terpenoid-based eutectic solvents, have been selected to increase the sustainability of the proposed process.

Eutectic solvents are two or more chemicals with a melting point depression caused by hydrogen bonding interactions between the hydrogen bond acceptor and donor [36–38]. The selection of the components of the mixture can tune their physicochemical properties. Eutectic solvents have been investigated given their advantageous characteristics of easy preparation for their application in numerous research fields such as analytical chemistry [39], development of new materials [40,41], use as reaction media [42,43], and separation and extraction processes [44–47]. Using natural compounds in their formulation has been considered to develop more sustainable processes by reducing toxicity and price and increasing biodegradability [48–51]. Among them, terpenes have been used to form hydrophobic eutectic solvents [52–60] due to the asymmetric polarity of many of them, giving rise to type V eutectic solvents [61,62].

Terpenes and terpenoids are nature's most diverse plant-derived compounds [63]. Their use would have a fewer environmental impact, improved safety and renewable nature compared to petroleum-derived solvents [54,64]. Because of their hydrophobic character, these solvents have been employed in the extraction of lipids, carotenoids and phenolic compounds from food products [65,66] and microalgae [67,68], volatile fatty acids [69], alcohols [70,71], and phenols [72,73] from aqueous solutions. In some cases, better results are obtained with pure terpenes than by forming eutectic solvents or comparing them with conventional solvents [45]. Although they can be competitive solvents, as they have high production and demand [54], research on the extraction of organic compounds using pure terpenes and terpenoids is still scarce [45].

For solvent selection, the COSMO-RS method [74,75] is a valuable tool for solvent screening, including eutectic solvents [61]. Among others, solubility information and extraction yields can be predicted. The aim of this work is the application of terpenes and terpene-based eutectic solvents for the extraction of drugs from hospital wastewater. A massive simulation of drugs with terpenes, eutectic solvents and conventional solvents was first carried out with COSMO-RS, predicting the types of interaction between solutes and solvent. Subsequently, the extraction with the most promising solvents of selected drugs per type of pharmaceutical has been tested, analysing the influence of the hospital wastewater matrix, drug concentration, pH, and solvent-to-feed ratio. To check the feasibility of the process, solvent reuse and regeneration tests have been carried out and their use in countercurrent extraction. Hence, this work shows the applicability of terpenes and eutectic solvents in the extraction of pharmaceuticals from hospital wastewater.

2. Experimental Section

2.1. Solvent screening with molecular simulation

Turbomole 7.4 software with COSMO continuum solvation method was used to optimise the geometries of the compounds with a BP86/TZVP computational level using the solvent effect. The optimisation was performed by a single-point calculation to obtain the geometry of minimum energy, and the information was easily stored in a *.cosmo file.

Table 1

Macroscopic characterisation of the raw hospital wastewater [80].

Parameters	Value
Chemical Oxygen Demand (mg/L)	332
Total Organic Carbon (mg/L)	111
TOC/COD ratio	0.33
Total Nitrogen (mg/L)	90.1
CO ₃ ²⁻ (mg/L)	365.5 ^a
Conductivity at 20 °C (μS/cm)	2360

^a Calculated from Total Inorganic Carbon measurement.

The obtained COSMO files were introduced in COSMOtherm software [76], version 19.0.4. The thermodynamic behaviour of the equimolar binary mixtures containing the pharmaceutical compounds and the different solvents was analysed by means of the excess enthalpies at 298.2 K as reference. Excess enthalpies have been calculated for 31 commonly used pharmaceuticals in 43 terpenoids, 11 terpenoid-based eutectic solvents, and 5 conventional organic solvents. The most promising solvents will be selected from the obtained values of excess enthalpies to extract drugs from hospital wastewater. The more negative the value of the excess enthalpy, the higher the affinity of the drug for the solvent, and the higher the extraction yields of the drug can be achieved experimentally. As shown in eq. (1), this excess enthalpy was further detailed in its three contributions (hydrogen bond, van der Waals forces, and electrostatic or misfit interactions):

$$H^E = H^E(H_{bond}) + H^E(VdW) + H^E(Misfit) \quad (1)$$

The particular case of eutectic solvents, composed of a binary mixture of compounds, was computed as a mixture at the molar composition of the eutectic point of hydrogen bond acceptor and donor compounds [57,77], as used in previous works [69,73,78,79].

2.2. Chemicals

Three terpenoids (eucalyptol, thymol and carvacrol), three eutectic solvents (thymol + octanoic (C₈OOH), decanoic (C₁₀OOH) and dodecanoic (C₁₂OOH) acids), and two conventional solvents (methyl isobutyl (MIBK) ketone and diisopropyl ether (DIPE)) have been used in extraction tests for the removal of pharmaceuticals from aqueous solutions. The 11 pharmaceutical compounds employed in the experimental study are 5 analgesics (acetaminophen, diclofenac, ibuprofen, naproxen, and phenazone), 1 antidepressant (carbamazepine), 4 antibiotics (sulfamethoxazole, tetracycline, ciprofloxacin, and trimethoprim), and 1 blood pressure regulator (atenolol). In Table S1 of the Supplementary Material suppliers, purities, CAS numbers, structures and physical properties of the chemicals employed in this work are collected. To prepare the eutectic solvents, the hydrogen bond acceptor and donor were gravimetrically added and stirred in a thermostatic bath MultiMix BHM9E OVAN at 323.2 K until a homogeneous liquid appeared. The eutectic solvents were prepared considering the eutectic point composition previously reported in the literature: a mole fraction of 0.33, 0.44, 0.56 of thymol in thymol + C₈OOH, thymol + C₁₀OOH, thymol + C₁₂OOH eutectic solvents, respectively [77]. In addition, ultrapure water was obtained from a Purelab flex Elga Veolia water purification system. Hospital wastewater effluent was collected from a hospital in the southern region of Madrid (Spain). This hospital has a size of 400 hospital beds and 2200 workers. In order to extrapolate the results obtained in this work with the results that would be obtained using other hospital wastewater as matrices, the effect of pH and initial concentration of pharmaceuticals, which would be the variables that could most affect the extraction yields, have been studied in depth. The macroscopic characterisation of the hospital wastewater employed is collected in Table 1 [80].

2.3. Liquid-liquid extraction of pharmaceutical compounds from aqueous solutions

A multicomponent aqueous solution of the 11 pharmaceutical compounds (acetaminophen, atenolol carbamazepine, ciprofloxacin, diclofenac, ibuprofen, naproxen, phenazone, sulfamethoxazole, tetracycline, and trimethoprim) with a concentration of 5 mg/L each was prepared using ultrapure water as the matrix. Additionally, 5 and 50 mg/L solutions were prepared using the hospital wastewater matrix to analyse the effect of initial concentration on extraction yields. The pH was measured using a 2002 pH meter (Crison), being 6.65 for the aqueous solution in ultrapure water and 7.75 for the ones in hospital wastewater at pH 7.75. Additionally, pH was adjusted using HCl 37 % for hospital wastewater matrix solutions with concentrations of drugs of 5 mg/L, obtaining solutions of pH 4.00 and 6.65 to study the effect of pH in the extraction process.

Pharmaceutical extraction was then performed at 7 different solvent-to-feed ratios (S/F) in volume of 0.05, 0.10, 0.25, 0.50, 1.00, 2.00 and 3.00. The feed and the solvents were stirred at 800 rpm in vials of 8 mL in a dry bath for 12 h at 323.2 ± 0.5 K and atmospheric pressure to ensure equilibrium. The separation of the phases was done for 12 h at 323.2 ± 0.5 K without stirring. Phase separation is then conducted with glass Pasteur pipettes to obtain the raffinate and the extracts.

Raffinates were analysed by HPLC Agilent System 1260 Infinity II with UV-Vis Diode Array Detector with a column Poroshell 120 EC- (4.6×150 mm, $4 \mu\text{m}$). The column oven temperature was set a 40°C , and it was used a 60 mm flow cell in the DAD. Mobile phase flow rate was 0.9 mL/min, using acetonitrile and acidified water (acetic acid 75 mM). The mobile phase compositions employed in the analysis were a gradient from 98 % acidified water to 94 % in 11 min, 94 % acidified water for 22 min, then a gradient to 80 % acidified water in 12 min, and 40 % acidified water for 10 min. Then the mobile phase was set to 98 % acidified water for 7 min to ensure column equilibrium for the subsequent analysis. All pharmaceutical compounds were measured at a wavelength of 275 nm, except acetaminophen at 230 nm.

2.4. Scale-up, solvent reuse, and regeneration.

Carvacrol and thymol + C_{12}OOH eutectic solvent were selected for solvent reuse studies. In these experiments, extract phases from the first extraction stage were then reused in a subsequent extraction with a new drug feed solution, using them in 5 stages. Feed solutions of 5 mg/L of each drug were used, with hospital wastewater matrix at initial pH of 4.00, and using with both solvents the S/F ratios in volume of 0.50 and 2.00. The extraction was performed in a thermostatic bath with magnetic stirring model MultiMix BHM9E OVAN at 323.2 ± 0.5 K at 800 rpm stirring speed. Raffinates were analysed by HPLC as described previously.

After five solvent reuse cycles, the extract phases were regenerated through vacuum distillation in an R-200 rotary evaporator (Büchi) at 437.2 K and 20 mbar. After 2 h, distillates and residues were obtained. The distillates were employed in an additional extraction stage to check the regenerated solvent's performance. Additionally, to ensure the solvents' stability, Attenuated Total Reflection with Fourier Transform Infrared (ATR-FTIR) spectra were obtained of pure solvents, stage 5 extracts, distillates, and residues between 500 and 4000 cm^{-1} in a Nicolet iS50 spectrometer with SpectraTech ATR Performer. Furthermore, thermogravimetric analyses (TGAs) were conducted in TGA-LABSYS evo DTA/DSC equipment with a heating rate of 10 K/min from 303.2 to 1073.2 K, under a He atmosphere with a flow rate of 30 mL/min, to verify thermic stability after reuse and regeneration processes.

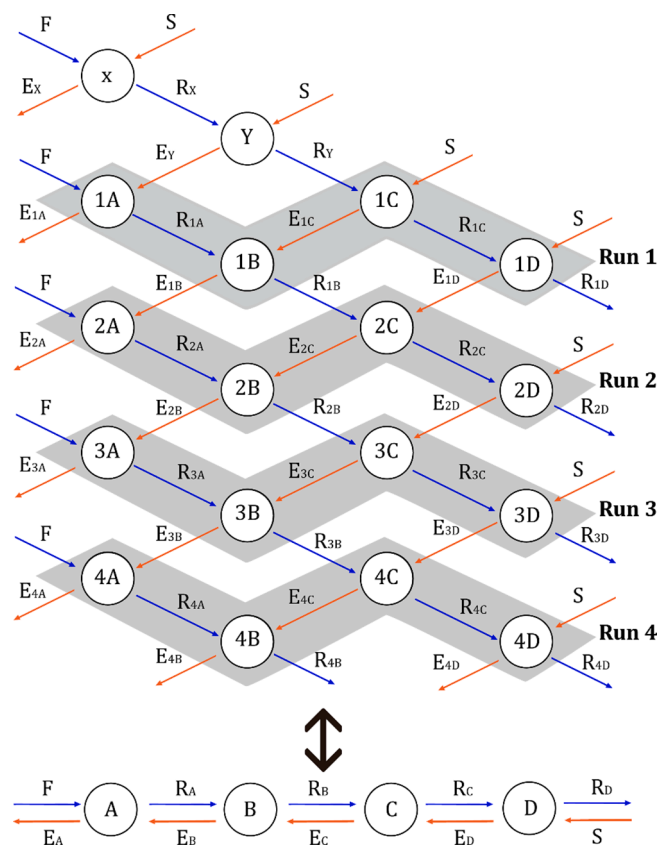


Fig. 1. Batch Simulation of Multistage Countercurrent Extraction (BSMCE) of 4 Stages and 4 runs.

2.5. Experimental batch simulation of multistage countercurrent extraction

To study the feasibility of the process at a larger scale, countercurrent extraction simulations were performed. Carvacrol was selected for these studies for being suitable for regeneration and liquid at room temperature (298.2 K). Firstly, an experimental Batch Simulation of Multistage Countercurrent Extraction (BSMCE) was performed. The process consists of a series of crosscurrent extractions to reproduce feed in each extraction stage. A BSMCE of 4 stages is illustrated in Fig. 1. Each run (grey area) approximates a multistage countercurrent extraction. An infinite number of runs would be necessary to reproduce the countercurrent extraction precisely. Nevertheless, 4 runs are sufficient to obtain a very close result [81,82]. This work has tested the extraction of pharmaceutical compounds using carvacrol at S/F in volume of 0.25, with BSMCE of 2, 3, and 4 stages and 4 runs each, as described in Fig. S1 and S2 of Supplementary Material, and Fig. 1, respectively. Feed solutions of 5 mg/L of each pharmaceutical compound were used, with a hospital wastewater matrix and initial pH of 4.00 at an S/F ratio in volume of 0.25. The extractions were carried out for 12 h at 800 rpm stirring speed at room temperature (298.2 K), as carvacrol is liquid in these conditions. The separation of the phases was done for 12 h at room temperature without stirring. Every raffinate of each run and extraction stage was analysed by HPLC as described previously.

2.6. Simulation of countercurrent extraction with Kremser method

Countercurrent extraction simulations have also been carried out using the Kremser method [83]. The Kremser method is based on experimental data since the experimental distribution ratios of all components are required to calculate the extraction factor (E_i) and the reciprocal of E_i (U_i). Distribution coefficients obtained in a packed

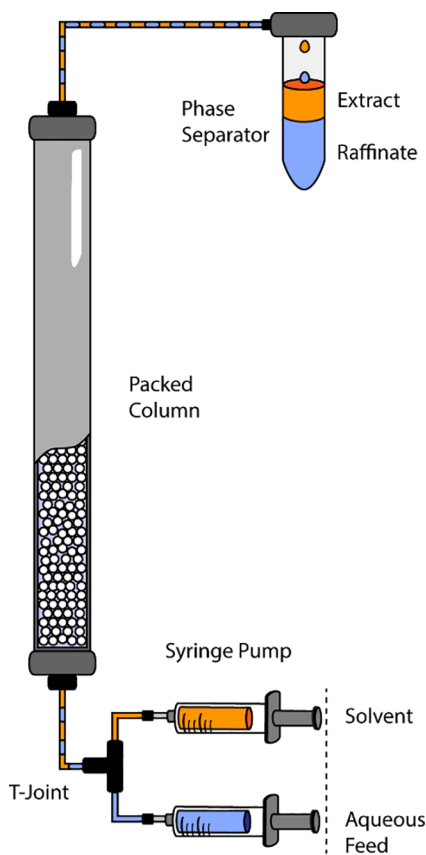


Fig. 2. Scheme of parallel liquid-liquid extraction of pharmaceutical compounds using a packed column.

column were used to simulate a countercurrent extraction by the Kremser method. A column of 8 mm internal diameter and 80 mm length was used, filled with a bed of glass spheres of 2 mm diameter. A total flow rate of 10 mL/h of the sum of solvent and drug feed was set using KDS 100 Legacy syringe pumps (Fisher Scientific) at an S/F ratio of 0.25 at room temperature (298.2 K) as with BSMCE. After extraction, phase separation was allowed in a decanter. The scheme of the installation is shown in Fig. 2. After this, the raffinate was measured in HPLC with the method described previously. The water content in the extract was additionally measured by Mettler Toledo DL 32 Karl Fisher Coulometer. The distribution coefficients obtained were used to obtain extraction yields by the Kremser method implemented in Microsoft Excel with iterative calculation, obtaining extraction yields using 2 to 6 countercurrent extraction stages.

2.7. COSMO-RS ad hoc validation and final use to explore massive pharmaceuticals' extraction

To validate the predictions of the COSMO-RS method, a liquid-liquid extraction calculation was performed using COSMOtherm. For this purpose, a first phase (S) containing pure solvent (carvacrol and thymol + fatty acids eutectic solvents) was specified, while the second feed phase (F) consisted of the pharmaceutical compound at the desired concentration (5 mg/L) and water. The S/F ratio was adjusted by changing the total mass of the S phase while the total mass of phase F is 1000 g. The concentration of pharmaceutical compounds recovered in the solvent was used to calculate the extraction yield related to the initial concentration designated in the F phase.

Recovery results obtained from COSMO-RS predictions were compared with those experimentally obtained, analysing the differences to infer the concentrations and pharmaceuticals that COSMO-RS can

model for extraction purposes. After validating COSMO-RS predictions of the recoveries, the extraction of the complete list of pharmaceuticals at an initial concentration of 1 mg/L is evaluated to draw a broader scope in the use of terpenoids and eutectic solvents in the extraction of pharmaceuticals from hospital wastewater.

3. Results and discussion

3.1. Molecular simulation solvent screening with COSMO-RS

An exhaustive list of the 31 most common drugs found in hospital wastewater has been selected at the molecular simulation level to choose the most suitable solvents for their extraction [3,84]. Different types of pharmaceuticals have been selected for the molecular simulation: analgesics (acetaminophen, diclofenac, ibuprofen, morphine, naproxen, phenazone, tramadol), antidepressants (carbamazepine, citalopram, fluoxetine, venlafaxine), antibiotics (amoxicillin, azithromycin, ciprofloxacin, clarithromycin, erythromycin, norfloxacin, ofloxacin, sulfadiazine, sulfamethizole, sulfamethoxazole, tetracycline, trimethoprim, clindamycin), and blood pressure regulators (atenolol, furosemide, gemfibrozil, metoprolol, propranolol, sotalol, valsartan).

The solvents considered comprise 43 terpenes, 11 eutectic solvents, and 5 conventional solvents. The σ -profiles of the compounds used in the calculations are listed in Figs. S6-S19 of Supplementary Material. The σ -profiles present the histogram of the polarised charge distribution on the electronic surface of molecules. In the σ -profiles, different regions can be distinguished depending on the values of the polarised charge density σ . The hydrogen bond donor segments region ($\sigma < -0.0082 \text{ e } \text{\AA}^{-2}$), the non-polar region ($-0.0082 \text{ e } \text{\AA}^{-2} < \sigma < 0.0082 \text{ e } \text{\AA}^{-2}$), and the hydrogen bond acceptor region ($\sigma > 0.0082 \text{ e } \text{\AA}^{-2}$) [85,86].

It is expected that compounds with intense segments in the non-polar region are best extracted with solvents with equivalent peak distribution. On the other hand, if the drugs have hydrogen bond donor groups, they would have a higher affinity for solvents with hydrogen bond acceptor groups and vice versa. In the σ -profiles obtained with the drugs, group segments can be seen in all three regions. However, it is worth mentioning that the hydrogen bond acceptor groups are in the majority compared to the donors and of high intensity. Therefore, solvents with hydrogen bond donors groups are expected to have a higher affinity for the drugs.

The σ -profiles have been used to calculate excess molar enthalpies (H^E) in equimolar mixtures of drugs and solvents. The results of the excess enthalpies obtained are given with terpenes in Fig. 3, eutectic solvents in Fig. 4, and conventional solvents in Fig. 5.

Excess enthalpies make it possible to define solvents with the highest affinity for solutes, similarly to using activity coefficients at infinite dilution. Additional information can be obtained on what interactions lead to this affinity. Exothermic mixture values would imply more affinity of compounds for solvents, whereas endothermic H^E values would cause worse extraction yields. These trends can be coupled with activity coefficients when the entropic contribution has a non-dominant role, as is the case here reported.

The H^E calculation results show that many solvent-drug pairs lead to exothermic mixtures with terpenes. Terpenes containing heteroatoms in their structure (in particular oxygen) result in the lowest H^E . On the other hand, terpenes without heteroatoms such as pinene or limonene exhibit endothermic mixtures. Among the drugs with the highest endothermic mixtures are furosemide, sulfamethoxazole, sulfadiazine and sulfamethizole, as opposed to drugs with the most exothermic mixtures such as clarithromycin or fluoxetine. Thymol and carvacrol stand out as the two terpenes with the lowest H^E values. They are followed by verbenone and eucalyptol. Thymol and carvacrol have strong hydrogen bond donor segments, making the molecular simulation of excess enthalpies lower than other compounds. Thymol, carvacrol and eucalyptol have been selected for the experimental extraction trials due to the promising H^E results with all drugs. Eucalyptol has been chosen

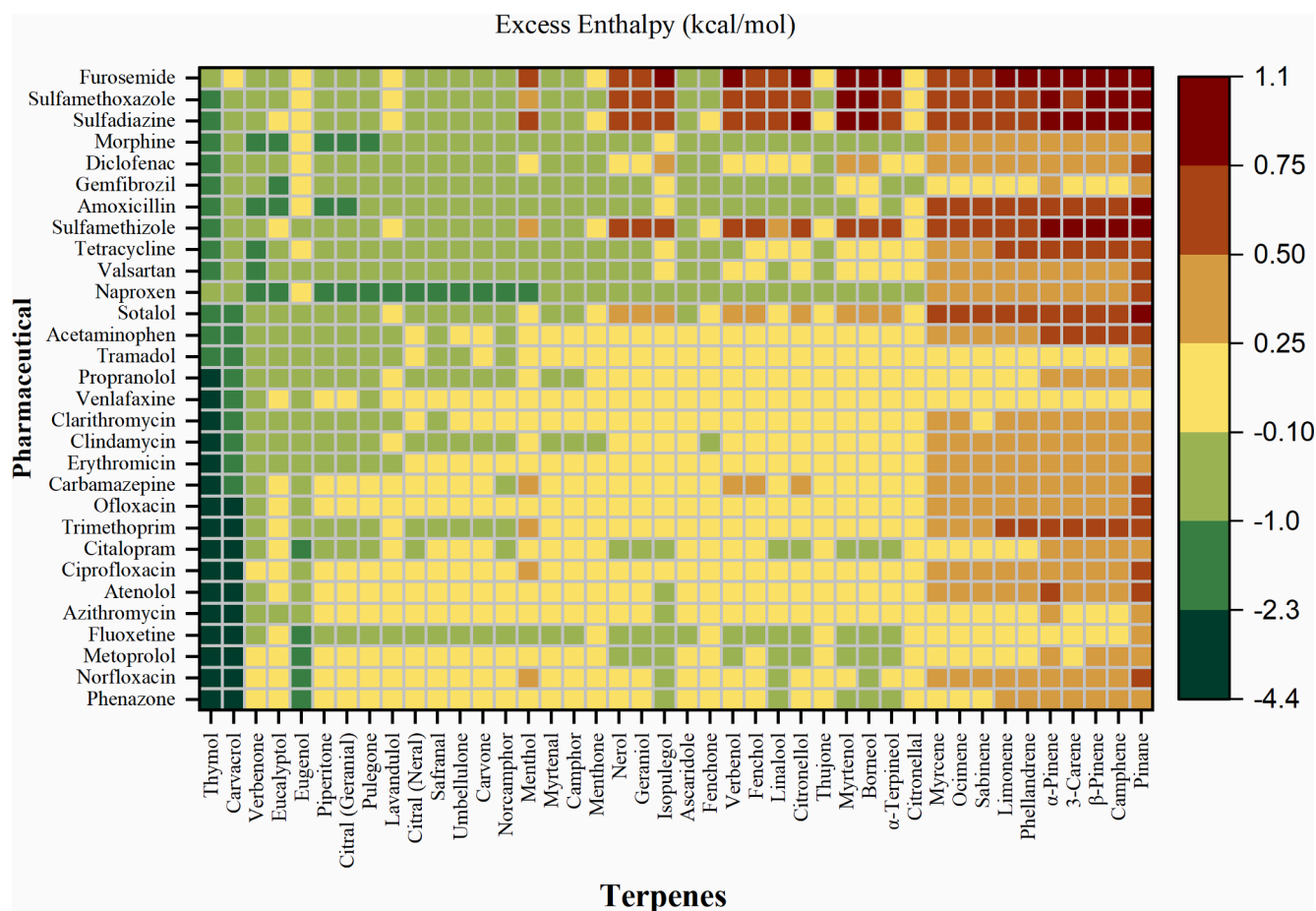


Fig. 3. Excess enthalpies in equimolar composition between terpenes and pharmaceutical compounds at 298.2 K.

over verbenone as it gives close enthalpy results and has a lower price, being 8–10 \$/kg [87] versus greater than 40 \$/kg [88] of verbenone.

As for the eutectic solvents, most of them result in exothermic mixtures, except for the eutectic solvent menthol + borneol. The eutectic solvents formed with thymol are the ones that obtain the lowest H^E , the most promising being those formed with thymol and fatty acids. The higher the alkyl chain, the lower the H^E obtained. This case is reversed for the menthol + fatty acids eutectic solvents, where the lowest H^E values are obtained for menthol + C_8OOH . Considering the H^E estimations, the three thymol + fatty acids eutectic solvents were chosen for the experimental tests.

Conventional solvents obtain exothermic H^E values with DIPE, ethyl acetate, and MIBK. In contrast, endothermic mixtures are obtained with *n*-heptane and toluene. The most promising solvents are DIPE and ethyl acetate, which were selected for experimental studies to compare them with terpenes and eutectic solvents. The obtained H^E estimation results show that natural solvents would have a higher affinity for drugs than conventional solvents.

With the selected solvents carvacrol, eucalyptol, thymol, thymol + C_8OOH , thymol + $C_{10}OOH$, thymol + $C_{12}OOH$, ethyl acetate and DIPE, H^E contributions from equation (1) have been decomposed for one of the drugs in each type in Fig. 6 for acetaminophen (analgesic), and in Supplementary Material Fig. S3 for atenolol (blood pressure regulator), Fig. S4 for carbamazepine (antidepressant), and Fig. S5 for ciprofloxacin (antibiotic).

The results show that the most significant contributions in the case of carvacrol, thymol and the eutectic solvents with thymol are due to H^E of hydrogen bond type interactions. The importance of these interactions has been seen when using ionic liquids [89] and eutectic solvents [90] to solubilise pharmaceuticals. In addition, contributions favour exothermic

mixtures due to electrostatic-misfit interactions. On the other hand, Van der Waals force interactions are low but would have the opposite effect with positive H^E values. Eucalyptol and DIPE behave similarly, where electrostatic-misfit interactions, in this case, lead to positive values.

3.2. Experimental pharmaceutical extraction with terpenoids, eutectic, and conventional solvents

The pollutants that have been used in the experimental studies by type of pharmaceutical are analgesics (acetaminophen, diclofenac, ibuprofen, naproxen, phenazone), antibiotics (ciprofloxacin, sulfamethoxazole, tetracycline, trimethoprim), antidepressants (carbamazepine), and blood pressure regulators (atenolol). Extractions from aqueous solutions have been performed using ultrapure water and a hospital wastewater matrix. In all cases, seven different S/F ratios in volume have been studied in each operating condition and with each solvent used. Extraction yields for each drug have been calculated using the concentrations in the raffinate before and after extraction, according to the following equation:

$$Yld_i(\%) = \frac{C_{i,0}^{aq} - C_i^{aq}}{C_{i,0}^{aq}} 100 \quad (2)$$

where ($C_{i,0}^{aq}$) is the initial concentration of pharmaceutical compound *i* in the aqueous feed and (C_i^{aq}) the concentration in the raffinate phase after the extraction. In addition, a global drug extraction yield has been calculated, considering the 11 drugs, according to the following equation:

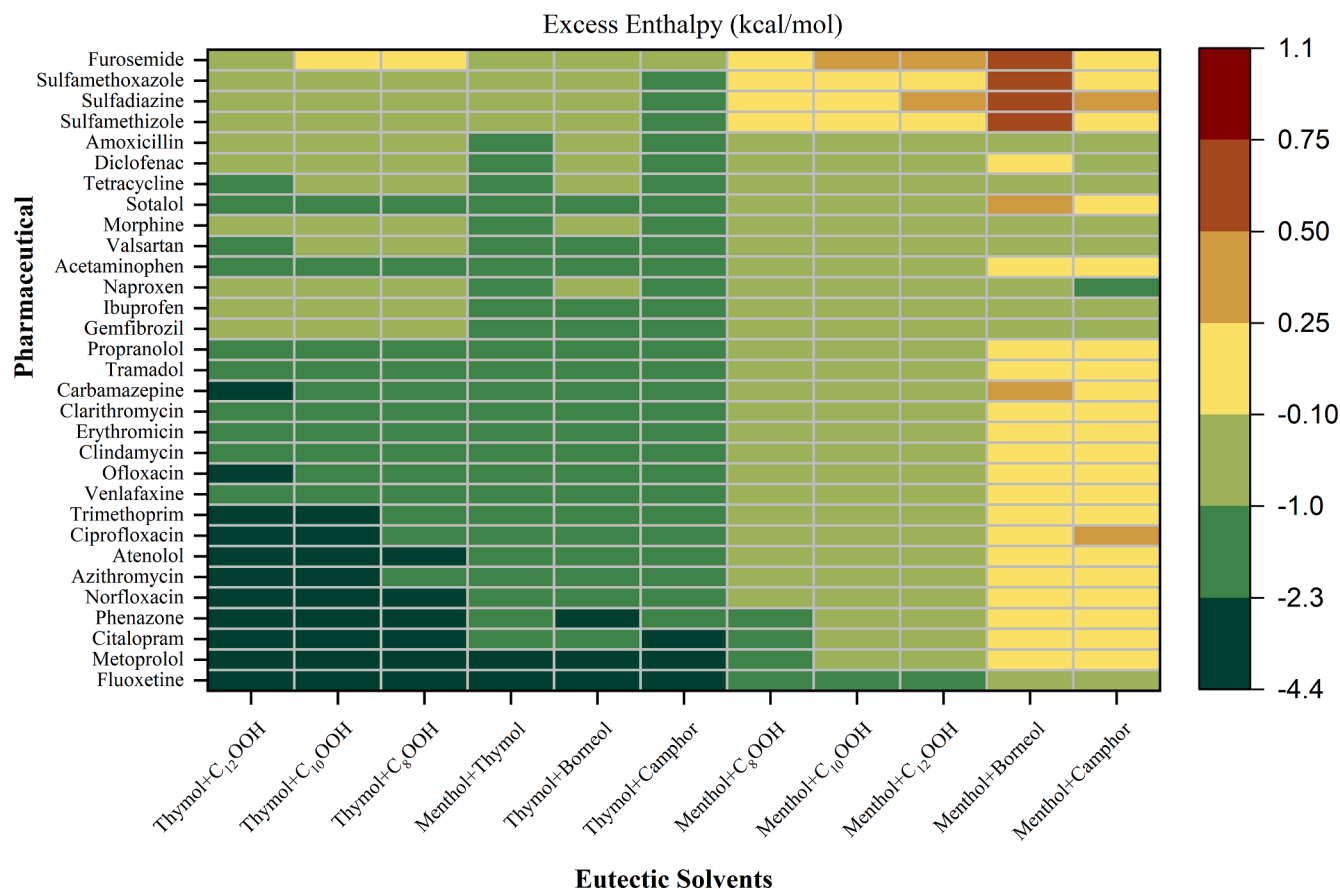


Fig. 4. Excess enthalpies in equimolar composition between eutectic solvents and pharmaceutical compounds at 298.2 K.

$$Yld_{Global}(\%) = \frac{\sum_i^{11} (C_{i,0}^{aq} - C_i^{aq})}{\sum_i^{11} (C_{i,0}^{aq})} 100 \quad (3)$$

Extraction yields have also been calculated grouping the drugs by types (analgesics, antibiotics, antidepressants, and blood pressure regulators), using the following equation:

$$Yld_{type}(\%) = \frac{\sum_i^{n_{type}} (C_{i,0}^{aq} - C_i^{aq})}{\sum_i^{n_{type}} (C_{i,0}^{aq})} 100 \quad (4)$$

where (n_{type}) is the number of pharmaceutical compounds of each type. To better analyse the results, they will be discussed in figures, but the complete data obtained are shown in Tables S3-30 of [Supplementary Material](#).

3.2.1. Extraction using ultrapure water matrix

Fig. 7 shows the results of global extraction yields using the ultrapure water matrix with the terpenoids carvacrol, thymol and eucalyptol, eutectic solvents thymol + C₈OOH, thymol + C₁₀OOH, thymol + C₁₂OOH, and the conventional solvents ethyl acetate and DIPE.

Thymol and carvacrol present the highest extraction yields among the terpenoids at all S/F ratios, as predicted by molecular simulation with COSMO-RS. Thymol obtains better extraction yields at low S/F ratios of 0.05 and 0.25. However, carvacrol outperforms it at the highest S/F ratios. It would also have the advantage over thymol of being liquid at room temperature since the melting point of thymol is 48 °C while carvacrol is 1 °C.

Regarding the eutectic solvents formed by thymol and the carboxylic acids, molecular simulations showed that the larger the alkyl chain of the acid, the higher the extraction yields. This trend is also shown in the experimental extraction results, with the highest results for the eutectic solvents formed by C₁₀OOH and C₁₂OOH, although the values are

almost coincident.

The eutectic solvents and the terpenoids carvacrol and thymol perform better than both conventional solvents at the different S/F ratios studied. Within the natural solvents, the eutectic solvents thymol + C₁₂OOH, and thymol + C₁₀OOH performed better than the pure terpenoids. This may be related to lowering the pH due to the slight dissolution of acids in the aqueous phase, as observed in previous work [34]. The effect of pH will be deeper studied in [Section 3.2.2](#). The extraction yields with ethyl acetate are superior to those for DIPE. With the predictions of the molecular simulations, DIPE comes out worse than the natural solvents, but this is not the case for ethyl acetate, which obtains high extraction yields.

It should be mentioned that extraction results above 60 % are obtained with the natural solvents despite using a low S/F ratio of 0.05, showing the pharmaceutical compounds' high affinity for the selected solvents. At an S/F ratio of 1.00, extraction results higher than 90 % are achieved with the three eutectic solvents and carvacrol.

The extraction results have also been divided by type of drugs in [Fig. 8](#), which shows the results of extractions in ultrapure water matrix at an S/F ratio of 1.00. Among the compound types, antibiotics achieve almost complete elimination using this S/F ratio, except when DIPE and eucalyptol are used as solvents. With carvacrol, thymol, and eutectic solvents, the lowest extraction yields are obtained for analgesics, mainly due to extraction yields for acetaminophen and naproxen.

In the case of DIPE and eucalyptol, low extraction yields are obtained for blood pressure regulators and antibiotics, the latter due to lower extraction yields for tetracycline and trimethoprim. This was also expected from the molecular simulation by COSMO-RS, where both solvents showed lower excess enthalpy values for analgesics than antibiotics.

Although it may have underestimated the performance of ethyl

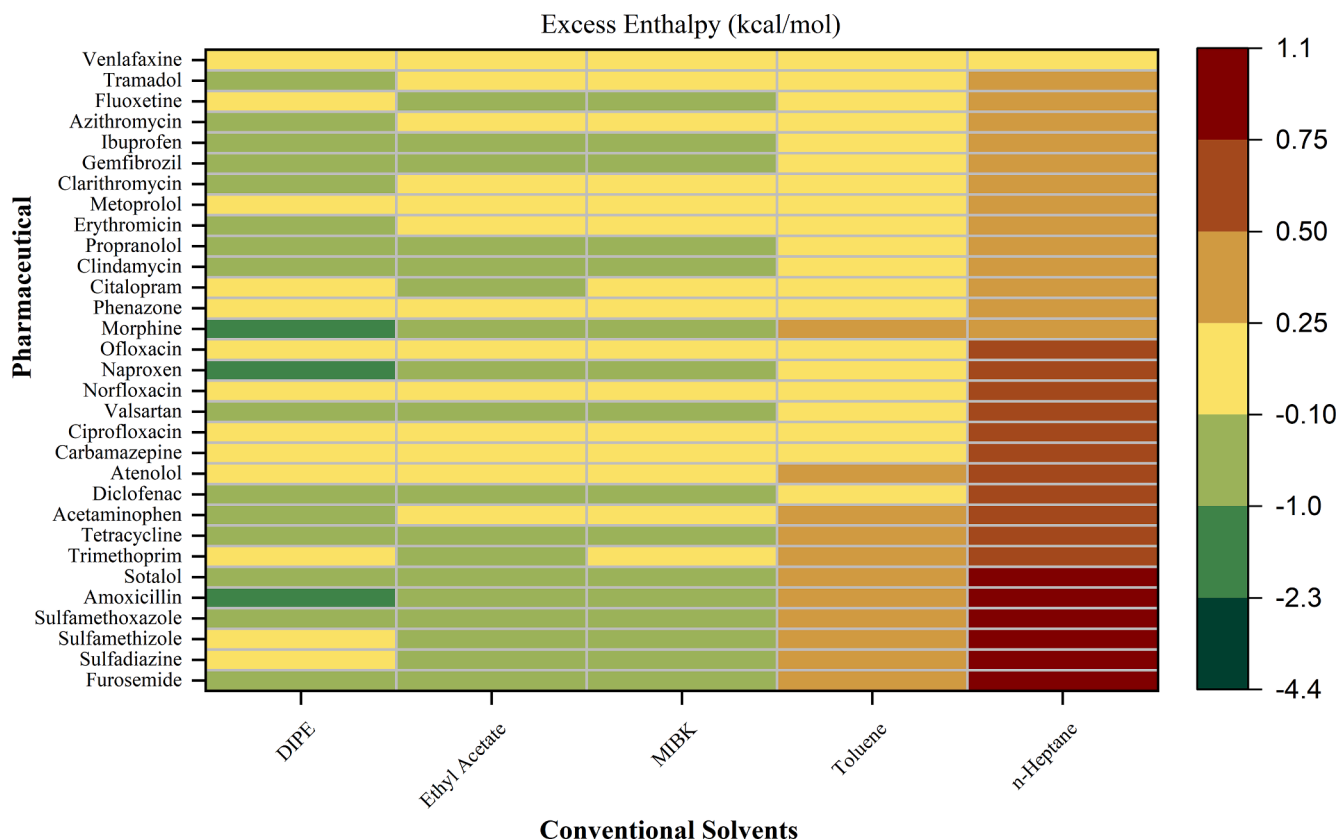


Fig. 5. Excess enthalpies in equimolar composition between conventional solvents and pharmaceutical compounds at 298.2 K.

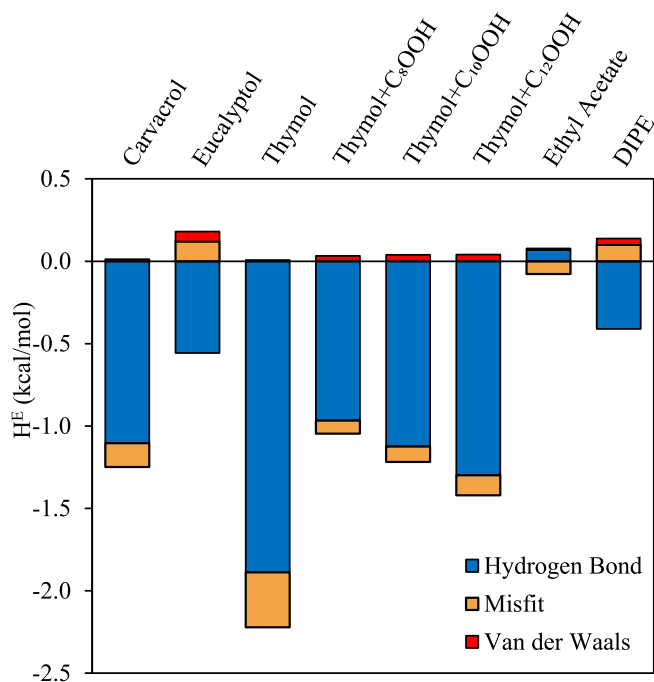


Fig. 6. Excess enthalpies contributions generated by COSMOtherm in equimolar composition between solvents and acetaminophen.

acetate, the molecular simulation by COSMO-RS proves to be a potent screening tool with the ability to predict which solvent and types of pharmaceuticals will extract better.

Due to the results obtained, the three eutectic solvents, thymol,

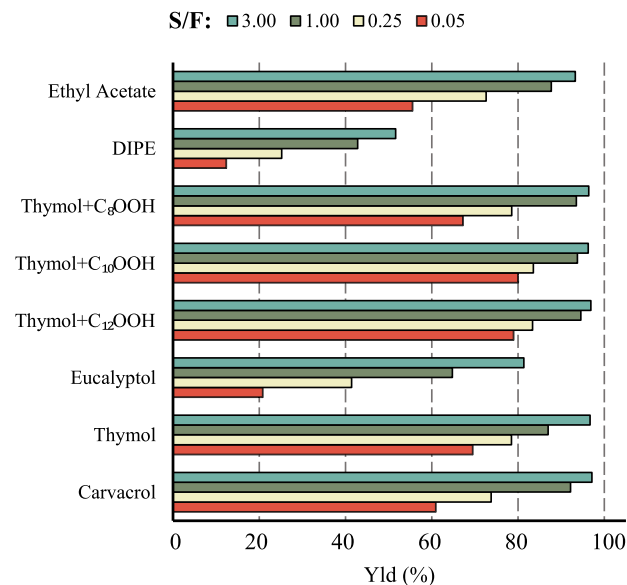


Fig. 7. Global extraction yields of pharmaceutical compounds at different S/F ratios with initial pH of 6.65 and a concentration of 5 mg/L of each drug in an ultrapure water matrix at 323.2 K.

carvacrol, and ethyl acetate have been chosen for the following tests using a hospital wastewater matrix.

3.2.2. Effect of pH

When adjusting the pH of the initial solution for drug extraction, the aim is to ensure that as many compounds as possible are in a neutral state, avoiding charged states that would improve the affinity for water

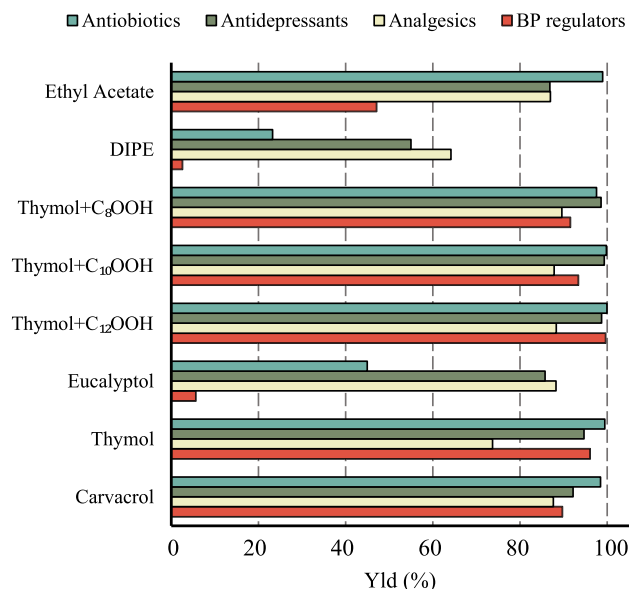


Fig. 8. Extraction yields of per type of pharmaceutical compounds at S/F ratio of 1.00 with initial pH of 6.65 and a concentration of 5 mg/L of each drug in an ultrapure water matrix at 323.2 K.

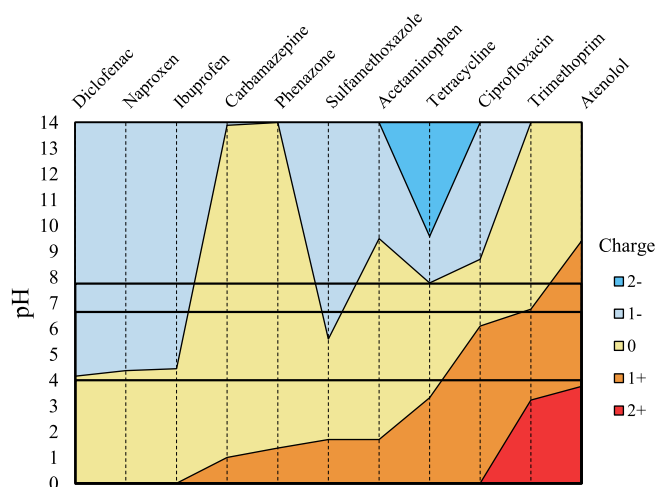


Fig. 9. Distribution of main charged form of pharmaceutical compounds as a function of pH. Solid horizontal lines are the pHs of the feeds used in this work.

[34]. For this purpose, the protonation equilibria of the different compounds must be considered, which are listed in Table S2 of Supplementary Material [91–93]. In addition, in Fig. 9, the areas of charge change of the compounds as a function of pH have been plotted, being the pKas the limits between these areas.

At the initial pH of 6.65, several drugs were found in the positively charged region, such as diclofenac, naproxen, ibuprofen, and sulfamethoxazole. This fact might explain the low extraction yields of these compounds in the previous section. pH 4.00 was chosen to maximise extraction yields, involving most neutral charge areas. However, we anticipated a drop in extraction yields for atenolol as it approaches its pKa of charge shift to 2+. Therefore, it was a trade-off situation.

Fig. 10 shows the results of the extraction yields using carvacrol and an S/F ratio of 1.00 at pH 7.75, 6.65, and 4.00 using hospital wastewater as the matrix. As they approach to their neutral state, a large increase in extraction yields is observed at pH (7.75 / 6.65 / 4.00) for sulfamethoxazole (23.71 / 47.87 / 95.67 %), naproxen (37.96 / 64.04 / 97.85 %), ibuprofen (76.54 / 88.59 / 99.29 %), diclofenac (69.61 / 84.36 / 98.86),

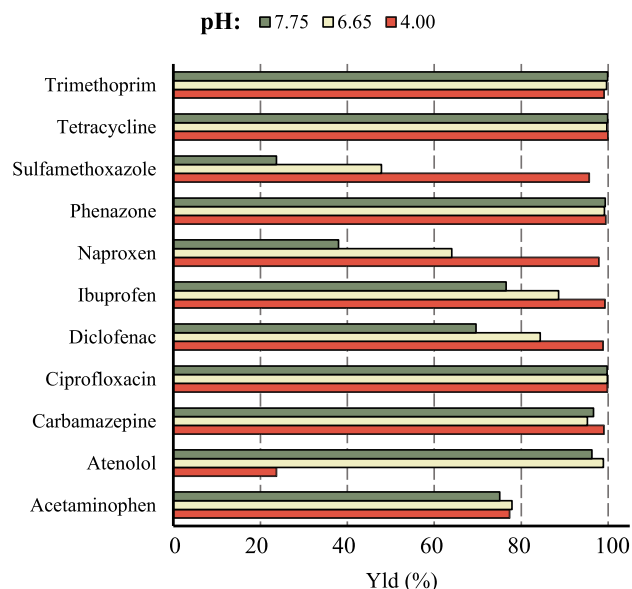


Fig. 10. Individual extraction yields of pharmaceutical compounds using carvacrol at S/F ratio of 1.00 with initial pH of 7.75, 6.65 and 4.00, and a concentration of 5 mg/L of each drug using a hospital wastewater matrix at 323.2 K.

respectively.

The results with tetracycline, phenazone, and carbamazepine were not significantly affected by the pH change as they were in the neutral region at all pHs. Slight increases in yields are seen when lowering pH for acetaminophen, perhaps due to a shift away from its pKa of 9.5.

On the other hand, trimethoprim and ciprofloxacin at high S/F ratios show no significant change in extraction yields, and at an S/F ratio of 1.00, they are entirely removed using carvacrol, as shown in Fig. 10. At lower S/F ratios, a decrease in yields is observed when the pH is lowered. At an S/F ratio of 0.10, trimethoprim goes from an extraction yield of 97.88 to 74.83 % and ciprofloxacin from 96.37 to 72.40 %, with the pH adjustment from 6.65 to 4.00. Consequently, atenolol has the most significant decrease in extraction yield with pH change from 98.88 to 23.68 % at an S/F ratio of 1.00 using carvacrol.

As for the other solvents, the increase in extraction yields of sulfamethoxazole, naproxen, and ibuprofen are also observed with decreasing pH. In the case of the eutectic solvents, the difference in yields with pH is also more remarkable when the alkyl chain of the organic acid is more significant, i.e. with thymol + C₁₂OOH, when comparing results in Tables S12–14 with Tables S17–19, and Tables S27–29 of Supplementary Material. This phenomenon may be due to the solubility of some of the acids in the aqueous solution, which slightly reduces the initial pH of the aqueous phases, as has been observed in our previous work [34]. The shorter the acid alkyl chain, the more soluble the carboxylic acids in the aqueous phase. Therefore, higher extraction yields were obtained with the eutectic thymol + C₈OOH than with thymol + C₁₂OOH at basic pHs, where predominate charged states. Measurements of the raffinate after the extraction process confirm this decrease from pH 6.65 to 4.73, 5.55, and 6.11 for the eutectic solvents thymol + C₈OOH, thymol + C₁₀OOH, and thymol + C₁₂OOH, respectively.

With the remaining solvents, similar trends to carvacrol are obtained in extracting tetracycline, phenazone and carbamazepine. The exception is ethyl acetate, which shows a decrease in the extraction yield of the tetracycline with lower pH, comparing results in Tables S15, S20 and S30 of Supplementary Material.

The drugs trimethoprim, ciprofloxacin, and atenolol, which are the ones that would extract worse at lower pH as in the case of carvacrol, behave in the same way with eutectic solvents. In this case, however, the

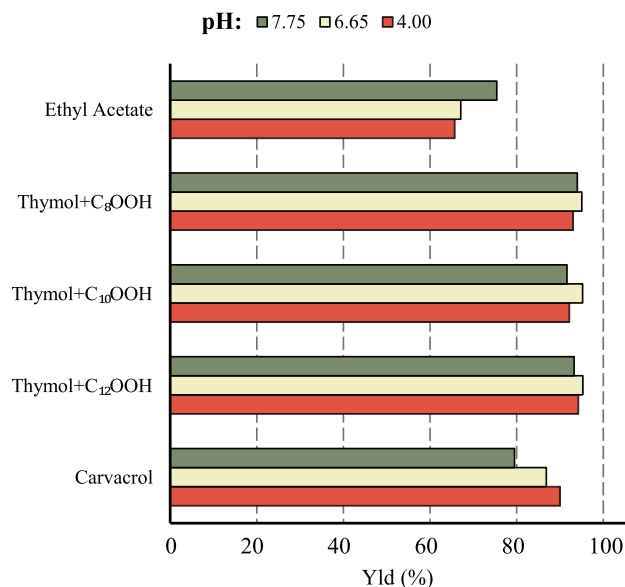


Fig. 11. Global extraction yields of pharmaceutical compounds at an S/F ratio of 1.00 with initial pH of 7.75, 6.65 and 4.00, and a concentration of 5 mg/L of each drug using a hospital wastewater matrix at 323.2 K.

most significant decreases in extraction yields are observed, especially at low S/F ratios, the lower the acid alkyl chain of the fatty acids. A pH reduction of 6.65 to 4.00 results in lower extraction yields for trimethoprim at an S/F ratio of 0.10 with thymol + C₈OOH (93.75 to 74.50 %), thymol + C₁₀OOH (99.89 to 93.16 %), and for thymol + C₁₂OOH (99.33 to 93.89 %). In the case of ciprofloxacin, the lowering of pH from 6.65 to 4.00 reduces the yields at an S/F ratio of 0.10 of thymol + C₈OOH (99.32 to 87.77 %), thymol + C₁₀OOH (99.89 to 92.86 %), and thymol + C₁₂OOH (99.78 to 95.06 %). Finally, with atenolol, they are reduced to a greater extent being at an S/F ratio of 1.00 thymol + C₈OOH (98.54 to 25.98 %), thymol + C₁₀OOH (96.97 to 34.81 %), and thymol + C₁₂OOH (96.76 to 42.16 %).

Previously, it has been shown that part of the fatty acids dissolve in the aqueous phase and decrease the pH, dissolving to a greater extent when the alkyl chain is shorter. This fact favours the extraction of compounds such as sulfamethoxazole, naproxen, and ibuprofen at neutral and basic pHs. At acid pH 4.00, however, it leads to a decrease in the extraction of trimethoprim, ciprofloxacin, and atenolol.

The same is valid for ethyl acetate as carvacrol, whereby the extraction yields of trimethoprim, ciprofloxacin and atenolol decrease with decreasing pH. In the case of atenolol, no significant difference is seen between pH 6.65 and 7.75. However, when the pH is lowered to 4.00, the extraction yields are zero at any S/F ratio when using ethyl acetate.

The results obtained reflect the relevance of pH in the extraction process. Adjusting the pH of the initial solution may favour the extraction of some drugs but worsen others. It is possible to predict through the pK_a values how this change would be and select the pH to maximise an objective, as in this case, increasing the global extraction yield. However, it must be considered how using some solvents or others would affect the pH, as in the case of eutectic solvents where the acid alkyl chain influences to a greater or lesser extent in the pH.

To sum up, global extraction yields at an S/F ratio of 1.00 as a function of the pH of the initial solution of all drugs with ethyl acetate, carvacrol, and the eutectic solvent of thymol + fatty acids are shown in Fig. 11 to compare the solvents with each other.

Carvacrol shows an increase in global extraction yields from 79.51, 86.84, and 90.00 % global yield with pH adjustment from 7.75, 6.65 to 4.00. This is due to the improvement in the extraction yields of naproxen, diclofenac, ibuprofen, and sulfamethoxazole, which compensates

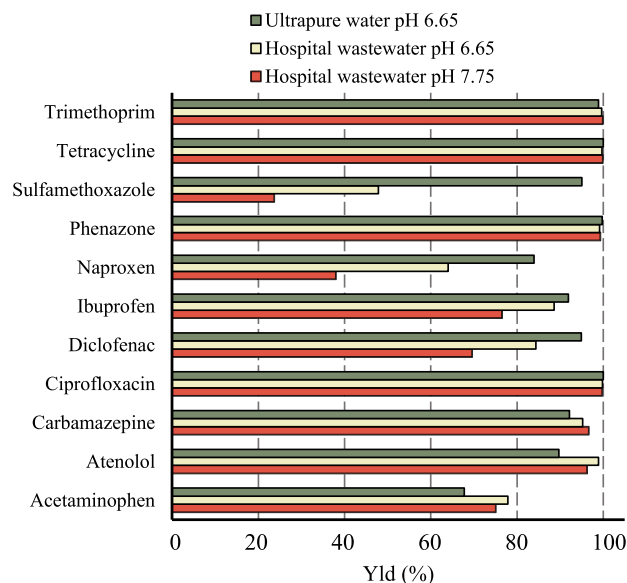


Fig. 12. Individual extraction yields of pharmaceutical compounds using carvacrol at an S/F ratio of 1.00 with initial pH of 6.65 and 7.75 and a concentration of 5 mg/L of each drug using different matrices at 323.2 K.

for a decrease in the yields of trimethoprim, ciprofloxacin, and atenolol.

For eutectic solvents, the best performances are achieved at pH 6.65. This is due, as mentioned above, to the change in pH. At pH 6.65, the dissolution of part of the carboxylic acids lowers the pH, increasing the yields, but at pH 4.00, the yields of trimethoprim, ciprofloxacin and atenolol worsen.

With ethyl acetate, decreased extraction yields are observed with decreasing pH, reversing the trend for carvacrol. This is due to a significant fall in extraction yields of tetracycline, trimethoprim, ciprofloxacin, and atenolol, which do not occur as markedly with the other solvents.

When comparing the solvents, carvacrol and the eutectic solvents achieve better extraction yields than ethyl acetate. At pH 4.00, the best solvent would be thymol + C₁₂OOH with an extraction yield of 94.24 % at an S/F ratio of 1.00. Carvacrol yields 90.00 % and ethyl acetate 65.68 % for the same conditions. On the other hand, the prices of natural solvents are higher than ethyl acetate. The estimated prices are 0.7–1.0 \$/kg for ethyl acetate [94], 0.8–2.0 \$/kg for octanoic acid [95], 9–11 \$/kg for thymol [96], and 10–25 \$ for carvacrol [88]. Although ethyl acetate has the lowest cost, the price gap can be competitive, especially for thymol + C₁₂OOH.

3.2.3. Effect of aqueous phase matrix

Experiments were then conducted using a hospital wastewater matrix in the aqueous feed. The pH of the initial solutions with the hospital wastewater matrix is 7.75, so the pH was adjusted to 6.65 to compare the results with ultrapure water at the same pH. The results in Fig. 12 show the comparison of the extraction yield results obtained with ultrapure water and hospital matrix using carvacrol at an S/F ratio of 1.00. The presence of ions in the matrix can reduce extraction yields by interacting with other charged organic molecules. On the other hand, they may increase the extraction yields of neutral molecules by reducing their solvation due to the salting-out effect, or conversely by salting-in, depending on the type of ions.

Trimethoprim, tetracycline, ciprofloxacin, and phenazone obtain very similar eliminations in Fig. 12, comparing them at the same pH, showing that the effect of the matrix is negligible at an S/F ratio of 1.00. These results are comparable with those obtained with the eutectic solvents. The matrix effect is not noticeable at high S/F ratios with these drugs. However, it is slightly appreciable at lower S/F ratios, i.e. at an S/

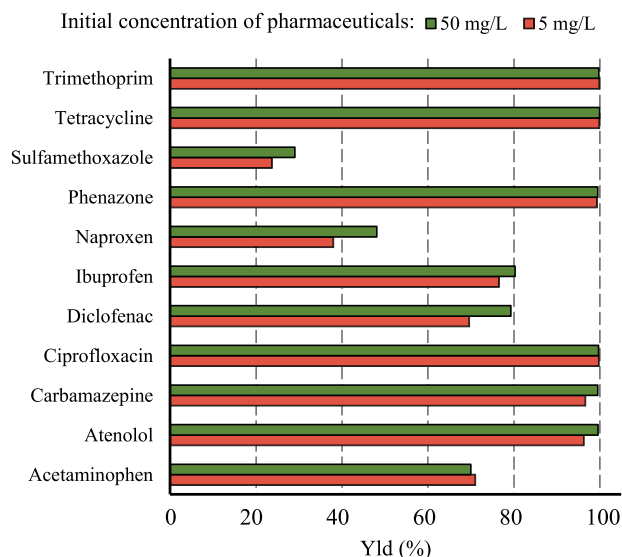


Fig. 13. Individual extraction yields of pharmaceutical compounds using carvacrol at an S/F ratio of 1.00 with initial pH of 7.75, initial concentration of 5 and 50 mg/L of each drug using hospital wastewater matrix, at 323.2 K.

F ratio of 0.05, ciprofloxacin presents a reduction from 99.98 to 92.20 %. On the other hand, the ethyl acetate values change significantly for tetracycline and trimethoprim, where the use of the hospital matrix at pH 6.65 and an S/F ratio of 1.00 leads to an absolute reduction in extraction yield of 53 % and 63 % for trimethoprim and tetracycline, respectively, as seen in Tables S10 and S15 of [Supplementary Material](#).

Comparing sulfamethoxazole, naproxen, ibuprofen, and diclofenac, yield reductions are observed using carvacrol. Sulfamethoxazole and, to a lesser extent, naproxen show differences in extraction yields of more than 40 and 20 %, respectively. If the values are compared with eutectic solvents, the same trends in the matrix effect are observed, although there is not as much difference as when carvacrol is used. This is also more accentuated when using sulfamethoxazole, as can be seen comparing Tables S6-8 with S12-14 of [Supplementary Material](#), respectively. On the other hand, the same is found for ethyl acetate except for naproxen, which has the opposite behaviour in Tables S10 and S15 of [Supplementary Material](#).

As observed, carbamazepine, atenolol, and acetaminophen increased yields with hospital wastewater. The case of acetaminophen is very noticeable, where the yields increase significantly, especially at low S/F ratios. The same trend is observed with the rest of the solvents as the eutectics as with ethyl acetate, in Tables S10 and S15 of [Supplementary Material](#).

This phenomenon may be due to the salting-out effect when using the hospital wastewater matrix. The presence of anions with high charge density in the matrix may cause a combination of electronic repulsion and increased hydrophobicity of organic molecules, resulting in the salting-out effect of organic molecules [97]. In the hospital wastewater matrix, CO_3^{2-} concentration of 342 mg/L is present, as shown in Table 1. It has been established that the effect of anions in the salting-out effect closely correlates with the well-known Hofmeister series [97,98]. This empirical series establishes an order of capacity of anions for protein precipitation, CO_3^{2-} being the first one in this series. Therefore, these anions may have a salting-out effect on the neutral organic molecules as a strong interacting anion, despite not being in high concentration.

Most non-polar organic molecules would be exposed to the salting-out effect. In this case, molecules in a neutral state at pH 6.65, such as acetaminophen and carbamazepine, could have more significant effects. In the case of acetaminophen and carbamazepine, they have salting-out or Setschenow constants values of 0.132 M^{-1} [99] and 0.212 M^{-1} [100] with NaCl at 25 °C in water. These values are intermediate between the

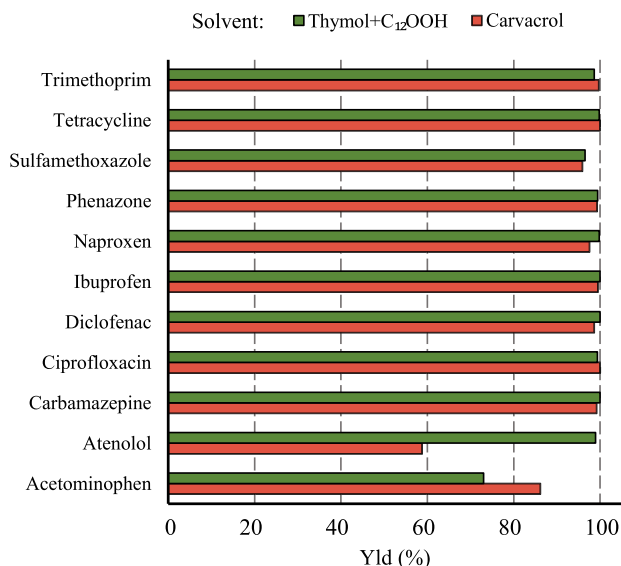


Fig. 14. Individual extraction yields of pharmaceutical compounds at an S/F ratio of 2.00 with initial pH of 4.00 and a concentration of 5 mg/L of each drug using a hospital wastewater matrix. (Thymol + C_{12}OOH) and carvacrol as solvents, at 323.2 K.

values for phenol 0.139 M^{-1} , and hexanoic acid 0.240 M^{-1} [101]. No measurements of Setschenow constants made with CO_3^{2-} have been found with the drugs tested in this work. Although these values help compare the effect of anions on different solutes, to be rigorous, values in two-phase systems should be considered where the influence of the solvent on this effect is also taken into account [97].

To summarise, dissolved salts in the matrix can be a disadvantage in terms of reduced extraction yields for charged organic molecules but an advantage for non-polar and neutral states. A change in pH of the initial solution could thus improve the extraction yields on the one hand by lower solvation of the organic molecules and an increase in their hydrophobicity coupled with a salting-out effect.

3.2.4. Effect of initial concentration of pharmaceuticals in hospital wastewater

Additionally, tests have been carried out by changing the initial drug concentration to observe how an increase in the initial drug concentration affects the extraction yields for the different solvents. Fig. 13 shows the extraction results with carvacrol at an S/F ratio of 1.00 for initial drug concentrations of 5 and 50 mg/L, using the hospital wastewater matrix with a pH of 7.75.

As can be appreciated, there is a slight decrease in solvent extraction yield as the initial drug concentration decreases. The drugs with the lowest extraction yields were naproxen and sulfamethoxazole. A decrease in concentration would lead to a decrease in driving force and drug partitioning. The only compound not following the trend is acetaminophen, which slightly increases the yield. The same trends with carvacrol results are found in the extraction yields with the eutectic solvents. This may be related to the fact that an increase in the acetaminophen concentration increases interactions with the ions present in water, as observed using ionic liquids [102,103]. This could be why a slight increase in extraction yield is obtained with increasing drug concentration.

In the case of ethyl acetate, significant reductions in extraction yields are observed in Tables S20 and S25 of [Supplementary Material](#) for drugs other than tetracycline, sulfamethoxazole, naproxen, atenolol, and ibuprofen with increasing initial concentration. With ciprofloxacin, significant yield reductions are observed, i.e. at an S/F ratio of 1.00 with yields changing from 83.00 to 7.73 % with increasing concentration. Thus, the natural solvents show a high extraction capacity at low and

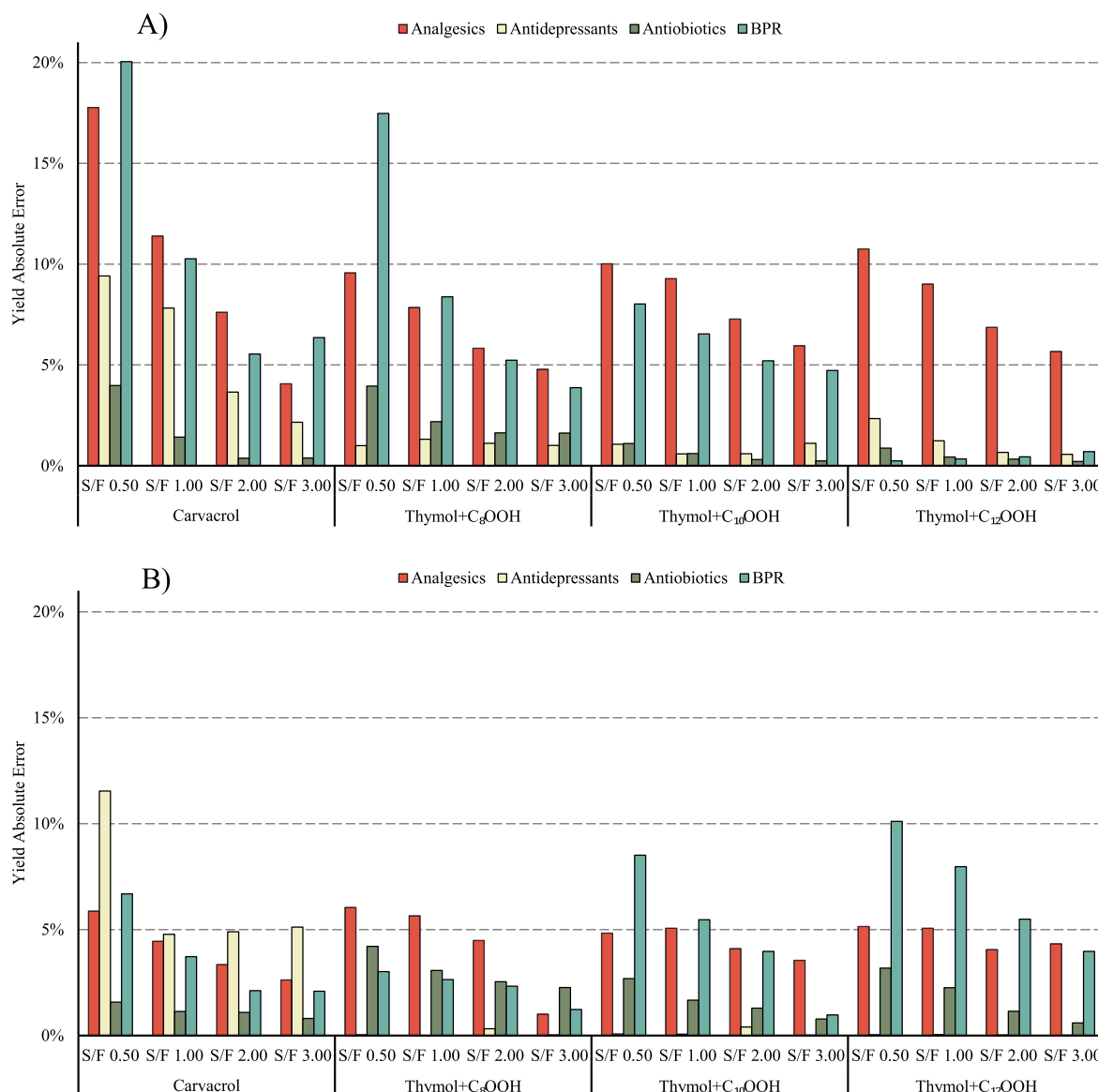


Fig. 15. Extraction yield (%) absolute error between experimental global extraction yields and simulated with COSMOtherm. Pharmaceuticals' initial concentration of 5 mg/L. Scenario A: Experimental yields were selected at pH 6.65. Scenario B: Adjusting pH. Diclofenac, naproxen, ibuprofen, and sulfamethoxazole pH 4.00. Tetracycline, phenazone, carbamazepine, and acetaminophen at a pH of 6.65. Ciprofloxacin, trimethoprim, and atenolol at a pH of 7.75.

high concentrations. In contrast, ethyl acetate shows a solvent saturation and a decrease in partitioning with increasing drug initial concentration.

3.2.5. Comparison between carvacrol and thymol + C₁₂OOH

The results of carvacrol and thymol + C₁₂OOH extraction with an S/F ratio of 2.00 and a pH of 4.00 are shown in Fig. 14. These results show the almost complete extraction of the drugs with both solvents except for acetaminophen and atenolol. The global yields obtained with carvacrol would be 94.06 %, while with thymol + C₁₂OOH, it is 96.86 %. Florindo et al. [29] have applied mixtures of C₁₂OOH + C₁₀OOH fatty acids in the extraction of ciprofloxacin, with an initial concentration of 10 mg/L, an S/F ratio of 1.00, and a pH of 6.4, obtaining an extraction yield of 75 %. Bergua et al. have extracted quercetin, nitrofurantoin, and tetracycline with mixtures of menthol [33] and thymol [31] with octanoic and decanoic acids. At an S/F of 1.00, they obtained results of around 49 % with menthol + C₈OOH (1:2) and 95 % using thymol + C₈OOH (1:1), with an initial concentration of 75 μM of tetracycline, at 298 K. These results are indicative, as well as those obtained in this work, of the improvement that thymol produces in drug extraction when used

together with fatty acids in the eutectic solvent, compared with pure thymol and fatty acids mixtures eutectic solvents.

In the previous work on the extraction of sulfamethoxazole, trimethoprim, and ciprofloxacin, [34] it was observed that carvacrol was the solvent that obtained the best extraction yields between the tested natural solvents. In this work, the simultaneous extraction of 11 drugs has been considered, and both thymol + C₁₂OOH and carvacrol have obtained high extraction yields.

Both solvents have been selected for the subsequent reuse tests, and a pH of 4.00 has been set. Thymol + C₁₂OOH has been used as it is the best performing eutectic solvent at pH 4.00. This pH was chosen because it resulted in the highest extraction yields with carvacrol. It should be mentioned that carvacrol has the advantage over thymol + C₁₂OOH that it is liquid at room temperature.

3.3. Reliability assessment of COSMO-RS predictions

Pharmaceutical extraction yields have also been calculated using COSMOtherm. The calculations have been carried out to compare them

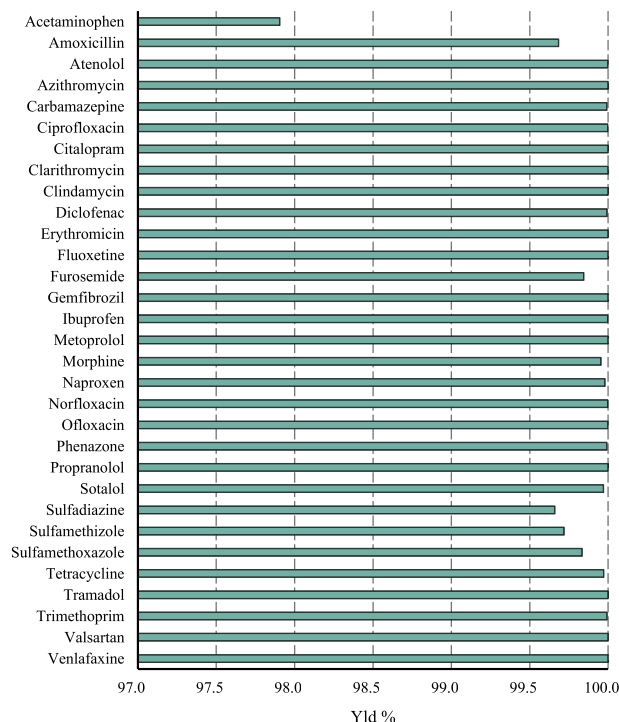


Fig. 16. Extraction yields simulated with COSMOtherm. Carvacrol S/F ratio of 2.00 and initial concentration of 1 mg/L.

with the experimental results and verify the reliability of this method in calculating the extraction yields. It should be noted that this simulation takes the drugs as neutral structures. Two scenarios were selected for this comparison. On the one hand, the absolute error of the drugs' extraction yields (%) with respect to the values obtained at pH 6.65 with the hospital wastewater matrix (scenario A) was calculated. These values are represented in Fig. 15A using S/F ratios of 0.50, 1.00 and 2.00 and 3.00 for carvacrol and the eutectic solvents thymol + C₈OOH, thymol + C₁₀OOH, and thymol + C₁₂OOH.

On the other hand, errors have been calculated in the second scenario (B) by grouping the experimental results by drugs and extractions at different pHs. The extraction values for diclofenac, naproxen, ibuprofen and sulfamethoxazole have been selected at pH 4.00. Tetracycline, phenazone, carbamazepine and acetaminophen at pH 6.65. Ciprofloxacin, trimethoprim, and atenolol at pH 7.75. The results are shown in Fig. 15B.

The second scenario (B) has been selected, as seen in the vial extraction section, because of the influence of pH on pharmaceutical

extraction. These pHs were selected to select the pHs at which pharmaceuticals were in their neutral state. If comparing both scenarios, COSMO-RS calculations are adequate when treating as a neutral molecule, as the errors are significantly reduced. The deviations made by the simulation at the different ones are minor with increasing S/F ratios. In the case of scenario B, deviations of less than 5 % are obtained for analgesics, significantly reducing the deviations committed in scenario A, which in some cases exceeded 15 % extraction yield absolute error. The results obtained highlight the importance of pH in extraction yields, both those obtained experimentally and those that could be obtained by molecular simulation.

The COSMO-RS simulations accurately reflect the experimental results when the species are neutral. They serve as a basis for the performances expected when conducting experiments in which a pH has been selected for when the drugs are in a neutral state. Because of this, extraction yields were calculated at an S/F ratio of 2.00 with an initial drug concentration of 1 mg/L for the 31 drugs used in the initial solvent screening. In this way, the COSMO-RS predictions for drug extraction are determined. The values calculated using carvacrol as solvent are presented in Fig. 16.

The predictions show that extraction yields above 97.5 % would be obtained for each drug with carvacrol. The lowest results would be obtained for acetaminophen. Amoxicillin, furosemide, sulfadiazine, sulfamethizole, and sulfamethoxazole would obtain lower yields but higher than 99.5 %. The rest of the drugs would be removed with yields close to 100 %. In conclusion, according to COSMO-RS predictions, carvacrol would achieve the extraction of all 31 drugs with almost complete removal from the aqueous medium.

3.4. Solvent reuse and regeneration

Carvacrol and thymol + C₁₂OOH were chosen for solvent reuse tests to check their influence on extraction yields. The same temperature as the previous extraction experiments of 323.2 K was employed, also a pH of 4.00, hospital wastewater matrix, and 5 mg/L of the 11 pharmaceuticals. Two S/F ratios were chosen for the study: 0.50 and 2.00, to compare low and high S/F ratios in the reusability of the solvents. It is expected that lower S/F ratios may drop extraction yields faster. In Fig. 17, the scheme of solvent reuse is shown, which has been reused in 5 cycles. Subsequently, the solvents were regenerated by vacuum distillation as described in the Experimental Section. Finally, the regenerated solvent was used again in a new extraction.

3.4.1. Extraction yields in each reuse stage

The extraction yields per type of compound are represented in Fig. 18A for an S/F ratio of 2.00 and 18B for an S/F of 0.50.

The results at an S/F ratio of 2.00 show no decrease in extraction yields after 5 reuse stages with thymol + C₁₂OOH, as seen in Fig. 18A.

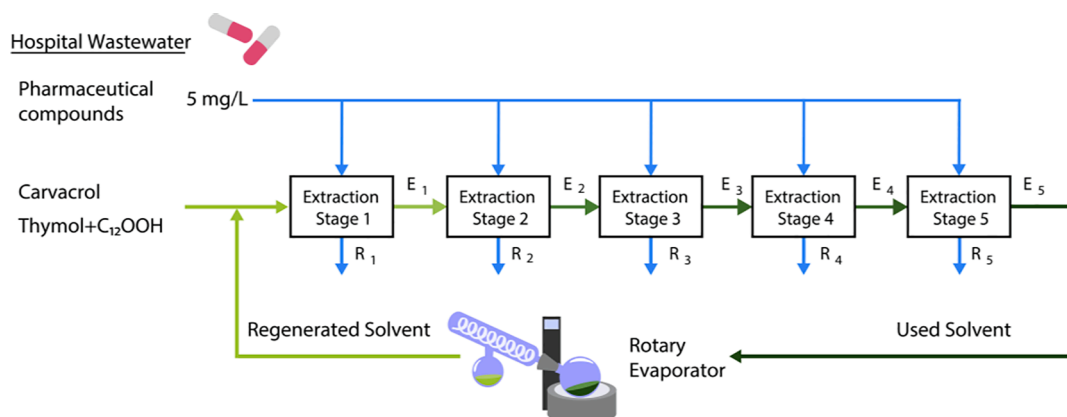


Fig. 17. Scheme of solvent reuse and solvent regeneration.

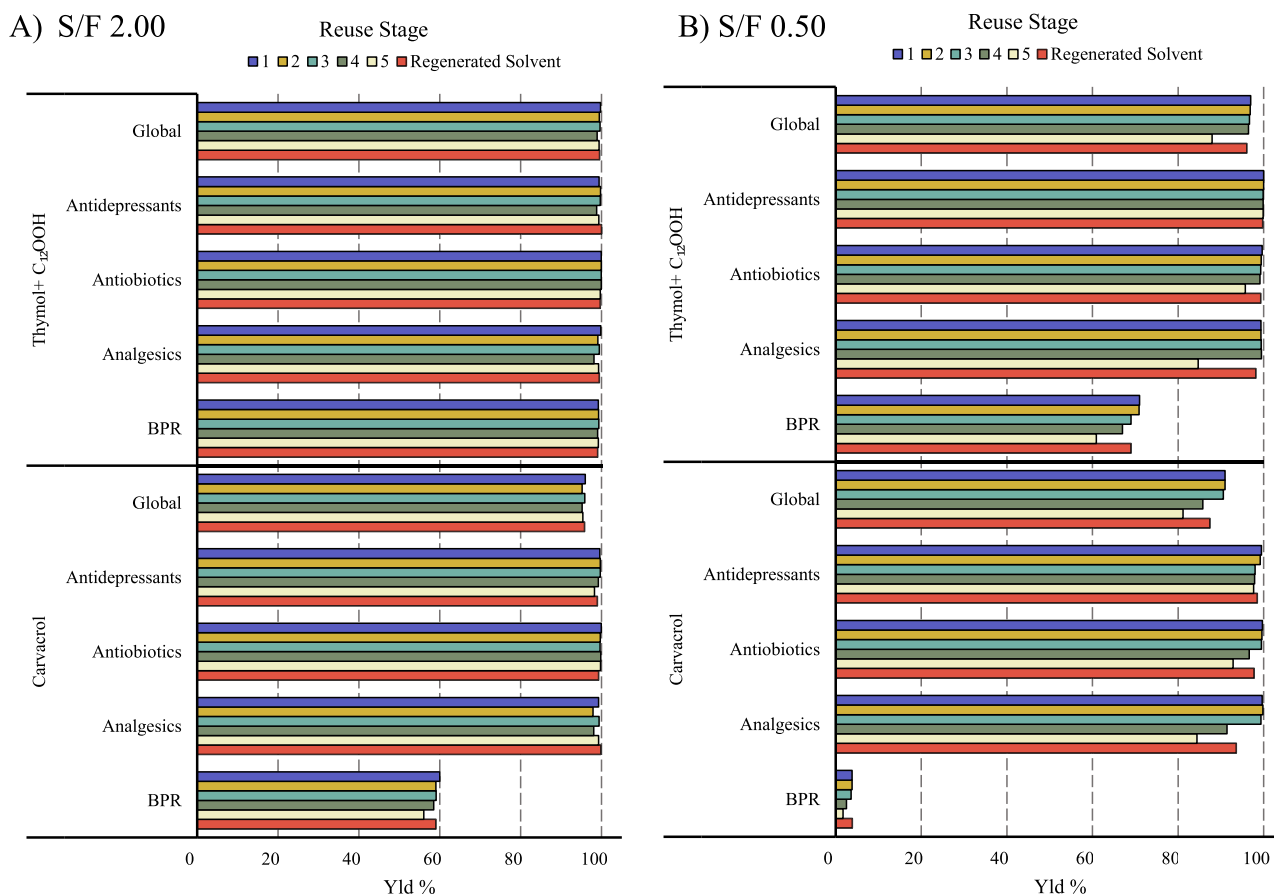


Fig. 18. Experimental extraction yields per type of pharmaceutical in solvent reuse and regeneration cycles. S/F ratio A) 2.00; B) 0.50, at 323.2 K.

The global extraction yields in all 5 stages are higher than 99 %. As the yields are so high, no difference is observed when the solvent regeneration process is performed. In this case, an excellent capacity for solvent reuse is shown at this S/F ratio of 2.00.

On the other hand, carvacrol does not decrease extraction yields at S/F of 2.00 except with atenolol, where a slight decrease is observed in stage 5. When the solvent is regenerated, a rise in the extraction yields of atenolol is observed, close to that of the fresh solvent. The global extraction yields in the five stages are all higher than 95 % in all stages.

The yields at an S/F of 0.50 show more significant differences, as shown in Fig. 18B. The results with thymol + C₁₂OOH show that the antidepressant extraction yields remain constant and close to 100 % in all 5 stages. On the other hand, with the rest of the types, there is a decrease in the yields in stage 5 of extraction, with the most significant decrease for analgesics from 99.46 to 84.69 %, mainly due to a decrease in the extraction yields of acetaminophen. The decrease in extraction yields of acetaminophen may also be related to the decrease in yields found in the vial study with increasing initial drug concentration. A higher concentration of organic solvents in the extraction seems to reduce the extraction yields of acetaminophen, which is observed when increasing the initial concentration or reusing the solvent. An improvement in extraction yields was observed upon regeneration but slightly lower when using a fresh solvent. Using this S/F ratio, the global extraction yields decreased from 96.95 to 84.69 % from stage 1 to 5 and increased to 96.06 % with the regenerated solvent.

Concerning carvacrol, we observe decreases in extraction yields with all four drug types at S/F of 0.5, especially in steps 4 and 5. In this case, the drop in extraction yields of antibiotics is not as pronounced as the one with thymol + C₁₂OOH. The extraction yields of BPR are low at this S/F in all stages, ranging from 3.80 to 1.72 % in stages 1–5. The global extraction yields decrease from 90.95 % in the first stage to 81.15 % in

stage 5. After the regeneration process, the yields increase for the previous stage but remain below the fresh solvent, reaching a global extraction yield of 87.40 %. The results show that the solvents can be reused, observing no drop at the S/F ratio of 2.00 and a slight reduction at S/F 0.50. High extraction yields are achieved at an S/F ratio of 0.50 and 2.00. The solvent regeneration process does improve the extraction yields compared to the last stage but almost reaches the extraction values of the fresh solvent. In the following section, the stability of the solvents in the extraction and regeneration process is studied.

3.4.2. Solvent chemical stability

To check the stability of the solvents in the reuse and regeneration process, FTIR spectra and TGA have been obtained for the pure solvents after being in contact with water, the solvents in stage 5 of reuse, and the distillates and residues obtained in the regeneration step by vacuum distillation. The main bands with the vibrations of the functional groups of carvacrol, thymol and C₁₂OOH have been identified in Figs. S20–22 of Supplementary Material, following the infrared spectra interpretation guidelines [104].

The FTIR spectra of carvacrol are given in Fig. 19A. The spectra of the pure solvent and extract phases show no difference between them after the extraction. The addition of water produces a slight broadening of the –OH stretch at 3377 cm^{–1}. This change is very subtle due to the high hydrophobicity of carvacrol. In addition, the stability of the solvent is maintained in the reuse and regeneration processes, obtaining identical spectra in the residue and distillate to the fresh carvacrol. The thermogravimetric analyses are shown in Fig. S23 of Supplementary Material and also show very similar results to the pure solvent, with the presence of water in the evaporation process having little effect. From 220 °C onwards, complete evaporation of the solvents was observed. FTIR and TGA results show the stability of carvacrol in the extraction

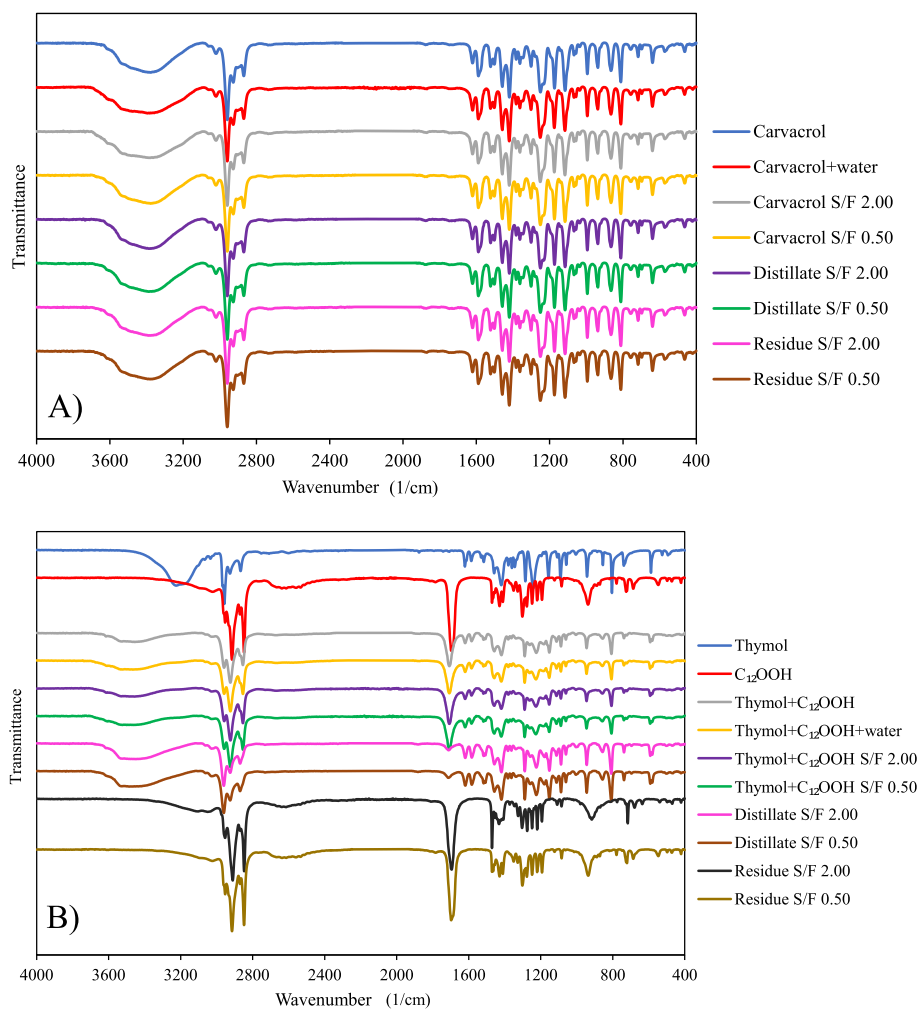


Fig. 19. FTIR spectra of carvacrol (A) and thymol + $C_{12}OOH$ (B) of reuse stage 5. Distillates and residues after vacuum distillation.

and regeneration process.

For the eutectic solvent thymol + $C_{12}OOH$, the FTIR spectra are shown in Fig. 19B. In this case, there are notable differences between the spectra. Due to the $-OH$ stretch, the thymol shows a broad peak at 3226 cm^{-1} . In the formation of the eutectic thymol + $C_{12}OOH$, this is shifted to $3500\text{--}3420\text{ cm}^{-1}$ by the hydrogen bond interactions of the eutectic solvent. The spectra do not change with the addition of water, corroborating the hydrophobic character. After performing the five solvent reuse stages, no changes are observed, so the eutectic solvent is stable in the reuse process.

On the other hand, after the regeneration of the solvents, differences were observed between the peaks of residues and distillates compared to the initial eutectic solvent. In the residues, the peaks at 1700 cm^{-1} correspond to the $C=O$ stretch of the $C_{12}OOH$, and the 2848 cm^{-1} peak of the $C-H$ stretch, which is very prominent in the spectrum of the $C_{12}OOH$, increases notably. In addition, the $-OH$ stretch peak of the thymol disappears. Consequently, the same peaks at 1700 and 2848 cm^{-1} are reduced in the distillates and the $-OH$ stretch peak increased. These results imply a further enrichment of the distillate in thymol and reduction of the fatty acid, thus changing the ratio of the eutectic point of the initial solvent. Thermogravimetric analyses of the solvents in Fig. S24 of Supplementary Material show a mass loss for the pure compounds at $265\text{ }^{\circ}\text{C}$ for $C_{12}OOH$ and $201\text{ }^{\circ}\text{C}$ for thymol. In the case of the extract phases, similar thermograms to the fresh eutectic solvents are obtained, confirming the stability in the extraction step. On the other hand, the distillates are closer to those obtained with thymol, and the residues are closer to $C_{12}OOH$, confirming the change in the composition

of the eutectic solvent during the regeneration.

In short, both carvacrol and thymol + $C_{12}OOH$ are stable in the reuse extraction process. Carvacrol is also stable in the regeneration process. In contrast, the eutectic solvent thymol + $C_{12}OOH$ changes the composition in the regeneration by distillation process, increasing the thymol composition in the distillates and decreasing it in the residues due to boiling point differences. The eutectic solvent distillates did show increases in extraction yields compared to stage 5 despite the change in composition. However, in the following reuse and regeneration, $C_{12}OOH$ would be lost and would have to be replenished to avoid losing the composition of the eutectic point. It is challenging to regenerate eutectic mixtures with constituents with different boiling points [105], here properly evaluating the regeneration of the eutectic solvent. Only properly selecting HBD and HBA with equivalent boiling points and solubilities in water can allow regeneration feasible. However, the concept of improving interaction by a mixture imposes that HBD and HBA will be of different nature and, thus, these differences will impose challenging regeneration steps. Therefore, we consider carvacrol a more suitable solvent considering the complete process of extraction and regeneration. Although the yields were slightly lower with carvacrol than with the eutectic solvent thymol + $C_{12}OOH$, it was selected for the following countercurrent tests because it is liquid at room temperature and can be regenerated without losing its composition.

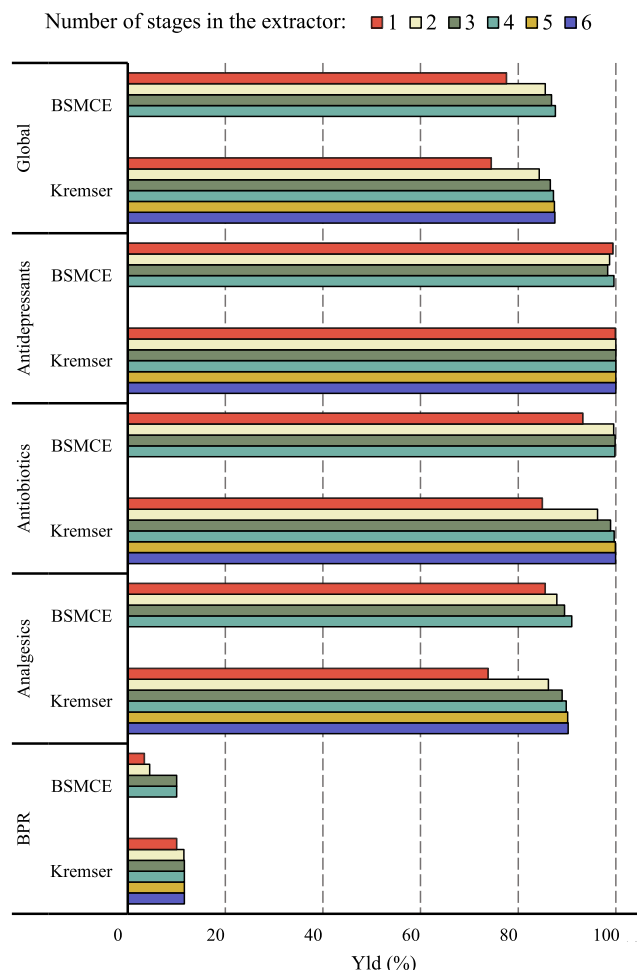


Fig. 20. Countercurrent per type extraction yields of pharmaceutical compounds obtained with Batch Simulation of Multistage Countercurrent Extraction (BSMCE) and simulation with Kremser method as a function of the number of countercurrent extraction stages. Initial concentration of 5 mg/L of each drug, pH 4.00, using hospital wastewater matrix, carvacrol as the solvent at S/F 0.25, and room temperature (298.2 K).

3.5. Countercurrent extraction of pharmaceuticals from hospital wastewater

Countercurrent extraction experiments were performed using carvacrol as solvent. The studies were carried out at room temperature (298.2 K), using a hospital wastewater matrix and an initial concentration of each drug of 5 mg/L. The S/F ratio selected was 0.25, testing the improvement of using a countercurrent arrangement versus a single-stage extraction.

On the one hand, BSMCE has been used for the experimental simulation of a countercurrent process. The description of these studies can be found in the *Experimental Section*. 4 runs were performed on this process to ensure results equivalent to multistage countercurrent operation. [Figure S25 of Supplementary Material](#) shows the results obtained for each run and 2, 3 and 4-stage countercurrent schemes. The global extraction yields of pharmaceuticals with respect to the feed solution have been obtained. The extraction yields were obtained for each stage (A, B, C, D), where A is the feed (F) input stage and the final extract (E) output stage.

Rapid stabilisation of the extraction yields is observed in the runs. In all cases, the extraction yields increase at each intermediate stage (A, B, C, D). In the results obtained, no variations in the final raffinates are observed for using 2, 3 and 4 stages when comparing different runs. On

the other hand, variations are observed in intermediate stages that stabilise in runs 3 and 4, with the values that undergo the most significant change being those of the stage A raffinate (R_A). Due to the rapid stabilisation of the yields, these are considered good results that serve as a basis for comparison with results from simulations and calculations that approximate the results of a countercurrent extraction. In addition, they serve as operating limits since the extraction is considered to have reached equilibrium in each stage.

The results obtained in the Batch Simulation of Multistage Countercurrent Extraction (BSMCE) in a single-stage at room temperature (298.2 K) also allow for evaluating the effect of temperature on the extraction yields when compared to the results previously discussed at 323.2 K. According to the results shown in [Table S31 of the Supplementary Material](#), no significant effect of temperature on the extraction yields has been observed, so it seems appropriate to select the room temperature to save heating costs in the extraction unit.

The Kremser method was chosen as the method for calculating countercurrent stages. This method, used successfully in previous works [\[69,73\]](#), considers constant distribution coefficients when performing the countercurrent extraction. As described in the *Experimental Section*, distribution coefficients were obtained using a packed column with a concurrent extraction. The results of the distribution coefficients obtained are given in [Table S32 of Supplementary Material](#).

The packed column assays check if a quick extraction of the drugs is carried out and if there is a fast mass transfer, thus approaching an industrial way of extraction. In addition, the use of the Kremser method serves to check the reliability of the calculation method with complex samples compared to the data obtained by BSMCE. Also, the results obtained with BSMCE are very laborious to obtain experimentally with a high number of stages, whereas the Kremser method does allow such calculations.

The results of extraction yields per type of drugs obtained by BSMCE from the final raffinate in each extraction scheme and run 4, and those obtained by the Kremser method are shown in [Fig. 20](#). In the case of the simulation with the Kremser method, up to 6 extraction stages have been simulated. In addition, the results of the single extraction in a vial for BSMCE, and the results of column extraction in the simulation with the Kremser method have been added.

The single-stage global extraction yield results are 77.59 % for batch extraction and 74.47 % for packed column extraction. This slight difference implies a low mass transfer limitation in the extraction process. This phenomenon is related to the solvents' low viscosity, which facilitates a good solute transfer. Because of this, the extraction results by the Kremser method are slightly below those obtained by BSMCE. The results between the two methods are very close to each other, which implies the high reliability of the Kremser method as a calculation method and the assumption that the distribution coefficients are constant when working in multistage countercurrent extraction.

From stage 4 onwards, the extraction yields do not increase when performing simulations with 5 and 6 stages using the Kremser method, as seen in [Fig. 20](#). It is worth mentioning that almost complete removal of the antibiotic and antidepressant types of pharmaceuticals is observed with this number of stages. The global extraction yields increase from 77.59 to 85.50 % with 4 stages. The extraction yields with the Kremser method increase from 74.74 % with stage 1, to 87.51 % when using 6 stages. It should be mentioned that a low S/F ratio of 0.25 is used.

The countercurrent extraction results show a fast mass transfer of the drugs using carvacrol. Furthermore, the Kremser method is reliable for realising countercurrent extraction scenarios from single-stage distribution coefficients. Higher S/F ratios could almost eliminate the drugs when working in countercurrent mode. A global removal of more than 87 % of the 11 drugs could be achieved with carvacrol at an S/F ratio of 0.25, showing the high capacity of the solvent in the extraction of the drugs.

Finally, a simulation of the countercurrent extraction column using the Kremser method has been carried out using carvacrol at S/F ratios of

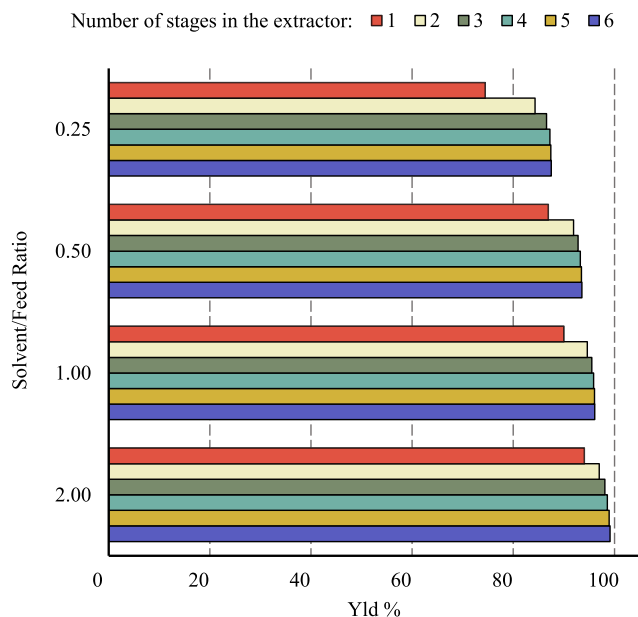


Fig. 21. Global countercurrent extraction yields of pharmaceutical compounds obtained with simulation by the Kremser method as a function of the number of countercurrent extraction stages at different S/F ratios. Initial concentration of 5 mg/L of each drug, pH 4.00, using hospital wastewater matrix, carvacrol as the solvent, and room temperature (298.2 K).

0.25, 0.50, 1.00, and 2.00 to determine the conditions under which a complete extraction of the drugs from the hospital water would be obtained. Fig. 21 shows the global extraction yields obtained in these simulations.

As can be seen, an increase in the value of the S/F ratio leads to an increase in the removal yield of drugs from hospital wastewater. Using S/F ratios of 0.25 and 0.5, the extraction yield achieved in a countercurrent column with carvacrol would be less than 90 %. Therefore, to completely remove the drugs from the hospital wastewater, it would be necessary to increase the flow rate of carvacrol. According to the simulation results, almost complete extraction of drugs from hospital water would be achieved using carvacrol with a solvent-to-feed ratio of 2.00 in a countercurrent extraction column with six equilibrium steps at room temperature. Thus, the proposed technology of extracting pharmaceuticals from hospital water using the naturally occurring terpenoid carvacrol as a solvent has proven to be a technically feasible alternative.

4. Conclusions

In this work, the feasibility of using a liquid–liquid extraction technology to extract drugs from hospital water with terpenoids and eutectic solvents of natural origin has been studied. The reliability of the predictions of the COSMO-RS method in selecting solvents for this application has been studied, using the most experimentally promising solvents. The regeneration and reuse of solvents and the parallel column and countercurrent extraction have also been studied experimentally. Finally, the extraction process was simulated using the Kremser method to determine the conditions that would allow the complete removal of drugs from hospital wastewater.

COSMO-RS method was confirmed as a valuable tool for broad screening of solvents and drugs. The best solvents experimentally tested in this work were carvacrol and the eutectic solvent formed by thymol and dodecanoic acid. In the extraction mechanism, the pH of the aqueous solution of the hospital wastewater was crucial in changing the extraction yields to a large extent. Adjustments of the pH improved the extractions of target drugs and improved global extraction yields by favouring the presence of neutral states. The matrix can also affect the

yields obtained, although milder than pH. Carvacrol and thymol + C₁₂OOH were reused multiple times to obtain global extraction yields close to 100 %. However, the eutectic solvent was not suitable for the regeneration process proposed in this work. According to the results obtained experimentally and in simulations, a countercurrent extraction column at room temperature with carvacrol as solvent could be used to completely remove pharmaceuticals from hospital wastewater.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors are grateful to Comunidad Autónoma de Madrid for financial support of Projects P2018/EMT-4341 and PR65/19-22441 and to Ministerio de Ciencia, Innovación y Universidades for financial support of Project CTM2017-84033-R. This work has been supported by the Madrid Government (Comunidad de Madrid- Spain) under the Multi-annual Agreement with Complutense University in the line Program to Stimulate Research for Young Doctors in the context of the V PRICIT (Regional Programme of Research and Technological Innovation). Diego Rodríguez-Llorente thanks Ministerio de Ciencia, Innovación y Universidades for awarding an FPU grant (FPU18/01536). Elisa Hernández thanks Spanish Ministerio de Universidades for awarding an FPU grant (FPU20/03198). Finally, we thank Centro de Computación Científica de la Universidad Autónoma de Madrid for computational facilities, and Spectroscopy and Correlation Centre of Complutense University of Madrid for FTIR analysis.

Appendix A. Supplementary data

Chemicals. Excess enthalpies contributions with COSMO-RS. Sigma profiles. Protonation equilibria of pharmaceuticals. Experimental extraction yields values in vial. FTIR spectra and main vibrational groups of carvacrol, thymol and dodecanoic acid. TGAs curves. Batch Simulation of Multistage Countercurrent Extraction (BSME) schemes for 2 and 3 stages. Stabilisation of extraction yields with BSME. Effects of temperature on extraction yields. Distribution coefficients obtained in packed column. Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cej.2022.138544>.

References

- [1] M.C. Villarín, S. Merel, Paradigm shifts and current challenges in wastewater management, *J. Hazard. Mater.* 390 (2020), 122139, <https://doi.org/10.1016/j.jhazmat.2020.122139>.
- [2] K. Kümmerer, The presence of pharmaceuticals in the environment due to human use - present knowledge and future challenges, *J. Environ. Manage.* 90 (2009) 2354–2366, <https://doi.org/10.1016/j.jenvman.2009.01.023>.
- [3] A.S. Adeleye, J. Xue, Y. Zhao, A.A. Taylor, J.E. Zenobio, Y. Sun, Z. Han, O. A. Salawu, Y. Zhu, Abundance, fate, and effects of pharmaceuticals and personal care products in aquatic environments, *J. Hazard. Mater.* 424 (2022), <https://doi.org/10.1016/j.jhazmat.2021.127284>.
- [4] L. Castillo Meza, P. Piotrowski, J. Farnan, T.L. Tasker, B. Xiong, B. Weggler, K. Murrell, F.L. Dorman, J.P. vanden Heuvel, W.D. Burgos, Detection and removal of biologically active organic micropollutants from hospital wastewater, *Sci. Total Environ.* 700 (2020), 134469, <https://doi.org/10.1016/j.scitotenv.2019.134469>.
- [5] A. Majumder, A.K. Gupta, P.S. Ghosal, M. Varma, A review on hospital wastewater treatment: A special emphasis on occurrence and removal of pharmaceutically active compounds, resistant microorganisms, and SARS-CoV-2, *J. Environ. Chem. Eng.* 9 (2021), 104812, <https://doi.org/10.1016/j.jece.2020.104812>.

- [6] D. Papagiannaki, M.H. Belay, N.P.F. Gonçalves, E. Robotti, A. Bianco-Prevot, R. Binetti, P. Calza, From monitoring to treatment, how to improve water quality: The pharmaceuticals case, *Chem. Eng. J. Adv.* 10 (2022), 100245, <https://doi.org/10.1016/j.cej.2022.100245>.
- [7] A.S. Oberoi, Y. Jia, H. Zhang, S.K. Khanal, H. Lu, Insights into the Fate and Removal of Antibiotics in Engineered Biological Treatment Systems: A Critical Review, *Environ. Sci. Technol.* 53 (2019) 7234–7264, <https://doi.org/10.1021/acs.est.9b01131>.
- [8] R. Tormo-Budowski, J.C. Cambronero-Heinrichs, J.E. Durán, M. Masís-Mora, D. Ramírez-Morales, J.P. Quirós-Fournier, C.E. Rodríguez-Rodríguez, Removal of pharmaceuticals and ecotoxicological changes in wastewater using Trametes versicolor: A comparison of fungal stirred tank and trickle-bed bioreactors, *Chem. Eng. J.* 410 (2021), 128210, <https://doi.org/10.1016/j.cej.2020.128210>.
- [9] S. Hena, L. Gutierrez, J.-P. Croué, Removal of pharmaceutical and personal care products (PPCPs) from wastewater using microalgae: A review, *J. Hazard. Mater.* 403 (2021), 124041, <https://doi.org/10.1016/j.jhazmat.2020.124041>.
- [10] K. Tang, A. Spiliotopoulou, R.K. Chhetri, G.T.H. Ooi, K.M.S. Kaarsholm, K. Sundmark, B. Florian, C. Kragelund, K. Bester, H.R. Andersen, Removal of pharmaceuticals, toxicity and natural fluorescence through the ozonation of biologically-treated hospital wastewater, with further polishing via a suspended biofilm, *Chem. Eng. J.* 359 (2019) 321–330, <https://doi.org/10.1016/j.cej.2018.11.112>.
- [11] Y. Gao, Q. Wang, G. Ji, A. Li, Degradation of antibiotic pollutants by persulfate activated with various carbon materials, *Chem. Eng. J.* 429 (2022), <https://doi.org/10.1016/j.cej.2021.132387>.
- [12] T. Velepini, E. Prabakaran, K. Pillay, Recent developments in the use of metal oxides for photocatalytic degradation of pharmaceutical pollutants in water—a review, *Mater. Today Chem.* 19 (2021), <https://doi.org/10.1016/j.mtchem.2020.100380>.
- [13] C. Du, Y. Zhang, Z. Zhang, L. Zhou, G. Yu, X. Wen, T. Chi, G. Wang, Y. Su, F. Deng, Y. Lv, H. Zhu, Fe-based metal organic frameworks (Fe-MOFs) for organic pollutants removal via photo-Fenton: A review, *Chem. Eng. J.* 431 (2022), <https://doi.org/10.1016/j.cej.2021.133932>.
- [14] S.W. Lv, Y. Cong, X. Chen, W. Wang, L. Che, Developing fine-tuned metal–organic frameworks for photocatalytic treatment of wastewater: A review, *Chem. Eng. J.* 433 (2022), <https://doi.org/10.1016/j.cej.2021.133605>.
- [15] S. Kundu, N. Karak, Polymeric photocatalytic membrane: An emerging solution for environmental remediation, *Chem. Eng. J.* 438 (2022), <https://doi.org/10.1016/j.cej.2022.135575>.
- [16] A.C. Álamo, C. González, M.I. Pariente, R. Molina, F. Martínez, Fenton-like catalyst based on a reticulated porous perovskite material: Activity and stability for the on-site removal of pharmaceutical micropollutants in a hospital wastewater, *Chem. Eng. J.* 401 (2020), 126113, <https://doi.org/10.1016/j.cej.2020.126113>.
- [17] G.A. Kifle, Y. Huang, M. Xiang, W. Wang, C. Wang, C. Li, H. Li, Heterogeneous activation of peroxyls by iron-based bimetallic nanostructures for the efficient remediation of contaminated water: A review, *Chem. Eng. J.* 442 (2022), <https://doi.org/10.1016/j.cej.2022.136187>.
- [18] Y. Feng, Y. Tao, Q. Meng, J. Qu, S. Ma, S. Han, Y. Zhang, Microwave-combined advanced oxidation for organic pollutants in the environmental remediation: An overview of influence, mechanism, and prospective, *Chem. Eng. J.* 441 (2022), 135924, <https://doi.org/10.1016/j.cej.2022.135924>.
- [19] K. Fedorov, K. Dinesh, X.R.Z.S.G. Synergistic effects of hybrid advanced oxidation processes (AOPs) based on hydrodynamic cavitation phenomenon – A review, *Chem. Eng. J.* 432 (2022), <https://doi.org/10.1016/j.cej.2021.134191>.
- [20] M.F. Dapaah, Q. Niu, Y.Y. Yu, T. You, B. Liu, L. Cheng, Efficient persistent organic pollutant removal in water using MIL-metal–organic framework driven Fenton-like reactions: A critical review, *Chem. Eng. J.* 431 (2022), <https://doi.org/10.1016/j.cej.2021.134182>.
- [21] J.R. de Andrade, M.F. Oliveira, M.G.C. da Silva, M.G.A. Vieira, Adsorption of Pharmaceuticals from Water and Wastewater Using Nonconventional Low-Cost Materials: A Review, *Ind. Eng. Chem. Res.* 57 (2018) 3103–3127, <https://doi.org/10.1021/acs.iecr.7b05137>.
- [22] P. Krasucka, B. Pan, Y. Sik Ok, D. Mohan, B. Sarkar, P. Oleszczuk, Engineered biochar – A sustainable solution for the removal of antibiotics from water, *Chem. Eng. J.* 405 (2021), 126926, <https://doi.org/10.1016/j.cej.2020.126926>.
- [23] G. Alam, I. Ihsanullah, M. Naushad, M. Sillanpää, Applications of artificial intelligence in water treatment for optimization and automation of adsorption processes: Recent advances and prospects, *Chem. Eng. J.* 427 (2022), <https://doi.org/10.1016/j.cej.2021.130011>.
- [24] S. Wang, L. Li, S. Yu, B. Dong, N. Gao, X. Wang, A review of advances in EDCs and PhACs removal by nanofiltration: Mechanisms, impact factors and the influence of organic matter, *Chem. Eng. J.* 406 (2021), <https://doi.org/10.1016/j.cej.2020.126722>.
- [25] C. Gadipelly, A. Pérez-González, G.D. Yadav, I. Ortiz, R. Ibáñez, V.K. Rathod, K. v. Marathe, Pharmaceutical Industry Wastewater: Review of the Technologies for Water Treatment and Reuse, *Ind. Eng. Chem. Res.* 53 (2014) 11571–11592, <https://doi.org/10.1021/ie501210j>.
- [26] H.F.D. Almeida, I.M. Marrucho, M.G. Freire, Removal of Nonsteroidal Anti-Inflammatory Drugs from Aqueous Environments with Reusable Ionic-Liquid-Based Systems, *ACS Sustainable Chem. Eng.* 5 (2017) 2428–2436, <https://doi.org/10.1021/acssuschemeng.6b02771>.
- [27] M. Zawadzki, F.A.E. Silva, U. Domańska, J.A.P. Coutinho, S.P.M. Ventura, Recovery of an antidepressant from pharmaceutical wastes using ionic liquid-based aqueous biphasic systems, *Green Chem.* 18 (2016) 3527–3536, <https://doi.org/10.1039/c5gc03052h>.
- [28] F.A. e Silva, M. Caban, M. Kholany, P. Stepnowski, J.A.P. Coutinho, S.P. M. Ventura, Recovery of Nonsteroidal Anti-Inflammatory Drugs from Wastes Using Ionic-Liquid-Based Three-Phase Partitioning Systems, *ACS Sustainable Chem. Eng.* 6 (2018) 4574–4585, <https://doi.org/10.1021/acssuschemeng.7b03216>.
- [29] C. Florindo, F. Lima, L.C. Branco, I.M. Marrucho, Hydrophobic Deep Eutectic Solvents: A Circular Approach to Purify Water Contaminated with Ciprofloxacin, *ACS Sustainable Chem. Eng.* 7 (2019) 14739–14746, <https://doi.org/10.1021/acssuschemeng.9b02658>.
- [30] H. Sereshti, G. Abdolhosseini, S. Soltani, F. Jamshidi, N. Nouri, Natural thymol-based ternary deep eutectic solvents: Application in air-bubble assisted-dispersive liquid-liquid microextraction for the analysis of tetracyclines in water, *J. Sep. Sci.* 44 (2021) 3626–3635, <https://doi.org/10.1002/jssc.202100495>.
- [31] F. Bergua, M. Castro, J. Muñoz-Embid, C. Lafuente, M. Arta, Hydrophobic eutectic solvents: Thermophysical study and application in removal of pharmaceutical products from water, *Chem. Eng. J.* 411 (2021), 128472, <https://doi.org/10.1016/j.cej.2021.128472>.
- [32] A.G. Pekel, E. Kurtulbaş, İ. Toprakçı, S. Şahin, Menthol-based deep eutectic solvent for the separation of carbamazepine: reactive liquid-liquid extraction, *Biomass Convers. Biorefin.* 12 (2022) 1249–1256, <https://doi.org/10.1007/s13399-020-00707-z>.
- [33] F. Bergua, M. Castro, J. Muñoz-Embid, C. Lafuente, M. Arta, L-menthol-based eutectic solvents: Characterization and application in the removal of drugs from water, *J. Mol. Liq.* 352 (2022), 118754, <https://doi.org/10.1016/j.molliq.2022.118754>.
- [34] P. Gutiérrez-Sánchez, D. Rodríguez-Llorente, P. Navarro, V.I. Águeda, S. Álvarez-Torrellas, J. García, M. Larriba, Extraction of antibiotics identified in the EU Watch List 2020 from hospital wastewater using hydrophobic eutectic solvents and terpenoids, *Sep. Purif. Technol.* 282 (2022), 120117, <https://doi.org/10.1016/j.seppur.2021.120117>.
- [35] K.H. Hama Aziz, H. Miessner, S. Mueller, D. Kalass, D. Moeller, I. Khorshid, M.A. M. Rashid, Degradation of pharmaceutical diclofenac and ibuprofen in aqueous solution, a direct comparison of ozonation, photocatalysis, and non-thermal plasma, *Chem. Eng. J.* 313 (2017) 1033–1041, <https://doi.org/10.1016/j.cej.2016.10.137>.
- [36] M.H. Zainal-Abidin, M. Hayyan, N.S. Jayakumar, New horizons in the extraction of bioactive compounds using deep eutectic solvents: A review, *Anal. Chim. Acta* 979 (2017) 1–23, <https://doi.org/10.1016/j.aca.2017.05.012>.
- [37] E. Riveiro, B. González, Á. Domínguez, Extraction of adipic, levulinic and succinic acids from water using TOPO-based deep eutectic solvents, *Sep. Purif. Technol.* 241 (2020), 116692, <https://doi.org/10.1016/j.seppur.2020.116692>.
- [38] D. Smink, S.R.A. Kersten, B. Schuur, Recovery of lignin from deep eutectic solvents by liquid-liquid extraction, *Sep. Purif. Technol.* 235 (2020), 116127, <https://doi.org/10.1016/j.seppur.2019.116127>.
- [39] L.B. Santos, R.S. Assis, J.A. Barreto, M.A. Bezerra, C.G. Novaes, V.A. Lemos, Deep eutectic solvents in liquid-phase microextraction: Contribution to green chemistry, *TrAC – Trend. Anal. Chem.* 146 (2022), <https://doi.org/10.1016/j.trac.2021.116478>.
- [40] L.I.N. Tomé, V. Baía, W. da Silva, C.M.A. Brett, Deep eutectic solvents for the production and application of new materials, *Appl. Mater. Today* 10 (2018) 30–50, <https://doi.org/10.1016/j.apmt.2017.11.005>.
- [41] J. Wu, Q. Liang, X. Yu, L. Qiu-Feng, L. Ma, X. Qin, G. Chen, B. Li, Deep Eutectic Solvents for Boosting Electrochemical Energy Storage and Conversion: A Review and Perspective, *Adv. Funct. Mater.* 31 (2021), <https://doi.org/10.1002/adfm.202011102>.
- [42] D.A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I.M. Pastor, D.J. Ramón, Deep Eutectic Solvents: The Organic Reaction Medium of the Century, *Eur. J. Org. Chem.* 2016 (2016) 612–632, <https://doi.org/10.1002/ejoc.201501197>.
- [43] G. di Carmine, A.P. Abbott, C. D'Agostino, Deep eutectic solvents: alternative reaction media for organic oxidation reactions, *React. Chem. Eng.* 6 (2021) 582–598, <https://doi.org/10.1039/D0RE00458H>.
- [44] X. Li, K.H. Row, Development of deep eutectic solvents applied in extraction and separation, *J. Sep. Sci.* 39 (2016) 3505–3520, <https://doi.org/10.1002/jssc.201600633>.
- [45] D. Rodríguez-Llorente, A. Cañada-Barcala, S. Álvarez-Torrellas, V.I. Águeda, J. García, M. Larriba, A Review of the Use of Eutectic Solvents, Terpenes and Terpenoids in Liquid–liquid Extraction Processes, *Processes* 8 (2020) 1220, <https://doi.org/10.3390/pr8101220>.
- [46] D. Jha, M.B. Haider, R. Kumar, M.S. Balathanigaimani, Extractive desulfurization of fuels using diglycol based deep eutectic solvents, *J. Environ. Chem. Eng.* 8 (2020), 104182, <https://doi.org/10.1016/j.jece.2020.104182>.
- [47] M.B. Haider, M. Dwivedi, D. Jha, R. Kumar, B. Marriyappan Sivagnanam, Azeotropic separation of isopropanol-water using natural hydrophobic deep eutectic solvents, *J. Environ. Chem. Eng.* 9 (2021), 104786, <https://doi.org/10.1016/j.jece.2020.104786>.
- [48] Y. Dai, J. van Spronsen, G.-J.-J. Witkamp, R. Verpoorte, Y.H. Choi, Natural deep eutectic solvents as new potential media for green technology, *Anal. Chim. Acta* 766 (2013) 61–68, <https://doi.org/10.1016/j.aca.2012.12.019>.
- [49] A. Paiva, R. Craveiro, I. Aroso, M. Martins, R.L. Reis, A.R.C. Duarte, Natural Deep Eutectic Solvents – Solvents for the 21st Century, *ACS Sustainable Chem. Eng.* 2 (2014) 1063–1071, <https://doi.org/10.1021/sc500096j>.
- [50] Y. Liu, J.B. Friesen, J.B. McAlpine, D.C. Lankin, S.N. Chen, G.F. Pauli, Natural Deep Eutectic Solvents: Properties, Applications, and Perspectives, *J. Nat. Prod.* 81 (2018) 679–690, <https://doi.org/10.1021/acs.jnatprod.7b00945>.
- [51] T.E. Phelps, N. Bhawawet, S.S. Jurisson, G.A. Baker, Efficient and Selective Extraction of 99mTcO₄⁻ from Aqueous Media Using Hydrophobic Deep Eutectic

- Solvents, *ACS Sustainable Chem. Eng.* 6 (2018) 13656–13661, <https://doi.org/10.1021/acssuschemeng.8b03950>.
- [52] D.J.G.P. van Osch, C.H.J.T. Dietz, J. van Spronsen, M.C. Kroon, F. Gallucci, M. van Sint Annaland, R. Tuinier, A Search for Natural Hydrophobic Deep Eutectic Solvents Based on Natural Components, *ACS Sustainable Chem. Eng.* 7 (2019) 2933–2942, <https://doi.org/10.1021/acssuschemeng.8b03520>.
- [53] N. Schaeffer, M.A.R. Martins, C.M.S.S. Neves, S.P. Pinho, J.A.P. Coutinho, Sustainable hydrophobic terpene-based eutectic solvents for the extraction and separation of metals, *Chem. Commun.* 54 (2018) 8104–8107, <https://doi.org/10.1039/C8CC04152K>.
- [54] B.D. Ribeiro, C. Florindo, L.C. Iff, M.A.Z.Z. Coelho, I.M. Marrucho, Menthol-based Eutectic Mixtures: Hydrophobic Low Viscosity Solvents, *ACS Sustainable Chem. Eng.* 3 (2015) 2469–2477, <https://doi.org/10.1021/acssuschemeng.5b00532>.
- [55] F. Bezold, M. Minceva, Liquid-liquid equilibria of n-heptane, methanol and deep eutectic solvents composed of carboxylic acid and monocyclic terpenes, *Fluid Phase Equilib.* 477 (2018) 98–106, <https://doi.org/10.1016/j.fluid.2018.08.020>.
- [56] R. Verma, M. Mohan, V.V. Goud, T. Banerjee, Operational Strategies and Comprehensive Evaluation of Menthol Based Deep Eutectic Solvent for the Extraction of Lower Alcohols from Aqueous Media, *ACS Sustainable Chem. Eng.* 6 (2018) 16920–16932, <https://doi.org/10.1021/acssuschemeng.8b04255>.
- [57] M.A.R. Martins, L.P. Silva, N. Schaeffer, D.O. Abranches, G.J. Maximo, S.P. Pinho, J.A.P. Coutinho, Greener Terpene-Terpene Eutectic Mixtures as Hydrophobic Solvents, *ACS Sustainable Chem. Eng.* 7 (2019) 17414–17423, <https://doi.org/10.1021/acssuschemeng.9b04614>.
- [58] S. Rozas, N. Alomari, S. Aparicio, M. Atilhan, Nanoscopic study on carvone-terpene based natural deep eutectic solvents, *J. Chem. Phys.* 155 (2021), 224702, <https://doi.org/10.1063/5.0074823>.
- [59] L. Zamora, C. Benito, A. Gutiérrez, R. Alcalde, N. Alomari, A. al Bodour, M. Atilhan, S. Aparicio, Nanostructuring and macroscopic behavior of type V deep eutectic solvents based on monoterpenoids, *PCPP* 24 (2022) 512–531, <https://doi.org/10.1039/D1CP04509A>.
- [60] S. Rozas, N. Alomari, M. Atilhan, S. Aparicio, Theoretical insights into the cineole-based deep eutectic solvents, *J. Chem. Phys.* 154 (2021), 184504, <https://doi.org/10.1063/5.0048369>.
- [61] D.O. Abranches, J.A.P. Coutinho, Type V deep eutectic solvents: Design and applications, *Curr. Opin. Green Sustainable Chem.* 35 (2022), 100612, <https://doi.org/10.1016/j.cogsc.2022.100612>.
- [62] D.O. Abranches, M.A.R. Martins, L.P. Silva, N. Schaeffer, S.P. Pinho, J.A. P. Coutinho, Phenolic hydrogen bond donors in the formation of non-ionic deep eutectic solvents: the quest for type V DES, *Chem. Commun.* 55 (2019) 10253–10256, <https://doi.org/10.1039/C9CC04846D>.
- [63] S. Zwenger Chhandak Basu, S. Zwenger, C. Basu, *Plant Terpenoids: Applications and Future Potentials*, *Biotechnol. Molec. Biol. Rev.* 3 (2008) 1–107.
- [64] C. Boutekedjiret, M.A. Vian, F. Chemat, Terpenes as Green Solvents for Natural Products Extraction, in: *Alternative Solvents for Natural Products Extraction. Green Chemistry and Sustainable Technology*, Springer Verlag Berlin Heidelberg, Berlin, Germany, 2014, pp. 205–219, https://doi.org/10.1007/978-3-662-43628-8_9.
- [65] S. Madji, S. Hilali, A.-S. Fabiano-Tixier, M. Tenon, A. Bily, M. Laguerre, F. Chemat, para-Menthane as a Stable Terpene Derived from Orange By-Products as a Novel Solvent for Green Extraction and Solubilization of Natural Substances, *Molecules* 24 (2019) 2170, <https://doi.org/10.3390/molecules24112170>.
- [66] K. Li, J.H. Nam, S. Kang, Y. Liu, J. Lee, Carvone and its eutectic mixtures as novel, biodegradable, and tunable solvents to extract hydrophobic compounds in substitution for volatile toxic solvents, *Food Chem.* 374 (2022), 131630, <https://doi.org/10.1016/j.foodchem.2021.131630>.
- [67] M.-T. Golmakani, J.A. Mendiola, K. Rezaei, E. Ibáñez, Pressurized limonene as an alternative bio-solvent for the extraction of lipids from marine microorganisms, *J. Supercrit. Fluids.* 92 (2014) 1–7, <https://doi.org/10.1016/j.supflu.2014.05.001>.
- [68] S. Hamiche, N. Bouzidi, Y. Daghbouche, A. Badis, S. Garrigues, M. de la Guardia, M. El Hattab, Eucalyptol-based green extraction of brown alga *Zonaria tournefortii*, *Sustainable Chem. Pharm.* 10 (2018) 97–102, <https://doi.org/10.1016/j.scp.2018.10.005>.
- [69] D. Rodríguez-Llorente, A. Bengoa, G. Pascual-Muñoz, P. Navarro, V.I. Águeda, J. A. Delgado, S. Álvarez-Torrellas, G. García, M. Larriba, Sustainable Recovery of Volatile Fatty Acids from Aqueous Solutions Using Terpenoids and Eutectic Solvents, *ACS Sustainable Chem. Eng.* 7 (2019) 16786–16794, <https://doi.org/10.1021/acssuschemeng.9b04290>.
- [70] H. Li, Z. Feng, L. Wan, C. Huang, T. Zhang, Y. Fang, (Liquid + liquid) equilibria of four alcohol–water systems containing 1,8-cineole at T = 298.15 K, *J. Chem. Thermodyn.* 101 (2016) 387–394, <https://doi.org/10.1016/j.jct.2016.06.010>.
- [71] L. Wan, H. Li, C. Huang, Y. Feng, G. Chu, Y. Zheng, W. Tan, Y. Qin, D. Sun, Y. Fang, Influence of the temperature on the (liquid + liquid) phase equilibria of (water + 1-propanol + linalool or geraniol), *J. Chem. Thermodyn.* 109 (2016) 109–116, <https://doi.org/10.1016/j.jct.2016.12.011>.
- [72] H. Li, L. Wan, G. Chu, W. Tan, B. Liu, Y. Qin, Y. Feng, D. Sun, Y. Fang, (Liquid+liquid) extraction of phenols from aqueous solutions with cineole, *J. Chem. Thermodyn.* 107 (2016) 95–103, <https://doi.org/10.1016/j.jct.2016.12.018>.
- [73] D. Rodríguez-Llorente, A. Cañada-Barcala, C. Muñoz, G. Pascual-Muñoz, P. Navarro, R. Santiago, V. Ismael Águeda, S. Álvarez-Torrellas, J. García, M. Larriba, Separation of phenols from aqueous streams using terpenoids and hydrophobic eutectic solvents, *Sep. Purif. Technol.* 251 (2020), 117379, <https://doi.org/10.1016/j.seppur.2020.117379>.
- [74] A. Klamt, Conductor-like Screening Model for Real Solvents: A New Approach to the Quantitative Calculation of Solvation Phenomena, *J. Phys. Chem.* 99 (1995) 2224–2235, <https://doi.org/10.1021/j100007a062>.
- [75] A. Klamt, V. Jonas, T. Bürger, J.C.W. Lohrenz, Refinement and Parametrization of COSMO-RS, *J. Phys. Chem. A* 102 (1998) 5074–5085, <https://doi.org/10.1021/jp980017s>.
- [76] F. Eckert, A. Klamt, Fast solvent screening via quantum chemistry: COSMO-RS approach, *AIChE J.* 48 (2002) 369–385, <https://doi.org/10.1002/aic.690480220>.
- [77] M.A.R. Martins, E.A. Crespo, P.V.A. Pontes, L.P. Silva, M. Bülow, G.J. Maximo, E. A.C. Batista, C. Held, S.P. Pinho, J.A.P. Coutinho, Tunable Hydrophobic Eutectic Solvents Based on Terpenes and Monocarboxylic Acids, *ACS Sustainable Chem. Eng.* 6 (2018) 8836–8846, <https://doi.org/10.1021/acssuschemeng.8b01203>.
- [78] M. Larriba, M. Ayuso, P. Navarro, N. Delgado-Mellado, M. Gonzalez-Miquel, J. García, F. Rodríguez, Choline Chloride-Based Deep Eutectic Solvents in the Dearomatization of Gasolines, *ACS Sustainable Chem. Eng.* 6 (2018) 1039–1047, <https://doi.org/10.1021/acssuschemeng.7b03362>.
- [79] D. Rodríguez-Llorente, P. Navarro, R. Santiago, V.I. Águeda, S. Álvarez-Torrellas, J. García, M. Larriba, Extractive removal and recovery of bisphenol A from aqueous solutions using terpenoids and hydrophobic eutectic solvents, *J. Environ. Chem. Eng.* 9 (2021), 106128, <https://doi.org/10.1016/j.jece.2021.106128>.
- [80] Y. Segura, A. Cruz del Álamo, M. Munoz, S. Álvarez-Torrellas, J. García, J. A. Casas, Z.M. De Pedro, F. Martínez, A comparative study among catalytic wet air oxidation, Fenton, and Photo-Fenton technologies for the on-site treatment of hospital wastewater, *J. Environ. Manage.* 290 (2021), <https://doi.org/10.1016/j.jenvman.2021.112624>.
- [81] A. Moure, D. Franco, J. Sineiro, H. Domínguez, M.J. Núñez, Simulation of multistage extraction of antioxidants from Chilean hazelnut (Gevuina avellana) hulls, *J. Am. Oil Chem. Soc.* 80 (2003) 389–396, <https://doi.org/10.1007/s11746-003-0709-x>.
- [82] U. Injarean, P. Pichestapong, P. Kewsuwan, J. Loahaphornchaiphon, Batch Simulation of Multistage Counter-current Extraction of Uranium in Yellow Cake from Monazite Processing with 5% TBP/Kerosene, *Energy Procedia* 56 (2014) 129–134, <https://doi.org/10.1016/j.egypro.2014.07.140>.
- [83] J.D. Henley, E.J. Seader, *Equilibrium-Stage Separation Operations in Chemical Engineering*, John Wiley and Sons, New York, 1981.
- [84] F. Orias, Y. Perrodin, Characterisation of the ecotoxicity of hospital effluents: A review, *Sci. Total Environ.* 454–455 (2013) 250–276, <https://doi.org/10.1016/j.scitotenv.2013.02.064>.
- [85] A. Casas, J. Palomar, M.V. Alonso, M. Oliet, S. Omar, F. Rodriguez, Comparison of lignin and cellulose solubilities in ionic liquids by COSMO-RS analysis and experimental validation, *Ind. Crops Prod.* 37 (2012) 155–163, <https://doi.org/10.1016/j.indcrop.2011.11.032>.
- [86] E. Hernández, R. Santiago, C. Moya, P. Navarro, J. Palomar, Multiscale evaluation of CO₂-derived cyclic carbonates to separate hydrocarbons: Drafting new competitive processes, *Fuel Process. Technol.* 212 (2021), 106639, <https://doi.org/10.1016/j.fuproc.2020.106639>.
- [87] Kirk-Othmer, ed., *Kirk-Othmer Chemical Technology of Cosmetics*, John Wiley & Sons, Hoboken, New Jersey; 2013.
- [88] Alibaba Group, (n.d.). www.alibaba.com (accessed March 16, 2022).
- [89] Y. Huang, D. Ouyang, Y. Ji, The role of H-bond in solubilizing drugs by ionic liquids: a molecular dynamics and density functional theory study, *AIChE J.* (2022), <https://doi.org/10.1002/aic.17672>.
- [90] M. Mokhtarpour, H. Shekaari, M.T. Zafarani-Moattar, S. Golgoun, Solubility and solvation behavior of some drugs in choline based deep eutectic solvents at different temperatures, *J. Mol. Liq.* 297 (2020), 111799, <https://doi.org/10.1016/j.molliq.2019.111799>.
- [91] J. Bones, K. Thomas, P.N. Nesterenko, B. Paull, On-line preconcentration of pharmaceutical residues from large volume water samples using short reversed-phase monolithic cartridges coupled to LC-UV-ESI-MS, *Talanta* 70 (2006) 1117–1128, <https://doi.org/10.1016/j.talanta.2006.02.026>.
- [92] G.G. Raymond, J.L. Born, An updated pKa listing of medicinal compounds, *Drug Intellig. Clin. Pharm.* 20 (1986) 683–686, <https://doi.org/10.1177/106002808602000910>.
- [93] K. Nödler, T. Licha, K. Bester, M. Sauter, Development of a multi-residue analytical method, based on liquid chromatography-tandem mass spectrometry, for the simultaneous determination of 46 micro-contaminants in aqueous samples, *J. Chromatogr. A* 1217 (2010) 6511–6521, <https://doi.org/10.1016/j.chroma.2010.08.048>.
- [94] Ben. Lake, Ethyl Acetate, *ICIS Chemical Business.* 291 (2017) 97.
- [95] Jackie. Wong, Fatty acids, *ICIS Chemical Business.* 296 (2019) 32.
- [96] *ICIS Chemical Business*, *ICIS*, 1. (2016) 4. <https://www.icis.com/> (accessed January 19, 2021).
- [97] A.M. Hyde, S.L. Zultanski, J.H. Waldman, Y.-L. Zhong, M. Shevlin, F. Peng, General Principles and Strategies for Salting-Out Informed by the Hofmeister Series, *Org. Process Res. Dev.* 21 (2017) 1355–1370, <https://doi.org/10.1021/acs.oprd.7b00197>.
- [98] T. Oncsik, G. Trefalt, M. Borkovec, I. Szilagyi, Specific Ion Effects on Particle Aggregation Induced by Monovalent Salts within the Hofmeister Series, *Langmuir* 31 (2015) 3799–3807, <https://doi.org/10.1021/acs.langmuir.5b00225>.
- [99] H. Chahiyani, F. Gharib, A. Farajtabar, Thermodynamic studies on solubility and protonation constant of acetaminophen at different ionic strengths and various temperatures, *J. Mol. Liq.* 199 (2014) 137–142, <https://doi.org/10.1016/j.molliq.2014.08.033>.
- [100] F.F. Liu, J. Zhao, S. Wang, P. Du, B. Xing, Effects of solution chemistry on adsorption of selected pharmaceuticals and personal care products (PPCPs) by

- graphenes and carbon nanotubes, *Environ. Sci. Technol.* 48 (2014) 13197–13206, <https://doi.org/10.1021/es5034684>.
- [101] A. Burant, G.V. Lowry, A.K. Karamalidis, Measurement and Modeling of Setschenow Constants for Selected Hydrophilic Compounds in NaCl and CaCl₂ Simulated Carbon Storage Brines, *Acc. Chem. Res.* 50 (2017) 1332–1341, <https://doi.org/10.1021/acs.accounts.6b00567>.
- [102] H. Shekaari, M.T.Z. Moattar, F. Ghaffari, Solvation properties of acetaminophen in aqueous ionic liquid, 1-hexyl-3-methylimidazolium bromide, solutions at different temperatures, *J. Mol. Liq.* 202 (2015) 86–94, <https://doi.org/10.1016/j.molliq.2014.12.015>.
- [103] H. Shekaari, B. Golmohammadi, S. Faraji, M. Mokhtarpour, A. Sadrmousavi, S. Gharouni Fattah, M. Taghi Zafarani-Moattar, Thermodynamic and computational study of paracetamol in aqueous solutions of some sustainable amino acid-based ionic liquids, *J. Chem. Thermodyn.* 155 (2021), 106348, <https://doi.org/10.1016/j.jct.2020.106348>.
- [104] J. Coates, Interpretation of Infrared Spectra, A Practical Approach, in: *Encyclopedia of Analytical Chemistry*, John Wiley & Sons, Ltd, Chichester, UK, 2006: pp. 1–23. <https://doi.org/10.1002/9780470027318.a5606>.
- [105] N. Delgado-Mellado, M. Larriba, P. Navarro, V. Rigual, M. Ayuso, J. García, F. Rodríguez, Thermal stability of choline chloride deep eutectic solvents by TGA/FTIR-ATR analysis, *J. Mol. Liq.* 260 (2018) 37–43, <https://doi.org/10.1016/j.molliq.2018.03.076>.