Extraction of antibiotics identified in the EU Watch List 2020 from hospital wastewater using hydrophobic eutectic solvents and terpenoids

Pablo Gutiérrez-Sánchez,[a] Diego Rodríguez-Llorente,[a] Pablo Navarro,[b] V. Ismael Águeda,[a] Silvia Álvarez-Torrellas,[a] Juan García,[a] Marcos Larriba[a,*]

[a]*Grupo de Catálisis y Procesos de Separación (CyPS), Departamento de Ingeniería Química y de Materiales, Universidad Complutense de Madrid, Avda. Complutense s/n, 28040 Madrid, Spain*
[b]*Departamento de Ingeniería Química, Universidad Autónoma de Madrid, C/ Francisco Tomás y Valiente 7, 28049 Madrid, Spain*

Abstract

The increasing consumption of pharmaceuticals, along with the ineffectiveness of conventional wastewater treatment, has resulted in an increased presence of these pollutants in both drinking water supplies and aquatic environments. The potential adverse health effects and environmental impact of these chemicals are drawing the attention of several bodies around the world. For instance, some antibiotics such as ciprofloxacin, trimethoprim, and sulfamethoxazole have been included in the most recent European Surface Water Watch List under the EU Water Framework Directive (Decision 2020/1161). The present work proposes the use of terpenoids and eutectic solvents, as effective and green solvents with low toxicity, for multicomponent liquid-liquid extraction of ciprofloxacin, trimethoprim, and sulfamethoxazole from ultrapure water and hospital wastewater. The COSMO-RS method was used for a predictive initial solvent screening. Thymol, carvacrol, eutectic solvents (thymol + fatty acids), and conventional solvents (methyl isobutyl ketone and ethyl acetate) were selected to be used in the experiments. The influence of the volume S/F ratio, aqueous matrix, and pH was analysed. Conventional solvents show significantly lower overall extraction yields than those observed for eutectic solvents and terpenoids at any pH and matrix. Carvacrol presented the most favourable conditions, reaching overall extraction yields above 98.0% (98.9% for trimethoprim, 99.5% for ciprofloxacin, and 97.0% for sulfamethoxazole) with hospital wastewater at pH 5.0 and S/F ratio of 1.00. Carvacrol showed a feasible operating in a continuous extraction column at room temperature, providing effective reuse and regeneration processes in this study.

Keywords: Antibiotics; Terpenoids; Eutectic solvents; Liquid-liquid extraction; Solvent recovery.

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[*] Corresponding author. Tel.: +34 91 394 4135. E–mail address: marcoslarriba@ucm.es (Marcos Larriba).

1. Introduction

The pharmaceutical industry has played a key role in both developed and developing countries, increasing life expectancy and having to adapt to changing policy environments [1,2]. Pharmaceuticals are substances used as medicinal drugs to produce a therapeutic effect, comprising a wide variety of organic compounds: antibiotics, blood lipid regulators, hormones, anti-inflammatory drugs, β-blockers, antiepileptic drugs, contrast media, and cytostatic drugs [3–5].

Nowadays, antibiotics are one of the most widespread pharmaceuticals all over the world, and their global consumption reaches values of around 100,000 and 200,000 tons per year. The United States of America stands out as one of the leading manufacturers, producing more than 20,000 tons of antibiotics annually, 60% for human use and 40% for veterinary applications. These compounds are used to treat bacterial and fungal infections and contain chemical subgroups such as macrolides, sulfonamides, or fluoroquinolones [5–7]. Many of them are derived wholly or partially from certain microorganisms, but some are synthetic [8]. So far, one of the most discussed topics related to the effects induced by pharmaceuticals is the development of antimicrobial resistance in bacterial populations, which is favored by the exposure to low concentrations of antibiotics [6,9–13].

In fact, pharmaceuticals are considered as one of the most critical emerging pollutants. They are released into the environment mainly due to their incomplete removal in Wastewater Treatment Plants (WWTP), in addition to other sources such as hospital effluents, waste from industry and livestock, and the disposal of unused or expired pharmaceutical products [4,14–16]. The average concentration of antibiotics in hospital effluents ranges from 5 to 10 times higher than that measured in WWTP effluents [17].

Due to the lack of data about the possible chronic health effects associated with the long-term ingestion of pharmaceuticals at low concentrations, these compounds are not either regulated or included in the models for the assessment of water quality index [4,6,18–20]. However, their potential environmental impact and adverse health effects have drawn the attention of health bodies and agencies worldwide. For this reason, antibiotics such as sulfamethoxazole, trimethoprim, and ciprofloxacin have been included in the second and the third versions of the EU Watch List of contaminants of emerging concern under the Water Framework Directive [21–23].

Over the last few years, several techniques have been studied for the removal of pharmaceuticals from wastewater, such as activated sludge treatment [24–27], membrane bioreactor [28–32], constructed wetland [33–37], adsorption [3,38–40], membrane filtration (ultrafiltration, nanofiltration and reverse osmosis) [41–46], and advanced oxidation processes (wet air oxidation; electrochemical oxidation; photolysis; ultrasound irradiation; heterogeneous photocatalysis; ozone and ozone/hydrogen peroxide treatment; and Fenton oxidation) [15,18,47–51].

Liquid-liquid extraction has also been studied in the pharmaceutical industry, although mainly applied to the isolation and purification of pharmaceutical compounds during their production, rather than for wastewater treatment [4,47,52,53]. This technique has traditionally presented drawbacks, such as excessive and unsustainable consumption of non-renewable and environmentally hazardous substances [54,55]. In this regard, terpenes and terpenoids, which are plant products derived from the basic isoprene unit, stand out as a group of renewable solvents [56–59]. They also show less toxicity than conventional petroleum-based solvents [60–64]. On the other hand, eutectic solvents might also be proposed as an emerging class of green solvents. They are a newly discovered sort of mixtures with depression in melting points in comparison to those for pure components, mainly due to hydrogen bonding interactions between the compounds of the mixture [65–74].

The aim of this research is to study the behavior of terpenoids and eutectic solvents as extractants to be used in the multicomponent extraction of ciprofloxacin, trimethoprim, and sulfamethoxazole from ultrapure water and hospital wastewater. As reported in the literature, these three antibiotics are frequently detected in this sort of sewage [75]. Making an initial selection of suitable solvents through molecular simulation with Conductor like Screening Model for Real Solvents (COSMO-RS) methodology, the following solvents were selected to move on to the experimental phase: 2 terpenoids (thymol and carvacrol), 3 hydrophobic eutectic solvents (thymol + dodecanoic acid, thymol + decanoic acid and thymol + octanoic acid) and 2 conventional solvents (ethyl acetate and methyl isobutyl ketone) [76,77]. In addition, the effect of pH and aqueous matrix on the liquid-liquid extraction process was analysed. Several experiments were carried out in vials (batch operation) and in a packed column (continuous operation), also evaluating the solvent reuse and recovery by vacuum distillation.

2. Experimental section

2.1. Materials

Chemical compounds used in this paper are listed in Table 1, also detailing chemical structures, suppliers, purities, melting points (T_m), and boiling temperatures (T_b). Ultrapure water was obtained from PURELAB® Flex Water Purification System (Veolia).

Hospital wastewater effluent was collected from a hospital located in the southern zone of Madrid (Spain), and its characterization is summarized in Table 2 [78]. This sample was used to test the antibiotic extraction from an environmentally-relevant aqueous matrix.

2.2. Screening of solvents using the COSMO-RS method.

An initial selection of suitable solvents was performed through molecular simulation with COSMO-RS method using COSMO*therm* software (version 19.0.4). Since terpenoids are not found as conventional compounds in COSMO*therm* database, COSMO continuum solvation model at the BVP86/TZVP calculation theory level was used to optimize their geometry and build the .cosmo file, whereas default BP_TZVP_19 parametrization was used to screen the solvents in COSMO*therm* software. For solvent screening, infinite dilution activity coefficients of ciprofloxacin, trimethoprim, and sulfamethoxazole were estimated in 43 terpenoids, 11 hydrophobic eutectic solvents, and 5 conventional solvents at 323.15 K, being the experimental temperature. To ensure working in the infinite dilution region, all simulations were carried out considering an antibiotic mole fraction of $5 \cdot 10^{-5}$ [79]. This approach has been successfully used in the liquid−liquid extraction of phenols and volatile fatty acids with terpenes, terpenoids and eutectic solvents composed by them [80,81]. As reported in the literature, the eutectic solvents were successfully described as a mixture of solvents at the eutectic composition [72,80–83].

2.3. Preparation of eutectic solvents

The three eutectic solvents selected from the screening described previously were prepared at their eutectic composition. The thymol mole fractions used were 0.56, 0.44, and 0.33 in the mixtures (thymol + dodecanoic acid), (thymol + decanoic acid), and (thymol + octanoic acid), respectively. At the eutectic point, melting temperatures for the previous eutectic solvents mentioned are 270.82, 287.00, and 306.30 K [83]. The compounds were weighed in an analytical balance M-420 CBC (Cobos CB-Complet, precision ± 0.001 g). The mixture was melted under stirring in a thermostatic bath at 323.2 ± 0.1 K and, once a homogenous liquid mixture appeared, it was cooled to room temperature.

Table 1. Physicochemical properties of the compounds used in this paper [84,85].

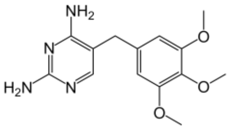
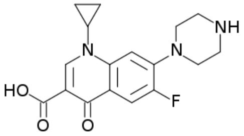
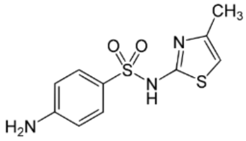
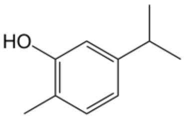
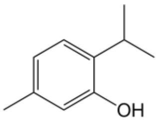
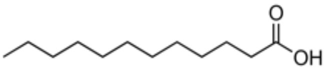
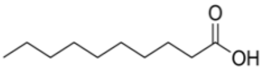
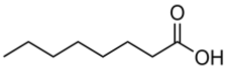
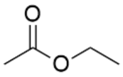
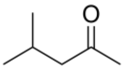
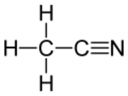
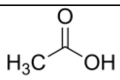
Chemical	Structure	Supplier	Purity (wt %)	T_m (K)	T_b (K)
Antibiotics					
Trimethoprim		Sigma-Aldrich	≥ 99	474.2	-
Ciprofloxacin		Sigma-Aldrich	≥ 98.0	-	-
Sulfamethoxazole		Sigma-Aldrich	≥ 98.0	442.7	-
Extraction solvents					
Carvacrol		Sigma-Aldrich	≥ 98.0	276.7	509.7
Thymol		Sigma-Aldrich	≥ 99.0	322.7	505.2
Dodecanoic acid		Sigma-Aldrich	98.0	318.2	571.2
Decanoic acid		Sigma-Aldrich	≥ 98.0	302.2	542.2
Octanoic acid		Sigma-Aldrich	≥ 98.0	289.2	510.2
Ethyl acetate		Fluka	> 99.5	189.5	350.1
Methyl isobutyl ketone (MIBK)		Sigma-Aldrich	99.0	189.1	389.6
Other chemicals					
Acetonitrile		Scharlau	≥ 99.9	227.5	354.8
Acetic acid		PanReac	≥ 99.7	289.9	391.2
Hydrochloric acid	H−Cl	Fluka	37	238.2	315.2

Table 2. Macroscopic characterization of the raw hospital wastewater [78].

Parameters	Value
pH	8.5
Chemical Oxygen Demand (mg/L)	332
Total Organic Carbon (mg/L)	286
Total Nitrogen (mg/L)	90.1
Total Dissolved Solids (mg/L)	0.5
CO_3^{2-} (mg/L)	365.5[a]
Conductivity at 20 ºC (μS/cm)	2360

a Calculated from Total Inorganic Carbon measurement.

2.4. Preparation of multicomponent aqueous solutions of antibiotics in ultrapure water and hospital wastewater

Firstly, a multicomponent aqueous solution of ciprofloxacin, trimethoprim, and sulfamethoxazole was prepared at 50 mg/L of each antibiotic in ultrapure water by using an analytical balance TE124S (Sartorius, precision ± 0.0001 g). This range of concentration has been previously reported by other authors [78,86–90]. The pH of the solution prepared in ultrapure water was measured by using a 2002 pH meter (Crison), reaching a value of 6.5.

To test the effect of the matrix, the aqueous solution mentioned above was also prepared using hospital wastewater, resulting in a pH of 8.0. Also, in order to study the effect of pH, two more solutions were prepared in hospital wastewater by adjusting the pH to 6.5 and 5.0 with hydrochloric acid 37 wt.%.

2.5. Multicomponent liquid-liquid extraction of antibiotics from water and hospital wastewater in vial

Liquid-liquid extraction of the previously prepared aqueous solutions was carried out with each of the 6 selected solvents: 2 terpenoids (thymol and carvacrol), 3 eutectic solvents (thymol + dodecanoic acid, thymol + decanoic acid and thymol + octanoic acid), and 2 conventional solvents (MIBK and ethyl acetate). Feed and solvent were mixed according to the following volumetric solvent/feed (S/F) ratios: 2.00, 1.00, 0.50, 0.25, and 0.10. Both phases were placed in 8 mL glass vials with magnetic stirring in a C-MAG HS 7 dry bath (IKA) at 323.2 ± 0.1 K for 12 h, time to ensure equilibrium conditions. This temperature was selected to ensure the liquid state of the 6 extraction solvents and to compare the results obtained under the same operating conditions. 4 hours after stirring, the two phases were settled and sampled using glass

Pasteur pipettes, maintaining a constant temperature of 323.2 ± 0.1 K for all the steps. The concentration of the organic compounds in the raffinate (aqueous phase at the bottom of the vial) was determined by using an analytical High Performance Liquid Chromatograph 1260 Infinity II with Diode Array Detector (Agilent), and a Poroshell 120 EC-C18 chromatographic column (4.6 x 150 mm, 4 µm). Thus, a mobile phase consisting of a mixture of acetonitrile and an aqueous acetic acid solution 75 mM was used. The volumetric flow rate was 0.9 mL/min and the column temperature was set at 313.2 K. The wavelengths to measure the concentration of antibiotics and organic solvents in the raffinate phase were 233 nm and 275 nm.

2.6. *Multicomponent liquid-liquid extraction of antibiotics from hospital wastewater in a packed column*

In order to study the mass transfer effect and evaluate the scale-up of the liquid-liquid extraction process, continuous parallel extraction was accomplished in a column of 8 mm internal diameter and 80 mm length, filled with a bed of glass spheres of 2 mm diameter. The multicomponent aqueous solution of antibiotics in hospital wastewater at pH 5.0 was used as feed, whereas carvacrol was the solvent selected due to the promising results obtained in the vial extraction tests (batch mode). By using a KDS 100 Legacy (Fisher Scientific) and an Orion Sage M361(Thermo Orion Sage) syringe pumps, feed and solvent were introduced into the column at 298.2 ± 1 K (room temperature) according to the following volumetric S/F ratios: 2.00, 1.00, and 0.50. This operating temperature was selected due to the low melting point of carvacrol (Table 1), which guarantees the liquid state of the solvent at room temperature and avoids the energy costs associated with heating. The total volumetric flow rate remained constant during the three experiments at 10 mL/h and the residence time in the column was 21 min. After leaving the column, both phases were settled and analyzed using the same procedure previously described in the batch extraction. A scheme of the packed column installation is included in Figure S1 of the Supplementary Material.

2.7. *Solvent reuse in consecutive* stages *of antibiotic extraction from hospital wastewater and solvent recovery*

Another key aspect for the implementation of an industrial-scale extraction process is the evaluation of the solvent reuse. For this purpose, multicomponent aqueous solution of ciprofloxacin, trimethoprim, and sulfamethoxazole in hospital wastewater with pH adjusted to 5.0 was used as feed. Regarding the solvent, and due to the promising results obtained in the vial extraction experiments, only carvacrol was selected at a volumetric S/F ratio of 1.00. Five consecutive extraction stages were carried out in 500 mL glass bottles with magnetic stirring at

298.2 ± 1 K (room temperature) for 12 hours, time to ensure the equilibrium. For the first extraction stage, 125 mL of feed and 125 mL of fresh solvent were brought into contact. For the rest, fresh feed and solvent from the previous stage were used. The volumes of each phase for stages 2 to 5 were 100, 80, 65, and 45 mL. The separation and characterization of the extract and the raffinate were carried out in a similar way as described for the batch process.

On the other hand, the regeneration of the solvent from stage 5 was carried out using an R-200 rotary evaporator (Büchi) at 437.2 K and 20 mbar. To check the extractive properties of the regenerated solvent, the latter was tested by doing an extraction in an 8 mL glass vial with magnetic stirring at 298.2 ± 1 K (room temperature) for 12 hours. 2 mL of regenerated carvacrol and 2 mL of multicomponent aqueous solution of antibiotics in hospital wastewater with pH adjusted to 5.0 were mixed. Then, the separation and characterization of the extract and the raffinate were carried out as described previously.

3. Results and Discussion

3.1. Screening of solvents using the COSMO-RS approach.

As widely reported in the literature, solvent screening can be performed by comparing the magnitude of activity coefficients of the solute in each of the solvents considered. In this regard, the lower the activity coefficient of a solute is, the higher affinity the extractant presents [55,91–93]. By using the COSMO-RS method, infinite dilution activity coefficients of ciprofloxacin, trimethoprim, and sulfamethoxazole in several terpenoids, eutectic solvents, and conventional solvents at 323.2 K were estimated. These values are shown in Figures 1-2. In this study, as multicomponent extraction is involved, it is essential to select a solvent showing the best compromise situation for the three considered solutes.

Among the terpenoids, the solvents with the lowest activity coefficient values for all three antibiotics are thymol and carvacrol. Furthermore, it is noteworthy that terpenes with no heteroatoms in their hydrocarbon skeleton (from pinene to myrcene in Figure 1) exhibit the highest activity coefficient values for each of the antibiotics, regardless of whether they are aromatic or not. The higher affinity for antibiotics of solvents with heteroatoms can be explained, among others, due to hydrogen bond or dipole-dipole interactions [94,95].

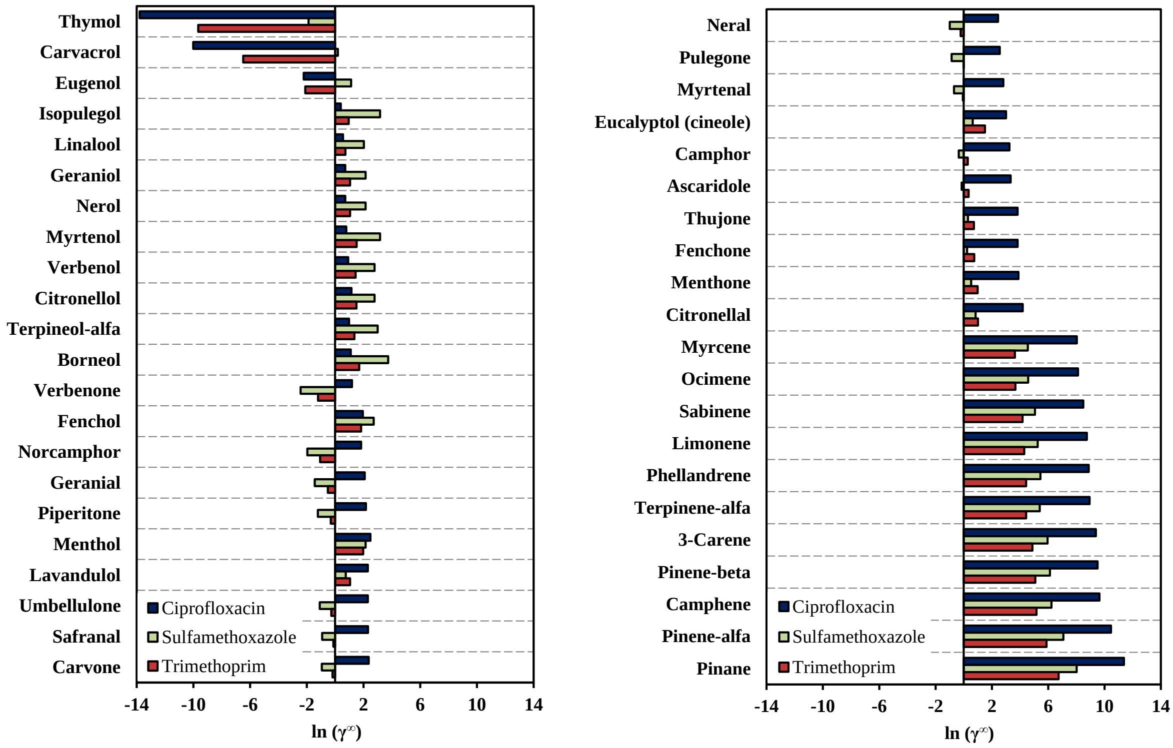


Figure 1. Activity coefficients at infinite dilution of ciprofloxacin, trimethoprim, and sulfamethoxazole in several terpenoids by using COSMO-RS approach and setting the temperature at 323.2 K.

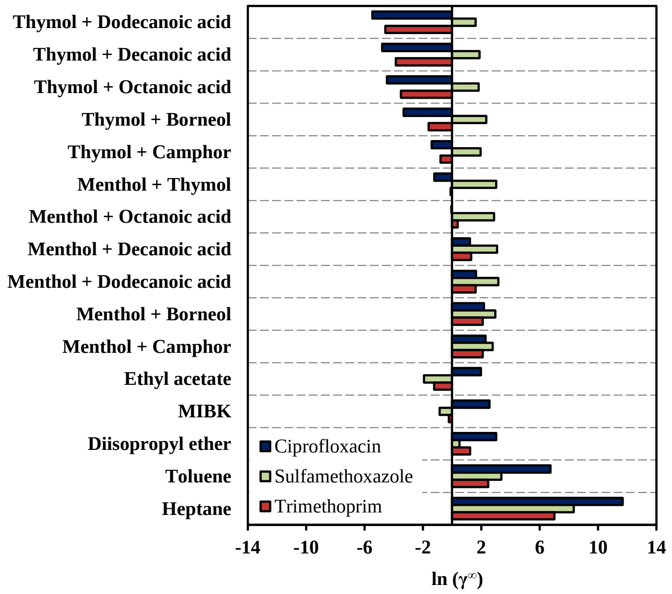


Figure 2. Activity coefficients at infinite dilution of ciprofloxacin, trimethoprim, and sulfamethoxazole in several eutectic solvents and conventional solvents by using the COSMO-RS approach and setting the temperature at 323.2 K.

For conventional solvents, the compounds that seem to present the best situation of compromise for the three antibiotics are ethyl acetate and MIBK, as shown in Figure 2. Compared to the results obtained for thymol and carvacrol, conventional solvents show a lower affinity for both ciprofloxacin and trimethoprim. However, for sulfamethoxazole, this behaviour does not seem to be as noticeable.

Regarding the eutectic solvents, the mixtures with thymol showed the lowest activity coefficients, especially those containing carboxylic acids: thymol + dodecanoic acid, thymol + decanoic acid, and thymol + octanoic acid. Compared to the results for sulfamethoxazole, these three solvents presented notably lower activity coefficients for ciprofloxacin and trimethoprim. It should be noted that, as mentioned in the literature, eutectic solvents can give better experimental extraction results than those predicted by molecular simulation [80,81].

Following the discussion above, solvent screening has been carried out. The compounds selected as the most suitable solvents to be used as extractants of ciprofloxacin, trimethoprim, and sulfamethoxazole are the following: terpenoids (thymol and carvacrol), eutectic solvents (thymol + dodecanoic acid, thymol + decanoic acid, and thymol + octanoic acid) and conventional solvents (ethyl acetate and MIBK). Moreover, sulfamethoxazole shows the lowest affinity for the solvent for both terpenoids and eutectic solvents listed before, while this antibiotic presents the opposite behaviour for organic solvents. Therefore, the compound that would limit the overall extraction yield of the process would be sulfamethoxazole for terpenoids and eutectic solvents. In contrast, for conventional solvents, it would be trimethoprim and ciprofloxacin.

3.2. Multicomponent liquid-liquid extraction of antibiotics from ultrapure water and hospital wastewater in vial

For each of the extraction solvents previously selected, three fundamental aspects will be reviewed here: the influence of the volume S/F ratio, the effect of the aqueous matrix, and the pH value.

The extraction yields of each antibiotic (Yld_i) and the overall extraction yields ($Yld_{Overall}$) were calculated from the concentration of antibiotics in the aqueous phase, in mg/L, before ($C_{i,0}^{aq}$) and after the extraction ($C_{i,f}^{aq}$), according to the following equations:

$$Yld_i\ (\%) = \frac{C_{i,0}^{aq} - C_{i,f}^{aq}}{C_{i,0}^{aq}} \cdot 100 \tag{1}$$

$$Yld_{Overall}\ (\%) = \frac{\sum_{i=1}^{3}(C_{i,0}^{aq} - C_{i,f}^{aq})}{\sum_{i=1}^{3} C_{i,0}^{aq}} \cdot 100 \tag{2}$$

Firstly, the influence of both the water matrix used for feed preparation and the pH value on the extraction of each of the three antibiotics will be discussed. This fact will be analysed according to the dissociation equilibria of the pharmaceuticals considered, which are shown together with pK_a values in Figure 3 [96,97]. Figures 4-7 show the extraction yields of trimethoprim, ciprofloxacin, sulfamethoxazole, and the overall value, respectively, from two matrices (feed in ultrapure water and in hospital wastewater at three different pH) by using different solvents at 323.15 K and volume S/F ratio of 0.25. The experimental results obtained for S/F ratios of 0.10, 0.25, 0.50, 1.00, and 2.00 are included in Tables S1-S5 of the Supplementary Material.

Before comparing different solvents, it should be noted that when the feed is brought into contact with them, a small amount is transferred to the aqueous phase. This fact can modify the pH of the raffinate and the state of the antibiotic (cationic, anionic, or neutral form) in the aqueous phase. For conventional solvents and terpenoids, the pH of the raffinate remained the same as the pH of the feed. However, for the three eutectic solvents considered, formed with dodecanoic acid, decanoic acid, and octanoic acid, the raffinate reached values between 4.9 and 6.5 when using the feed in hospital wastewater at pH 8.0, while it ranged from 3.7 and 4.5 for the feed in hospital wastewater at pH 5.0. Therefore, this will be considered when analyzing the ability of the solvent to solvate an antibiotic in a particular charged or non-charged state.

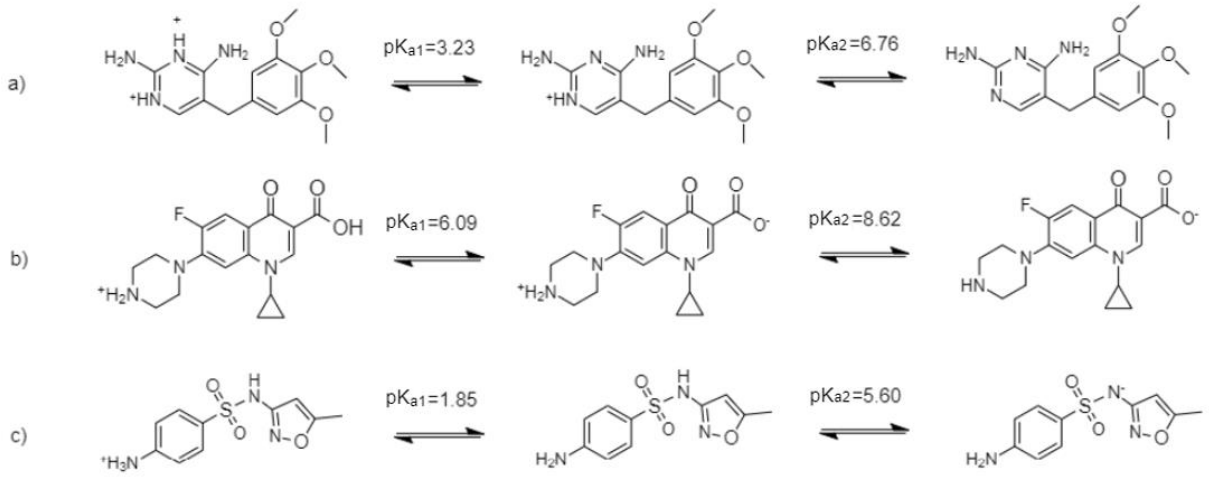


Figure 3. Dissociation equilibria and pK_a values of trimethoprim (a), ciprofloxacin (b), and sulfamethoxazole (c) [96,97].

For trimethoprim, as can be seen in Figure 4, decreasing the pH value of the feed in the hospital wastewater matrix reduces the extraction yields with all solvents, which can be explained due to the acid-base equilibrium of this diaminopyridine-derived compound (as shown in Figure 3). As widely discussed in the literature, the partitioning of the solute into one phase or the other depends on whether it is in its neutral or charged ionic state and the ability of both phases to dissolve that form of the solute. Generally, water interacts more strongly with charged solutes, favoring partitioning into the aqueous phase, while the nonionic ones usually favor partitioning into the organic phase [55,98–100].

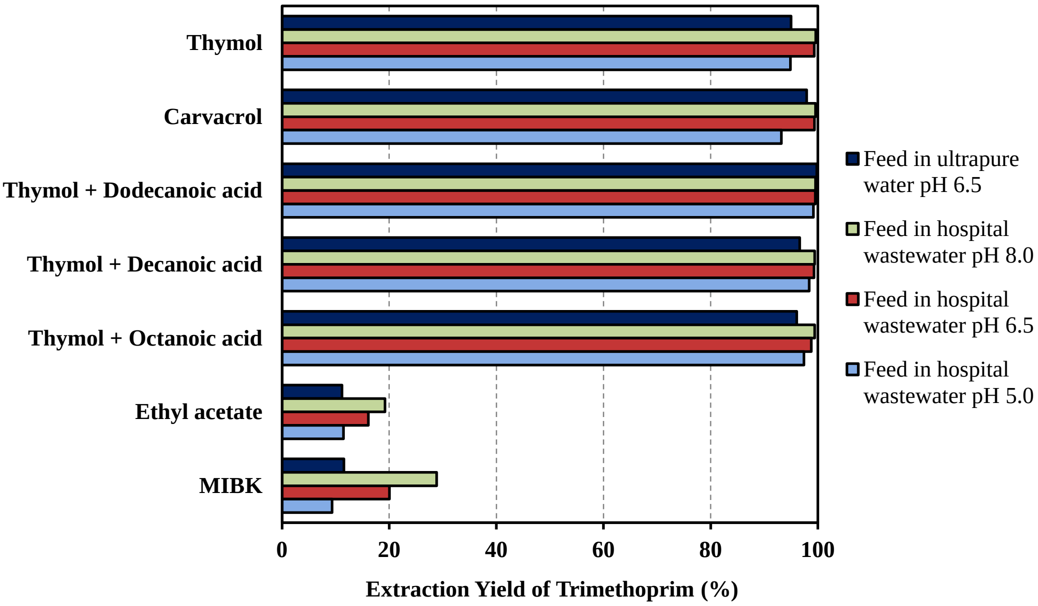


Figure 4. Extraction yields of trimethoprim from different matrices (ultrapure water and hospital wastewater at different pH) at 323.2 K and S/F 0.25.

In this case, increasing the pH increases the concentration of trimethoprim in its neutral form, improving the extraction yields. Conventional solvents show considerably poorer results than terpenoids and eutectic solvents at any pH value and matrix. In the case of eutectic solvents, yields drop when reducing the alkyl chain length of the carboxylic acid. This trend might be caused due to the decrease of hydrophobicity, which increases the partial solubility of the acid in water, decreasing the pH of the aqueous phase and favouring the presence of the protonated form of this antibiotic. At high pH, as trimethoprim in its neutral state predominates, both terpenoids and eutectic solvents showed similar results. However, when the solute in its ionic state prevails ($pH<pK_{a2}$), eutectic solvents seem to stabilise the positively charged ion more effectively, and the extraction yields are considerably higher than those for terpenoids, possibly due to the higher influence of hydrogen-bonding interactions [94,101].

Finally, in order to study the effect of the matrix, it is necessary to compare the feeds in ultrapure water and in hospital wastewater at the same pH value, 6.5. This allows to analyse the influence that the compounds in the wastewater matrix have on the extraction process, avoiding the pH effect on trimethoprim extraction. In this regard, for all solvents, higher extraction yields were observed when using the feed in hospital wastewater, indicating that the solutes in the matrix favour the transfer of trimethoprim into the organic phase. This effect might be caused by salting-out mechanism.

In the case of ciprofloxacin, as observed in Figure 5, the decrease of the pH value of the feed in hospital wastewater matrix shows two different trends, one for eutectic solvents and another for terpenoids and conventional solvents. The former presented higher yields with the feed at pH 8.0, while the latter exhibited better results with the feed at pH 6.5. As shown by the acid-base equilibrium of this quinolone in Figure 3b, pH 6.5 is approximately as close to the isoelectric point ($pH_{IEP} \approx 7.4$) as pH 8. The isoelectric point is defined as the pH at which the solute concentration as zwitterion is maximum and, therefore, the net charge is zero. As reported in the literature, analytes have their lowest solubility in water at the isoelectric point [102,103]. Therefore, the higher the solute concentration in its electrically neutral state, the larger the mass transfer to the organic phase should be.

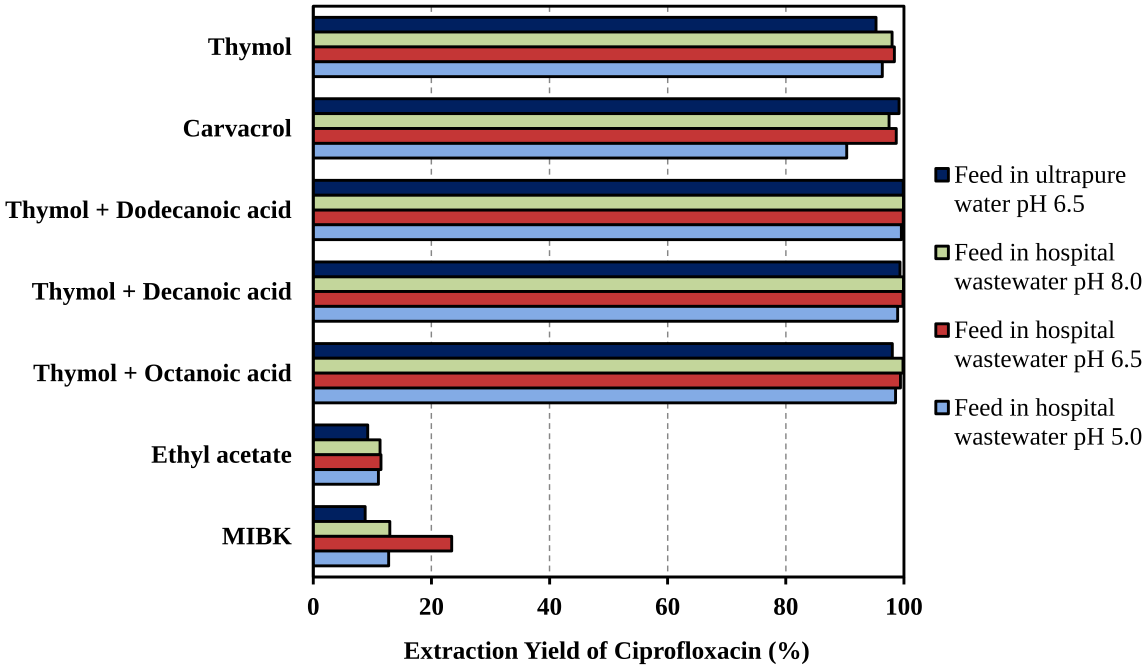


Figure 5. Extraction yields of ciprofloxacin from different matrices (ultrapure water and hospital wastewater at different pH) at 323.2 K and S/F 0.25.

For both terpenoids and conventional solvents, the extraction yields of ciprofloxacin can be ordered as follows: pH 6.5 > pH 8.0 > pH 5.0. Despite being approximately at the same distance from the pH_{IEP}, the higher yields obtained at pH 6.5 compared to those obtained at pH 8.0

indicate that these two solvent groups may solvate ciprofloxacin more effectively in its cationic state than in its anionic state. In the case of eutectic solvents, the extraction yields followed this order: pH 8.0 > pH 6.5 > pH 5.0. This might be due to the fact that when the feed is put in contact with the eutectic solvent, part of the carboxylic acid forming the eutectic solvent is transferred to the aqueous phase, lowering the pH considerably. Thus, the feed in hospital wastewater at pH 8.0 approaches the isoelectric point, increasing the extraction yield of ciprofloxacin. As the pH value of the feed decreases below 8.0, the pH of the raffinate moves increasingly away from the isoelectric point, and the concentration of the cationic form increases.

As with trimethoprim, conventional solvents show considerably lower extraction yields of ciprofloxacin than terpenoids and eutectic solvents at any pH value and matrix. With regard to eutectic solvents, for a given feed, the yield drops as the length of the alkyl chain of the carboxylic acid decreases. This can be attributed to the fact that in the pH range tested, the raffinate resulting from extraction with the eutectic solvents showed values below 6.5 ($pH < pH_{IEP}$). Thus, as the number of carbons of the acid decreases, its solubility in water rises, decreasing the pH of the raffinate and moving further away from the isoelectric point value. In general, the eutectic solvents showed higher extraction yields than those found for the terpenoids. This difference is considerably more significant when the concentration of ciprofloxacin in its charged state increases, i.e., when the pH value of the feed in hospital wastewater is 5.0. Therefore, as observed for trimethoprim, eutectic solvents solvate the charged species of ciprofloxacin more effectively.

Finally, when comparing the results obtained for feeds of ciprofloxacin in ultrapure water and in hospital wastewater at pH 6.5, higher extraction yields are observed in the real wastewater matrix. Therefore, as with trimethoprim, the solutes in the wastewater matrix favour the transfer of ciprofloxacin into the organic phase, which might be caused by salting-out effect.

In the case of sulfamethoxazole, as shown in Figure 6, reducing the pH value of the feed in the hospital wastewater matrix increases the extraction yields. This is due to the fact that in the pH range of the feed considered, i.e., between 5.0 and 8.0, decreasing the pH value increases the concentration of sulfamethoxazole in its neutral state, as shown in Figure 3. As previously evidenced and mentioned in the literature, uncharged solutes tend to solvate more efficiently in the organic solvent compared to their ionic forms.

For conventional solvents, MIBK shows similar yields to those for terpenoids at any pH value. However, ethyl acetate presents yields significantly higher than those for terpenoids at feed pH values between 6.5 and 8.0, i.e., when the solute predominates in its anionic state. On the other hand, when sulfamethoxazole predominates in its neutral state, at feed pH of 5.0, terpenoids show slightly higher extraction yields than ethyl acetate.

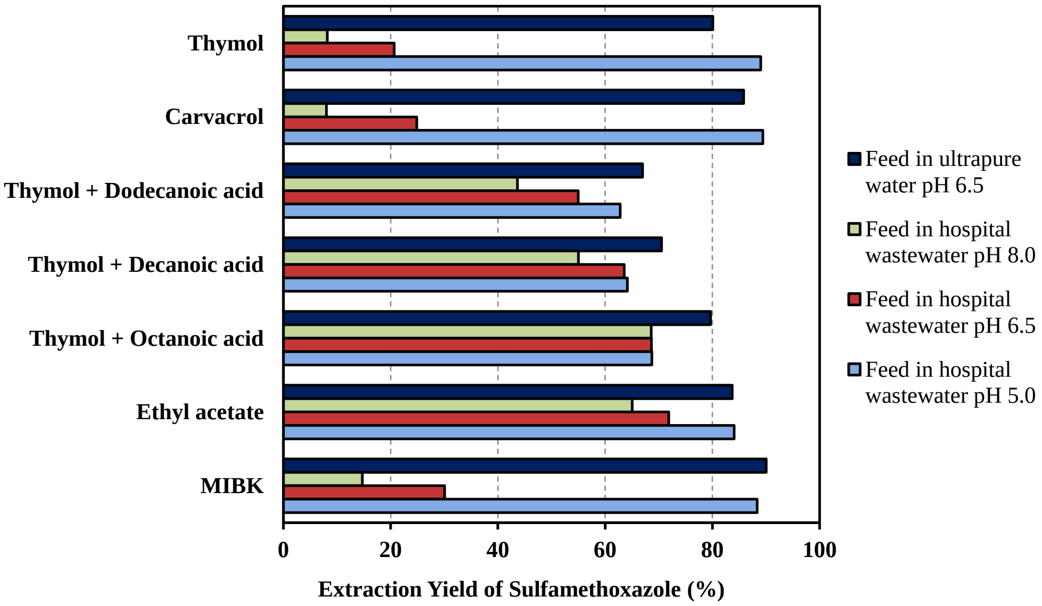


Figure 6. Extraction yields of sulfamethoxazole from different matrices (ultrapure water and hospital wastewater at different pH) at 323.2 K and S/F 0.25.

Among the eutectic solvents, for the same feed pH value and the same matrix, the yields rise as the length of the alkyl chain of the carboxylic acid decreases. This could be due to the diminishing hydrophobicity, which increases the solubility of the acid in water and, thus, the pH value and the concentration of the antibiotic in its neutral state. Regarding the feeds in hospital wastewater, at pH values of 8.0 and 6.5, eutectic solvents show better results since, as part of the carboxylic acid is being transferred to the aqueous phase, the pH of the raffinate is considerably lower than that of the fresh feed. In this way, the concentration of sulfamethoxazole in its anionic form decreases, increasing its neutral form and improving the mass transfer of the compound into the organic phase. On the other hand, for the feeds at pH 5.0 ($pH<pK_{a2}$), when the neutral form predominates, terpenoids show higher extraction yields than those with eutectic solvents. In other words, the carboxylic acid of the eutectic solvents decreases the pH value of the aqueous phase when the extraction solvent and the feed are in contact.

Finally, when comparing the results obtained for feeds in ultrapure water and in hospital wastewater at pH 6.5, clearly higher extraction yields are observed in the ultrapure water matrix. Therefore, solutes in the wastewater matrix seem to favour the solvation of sulfamethoxazole in the aqueous phase, decreasing its transfer to the organic phase. Compared to the results observed for trimethoprim and ciprofloxacin, both pH and matrix present a more noticeable influence on sulfamethoxazole extraction.

All the above-mentioned issues highlight the fact that there is no single pH value that presents the best results for the extraction of the three antibiotics. Therefore, as a multicomponent extraction, it is necessary to analyse the overall extraction yield of the three antibiotics, given by Eq. (2). As illustrated in Figure 7, conventional solvents show significantly lower overall extraction yields than those obtained for eutectic solvents and terpenoids at any pH and matrix.

Eutectic solvents seem to have a lower sensitivity to pH changes in the feed. As previously reported, this is due to the greater ease of solvating solutes in their ionic state and the decrease of the pH value as a consequence of the carboxylic acid transfer to the aqueous phase. However, the operating conditions with the highest antibiotic mass transfer to the organic phase, as an overall value, was with the feed in wastewater at pH 5.0 and using pure terpenoids. At this pH value, terpenoids present the highest compromise situation for the multicomponent extraction of the three antibiotics. For instance, at pH 5.0 and S/F 0.25, carvacrol achieved extraction yields of 93.2%, 90.3%, and 89.4% for trimethoprim, ciprofloxacin, and sulfamethoxazole, respectively, whereas the eutectic solvent thymol + octanoic acid exhibited values of 97.4%, 98.6%, and 68.0%. Therefore, the most adequate pH value of the feed seems to be 5.0.

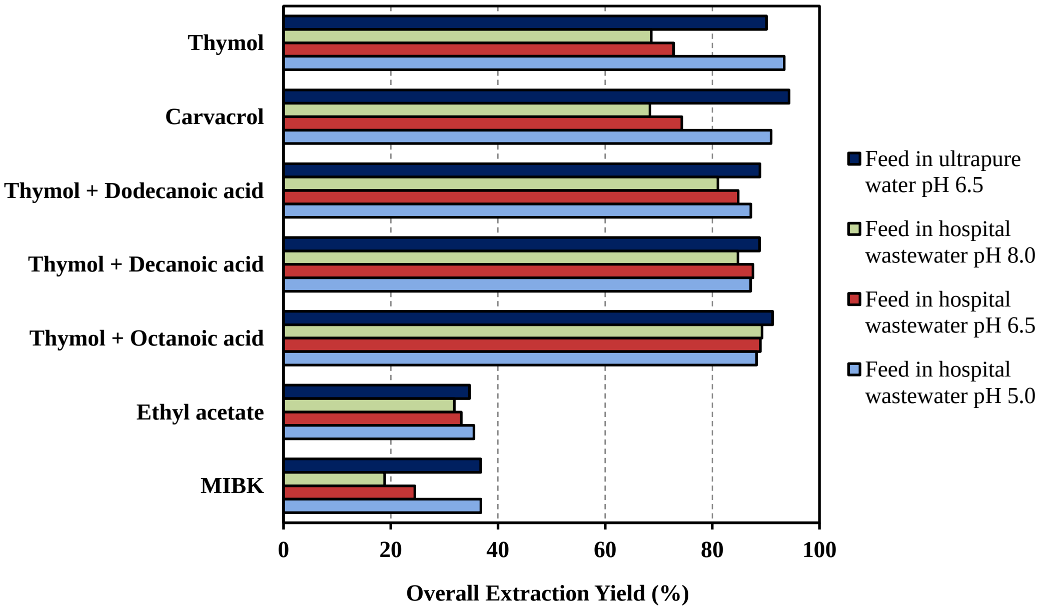


Figure 7. Overall extraction yields of antibiotics from different matrices (ultrapure water and hospital wastewater at different pH) at 323.2 K and S/F 0.25.

The third effect studied in this section was the influence of the S/F ratio on the overall extraction yields. According to Figure 8, the S/F ratio selected as the most suitable value for the extraction process is 1.00, as it allows overall extraction yields above 98% for terpenoids (> 99% for trimethoprim and ciprofloxacin, and 97% for sulfamethoxazole). Larger amounts of solvent do not justify the slight increase in the extraction yield, raising investment and operating costs.

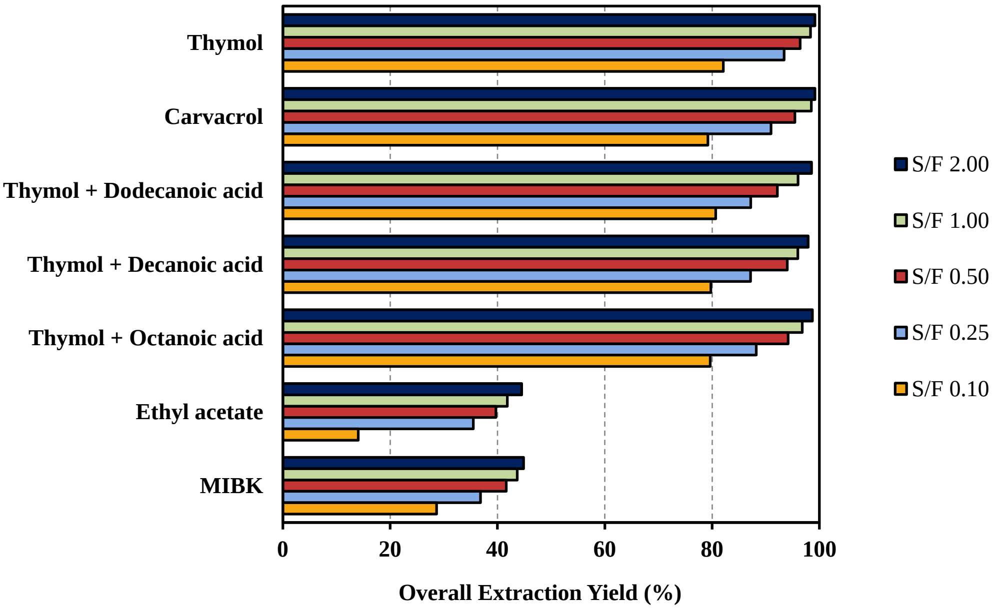


Figure 8. Influence of the volume S/F ratio on the overall extraction yields of antibiotics from hospital wastewater at pH 5.0 and 323.2 K.

Concerning organic solvent losses in the aqueous phase, higher solubility of conventional solvents was observed compared to terpenoids. The mass contents of thymol and carvacrol in the raffinate were 0.12-0.15 % and 0.12-0.14 %, respectively, while those for ethyl acetate and MIBK were 6.84-7.96 % and 1.38-1.48 %. Therefore, thymol and carvacrol showed considerably lower losses of solvent in water. Currently, large-scale sales prices of terpenes (thymol 9-11 $/kg [104] and carvacrol 10-25 $/kg [105]) are more expensive than those of conventional solvents (ethyl acetate 1.3 $/kg [106] and MIBK 1.0-1.5 $/kg [81]). However, the low S/F ratio required to accomplish high extraction yields, the small solvent losses in the raffinate, and their low toxicity and high sustainability compared to petroleum-based solvents place terpenes as potential extraction solvents for industrial application.

Generally, the use of pure solvents rather than mixtures is preferable on an industrial scale. This usually increases the simplicity of the extraction process and facilitates solvent recovery.

Hence, since the overall extraction yields were comparable for terpenoids and eutectic solvents, it is preferable to use a pure terpenoid. In particular, carvacrol shows the most favourable conditions to be selected as extractant, not only because of all the above-mentioned results for terpenoids but also because it has a low melting point compared to thymol (see Table 1). This allows its use at room temperature, without the need for heating. Therefore, the optimal conditions of the extraction process in this study, and which will be used for the subsequent sections, were: feed in hospital wastewater at pH 5.0, S/F ratio of 1.00, and carvacrol as extractant.

3.3. *Multicomponent liquid-liquid extraction of antibiotics from hospital wastewater in a packed column*

In order to test the scalability, a continuous parallel extraction process in a packed column has been studied. Carvacrol presents a relatively high viscosity (36.66 mPa s at 20 °C [107]) compared to the feed in hospital wastewater at pH 5.0, which may affect the mass transfer in the liquid-liquid extraction process. Therefore, although it was observed in the vial extraction experiments that the optimum value of S/F ratio is 1.00, the S/F ratios 0.50 and 2.00 have also been analysed. In this way, it can be observed whether the limitations to mass transfer vary considerably with the amount of carvacrol used. Thus, the extraction yields obtained in a packed column at different S/F ratios are shown in Table 5.

The results obtained were comparable to those obtained in the vial tests with carvacrol as extractant and using the feed in hospital wastewater at pH 5.0. This implies that extraction yields for the experiments in vial (prepared under 12 hours stirring) and in a packed column (using a residence time of 21 minutes) were similar, indicating that antibiotics mass transfer is not limited by the amount of carvacrol used in the S/F ratio range considered.

Table 5. Extraction yields of trimethoprim, ciprofloxacin, and sulfamethoxazole in a parallel extraction column at different S/F ratios.

S/F	Extraction Yield (%)			
	Trimethoprim	Ciprofloxacin	Sulfamethoxazole	Overall
0.50	99.30	98.57	95.65	97.84
1.00	99.69	98.85	96.25	98.26
2.00	99.82	99.71	98.71	99.41

3.4. Solvent reuse in consecutive stages of antibiotic extraction from hospital wastewater and solvent recovery

One of the key aspects to check the feasibility of scaling up an extraction process for industrial purposes is the evaluation of the reuse and recovery of the extractant. Therefore, this fact will be investigated following the optimal operating conditions obtained in the batch process, this is, carvacrol as extraction solvent, feed in hospital wastewater at pH 5.0, and S/F ratio of 1.00.

The process developed to evaluate the solvent reuse and recovery is represented in Figure 9. The liquid-liquid extraction was performed by reusing the solvent (extract phase) for five consecutive stages without intermediate solvent regeneration, thus using fresh solvent only in stage 1. Finally, the extract from stage 5 was regenerated by using a rotary evaporator at 437.2 K and 20 mbar.

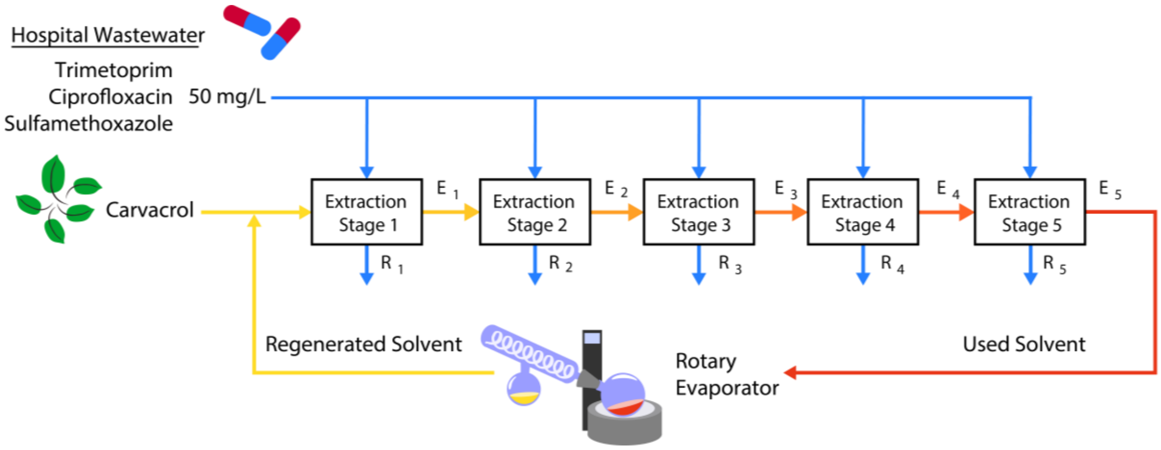


Figure 9. Scheme of solvent reuse and recovery.

As can be seen in Figure 10, the decrease of the extraction yields in each stage is most steep for sulfamethoxazole, followed by ciprofloxacin and trimethoprim. Reuse of the solvent, under the operating conditions described above, led to extraction yields higher than 83%, 96%, and 98% for sulfamethoxazole, ciprofloxacin, and trimethoprim, respectively, during the 5 stages. For the regenerated solvent, extraction yields were very close to those obtained with the fresh extractant (stage 1). Therefore, carvacrol not only allows the removal of more than 98% of the overall antibiotic content in a single step but also has been proven to be feasible operating in a continuous extraction column, and it can be regenerated using vacuum distillation.

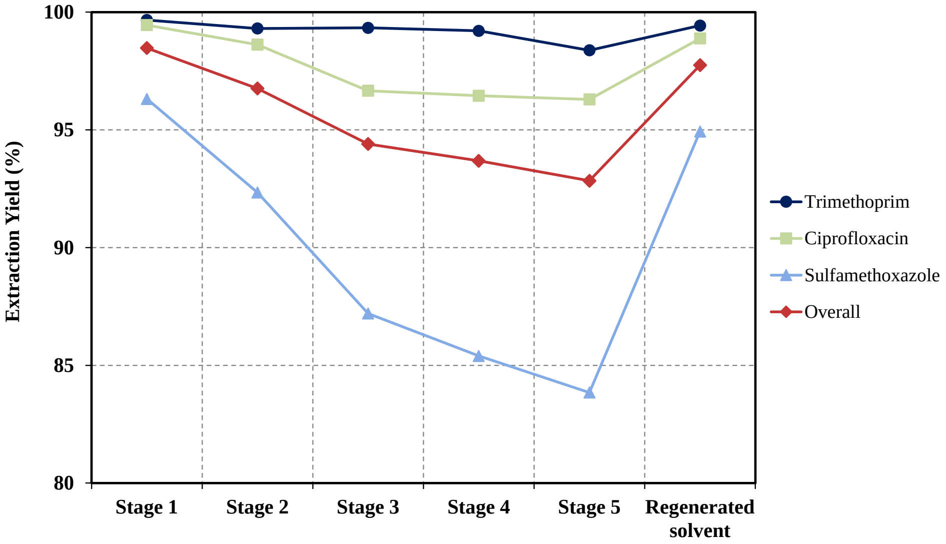


Figure 10. Evolution of the extraction yield with the number of consecutive extraction stages and after solvent regeneration. Extractions with carvacrol and feed in hospital wastewater at pH 5.0, S/F ratio 1.00, and 323.2 K.

4. Conclusions

Over the last few years, the demand for quality water has been steadily growing, bringing the importance of water treatment and reuse into focus. In this regard, multicomponent liquid-liquid extraction of three of the antibiotics included in the European Surface Water Watch List (ciprofloxacin, trimethoprim, and sulfamethoxazole) has been proposed using terpenoids and eutectic mixtures.

From the infinite dilution activity coefficient estimated by the COSMO-RS method, the compounds selected to move on to the experimental phase were the following: 2 terpenoids (thymol and carvacrol), 2 eutectic solvents (thymol + dodecanoic acid, thymol + decanoic acid, and thymol + octanoic acid), and 2 conventional solvents (ethyl acetate and MIBK).

Terpenoids and eutectic mixtures exhibited significantly higher overall extraction yields than those obtained for conventional solvents at any pH and aqueous matrix. However, no single pH value presented the best results for the extraction of the three antibiotics simultaneously, depending substantially on the dissociation equilibrium of each compound. Although eutectic solvents showed lower sensitivity to pH changes in the feed, terpenoids provided the operating conditions with the highest overall extraction yield with the feed in wastewater at pH 5.0 and volume S/F ratio of 1.00. Carvacrol emerged as the most favourable extractant, reaching extraction yields of 98.9% for trimethoprim, 99.5% for ciprofloxacin, and 97.0% for sulfamethoxazole from hospital wastewater at pH 5.0 and S/F ratio 1.00. In addition, the losses of thymol and carvacrol in the aqueous phase were substantially lower than those of conventional organic compounds.

The scalability of the extraction process was tested by performing a continuous process in a packed column, using low residence times, and obtaining no limitation to mass transfer. For industrial purposes, the reuse of carvacrol for five consecutive stages and its recovery by using a rotary evaporator at 437.2 K and 20 mbar was also successfully evaluated.

Acknowledgments

The authors are grateful to Comunidad Autónoma de Madrid for financial support of Project S2018/EMT-4341, IND2017/AMB-7720, 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 Autónoma de Madrid- Spain) under the Multiannual 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 to Ministerio de Ciencia, Innovación y Universidades for awarding an FPU grant (FPU18/01536). Finally, we thank Centro de Computación Científica de la Universidad Autónoma de Madrid for computational facilities.

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