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Extraction of ofloxacin from water using hydrophobic eutectic solvents

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ABSTRACT

Wastewater treatment plants do not cope well with emerging micropollutants, such as pharmaceuticals, because they are not effective to remove them. Therefore, this work aims to develop a process for the extraction of ofloxacin (OFX) based on a liquid-liquid extraction using hydrophobic eutectic solvents (HES), coupled with the Conductor-like Screening Model for Real Solvent (COSMO-RS) for solvent screening. First, COSMO-RS was used to predict the partition coefficient of OFX for four HES families: L-menthol: fatty acid, L-menthol: fatty alcohol, fatty acid: fatty acid and fatty acid: fatty alcohols, at three different molar ratios (2:1, 1:1, and 1:2). These results showed that HES formed by fatty acids, especially those with a longer alkyl chain and a higher fatty acid molar ratio, were the most suitable solvents for OFX extraction. Then, the most promising HES to extract OFX was evaluated experimentally. The HES decanoic acid: dodecanoic acid (C10 acid: C12 acid) in a molar ratio of 2:1 being the system with best extraction results of OFX was selected to optimize the extraction conditions of OFX, namely pH, HES: water ratio (v/v), and OFX concentration, using a response surface methodology (RSM). The results obtained showed that at a pH of 5.2, HES-water ratio (v/v) of 1.3, and 2.5 mg/ml of OFX that an extraction efficiency of OFX of (98.8 ± 0.9)% could be achieved. The results show that one-step OFX extraction is possible, but is significantly influenced by both the extraction parameters and the hydrophobic properties of the HES.

1. Introduction

The widespread use of pharmaceuticals has led to them entering wastewater through various routes, such as excretion, improper disposal and residues from medical facilities and the pharmaceutical sector [1]. However, many wastewater treatment plants are not able to effectively remove pharmaceutical compounds, which leads to contamination of the water and consequently the environment. Studies have shown that these substances can damage ecosystems by increasing mortality rates and disrupting the reproductive functions of aquatic organisms [2]. In addition, antibiotic residues in water sources promote the development of resistant bacteria, making it difficult to treat infections and posing a risk to public health [3]. Voogt et al. [4] emphasized the need to improve pharmaceutical removal from wastewater systems, focusing on fluoroquinolones such as ofloxacin (OFX). OFX, the second most widely used drug in the fluoroquinolone category, is used in human and veterinary medicine due to its broad spectrum of activity against various bacteria [5]. However, its low absorption rate is a problem for the environment as about 90% is excreted unchanged or as metabolites, contributing significantly to environmental pollution. This contributes to the persistence of OFX in wastewater systems [6,7], making it an emerging pollutant with remarkable resistance to biodegradation.

Conventional wastewater treatment processes, including adsorption and activated sludge treatment, are not specifically designed to efficiently remove pharmaceutical compounds such as OFX [8]. This leads to suboptimal treatment, as the effectiveness of these processes varies widely and is influenced by the unique properties of the compounds. [9]. Reports from different WWTPs reflect this inconsistency, with some achieving high OFX removal efficiencies of up to 86%, while others report much lower efficiencies of around 56% [10]. These differences highlight the limitations of conventional treatment methods, particularly due to the resistance of these compounds to microbial and chemical degradation, which makes them difficult to remove from wastewater systems [11]. Therefore, there is an urgent need for the development of cost-effective, environmentally sustainable technologies specifically tailored to the extraction of persistent pharmaceuticals, including

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fluoroquinolones such as OFX, from wastewater streams.

Solid phase extraction (SPE) [12] and liquid-liquid extraction (LLE) [13] have been established as alternative methods for the removal of pharmaceuticals. Although these methods are very efficient, they also have disadvantages such as high costs or considerable consumption of organic solvents, respectively [5,14]. Recently, environmentally friendly solvent-based LLE has emerged as a promising option for the removal of fluoroquinolones, using alternative solvents such as ionic liquids and deep eutectic solvents (DES) [15]. DES, a mixture of hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD), offers simple preparation and cost advantages over ionic liquids, although conventional organic solvents such as methanol are less expensive. On the other hand, DES is preferable to organic solvents due to their lower toxicity. However, the assessment of toxicity can be controversial and depends on the DES rather than the whole class [16]. The use of natural DES, i.e. components from natural sources such as sugars, polyols, organic acids, amino acids, can reduce the price. In addition, by selecting the components of the DES mixture, their physicochemical properties such as hydrophobicity and hydrophilicity can be tuned. Hydrophilic DES are often used for the extraction and purification of various compounds [17]. However, their high water solubility poses a challenge in applications such as wastewater treatment. In LLE a third component must be added to enable phase separation. Additionally, their recovery and reusability are usually not as straightforward and cost-effective as desired, which is one of the major drawbacks of DES for wide industrial application. Furthermore, hydrophilic DES are limited in their ability to extract highly hydrophobic molecules, such as pharmaceuticals.

To overcome these issues, hydrophobic DES, also known as hydrophobic eutectic solvents (HES), have been employed [18]. Numerous studies have demonstrated the efficacy of hydrophobic eutectic solvents (HES)-based LLE for various compounds, including pharmaceuticals (see Table S1 in Supplementary Material for more details) such as fluoroquinolones [19–21]. Although there have been some studies on the extraction of OFX using HES-based LLE, the extraction of OFX using these systems has not yet been deeply studied [20,21]. Li et al. [20] investigated seventeen HES based on monoterpenes, fatty acids and a benzoate ester for the quantification of fluoroquinolones in surface water using liquid-liquid microextraction (LLME). Thymol and heptanoic acid in a 2:1 ratio at a pH of 4–7 showed the highest extraction efficiency for OFX, with relative recoveries between 85% and 104%. Pochivalov et al. [21] investigated HES composed of thymol-fatty acids for extraction of fluoroquinolones using LLME followed by magnetic phase separation for concentration. Thymol-nonanoic acid-based HES with a molar ratio of 1:1 and at pH 6 showed high extraction yield for fluoroquinolones, especially for OFX. While LLME is very efficient, it requires specialized equipment and is generally used for low volume samples. In addition, the limited flexibility in solvent choice due to viscosity constraints may limit its attractiveness for certain applications. Considering these factors, LLE is a preferred platform for broader applications due to its robustness, scalability, simplicity and higher flexibility in solvent choice [22].

Although the potential of HES as viable eco-friendly has been demonstrated in numerous applications, researchers still face the challenge of quickly identifying the most effective HES in LLE in a fast way. The partition coefficient of a solute is a key factor in selecting the optimal solvent for LLE. However, since experimental measurements are costly and lengthy, the use of a thermodynamic model as a pre-screening tool can be very helpful. The COnductor-like Screening MOdel for Real Solvent (COSMO-RS) is an advanced computational method that applies the principles from quantum chemistry and statistical thermodynamics to predict the physicochemical and thermodynamic properties of mixed and pure compounds [23,24]. The COSMO-RS model has been successful in predicting the octanol-water partition coefficient of some compounds, such as small drug-like molecules [25] and numerous compounds from different pollutant categories [24], yet it has been used to estimate the partition coefficient for screening solvents in LLE in only a few studies [26–29]. Spieß *et al.* [26] used the model COSMO-RS, to screen the best hydrophobic organic solvents for the maximum conversion of alcohol dehydrogenase-catalyzed oxide reductions of prochiral ketones using LLE. Burghoff *et al.* [27] also applied the COSMO-RS model to the screening of nitrogen- and phosphorus-based solvents in phenol extraction by LLE. Ferreira and co-workers [28] compared the use of COSMO-RS and non-random activity coefficients for two liquid segments (NRTL-SAC) to predict the partition coefficients of four phenolic compounds - vanillin, ferulic acid, (S)-hesperetin and quercetin - in different LLE. Chagnoleau et al. [29] showed that COSMO-RS is able to predict partition coefficients for natural compounds (quercetin, apigenin, coumarin, β-ionone, and α-tocopherol) in organic biphasic systems with very different chemical structures. These systems were based on heptane, ethanol, and a selection of six different third components, including glycerol, ethylene glycol, levulinic acid, and the corresponding choline chloride-based DES.

In this work, the potential of four different families of HES based on menthol, fatty acids and fatty alcohols as alternative solvents for the extraction of OFX from water by LLE was investigated. In order to minimize the experimental effort and identify the best possible solvent, COSMO-RS was used as a screening tool to determine the most effective HES for the extraction of OFX from water. The best solvents selected from the screening were evaluated experimentally and for the best solvent a response surface methodology (RSM) was used to optimize the partition coefficient of OFX (K_{OFX}) and the extraction efficiency of OFX (EE_{OFX} %) by changing the operating conditions, namely pH, OFX concentration, and HES-water ratio (v/v). To the best of our knowledge, this is the first time that computational and experimental methods have been integrated to minimize the number of experiments required to develop a process for OFX extraction using HES-based LLE.

2. Materials and methods

2.1. Materials

The chemical compounds used in this study are listed in Table S2 in Supplementary Material. All experiments used ultrapure water subjected to a double distillation process, passed through a reverse osmosis system, and treated with a Milli-Q plus 185 water purifier.

The HES from four different families (L-menthol: fatty acid, L-menthol: fatty alcohol, fatty acid: fatty acid, and fatty acid: fatty alcohols), which here studied here are listed in Table 1. Those were evaluated at three different molar ratios of HBA:HBD (2:1, 1:1, 1:2), totaling 36 different HES used in the screening by COSMO-RS for the most effective solvents to extract OFX.

Finally, the selected HES were prepared by heating the mixture to 80 °C for 4–5 h in the desired molar ratio with constant stirring, and a clear and homogeneous liquid was obtained, as previously documented [30]. These HES did not undergo any visual changes after cooling, remaining stable at 25 °C (clear and homogeneous liquid). The only exception was

Table 1
List of HES studied in this work.

HBA	HBD	Abbreviation
L-menthol	Octanoic acid	L-menthol: C8 acid
	Decanoic acid	L-menthol: C10 acid
	Dodecanoic acid	L-menthol: C12 acid
	1-Decanol	L-menthol: C10 alcohol
	1-Dodecanol	L-menthol: C12 alcohol
Octanoic acid	Decanoic acid	C8 acid: C10 acid
	Dodecanoic acid	C8 acid: C12 acid
	1-Decanol	C8 acid: C10 alcohol
	1-Dodecanol	C8 acid: C12 alcohol
Decanoic acid	1-Decanol	C10 acid: C10 alcohol
	1-Dodecanol	C10 acid: C12 alcohol
	Dodecanoic acid	C10 acid: C12 acid

L-menthol: C12 acid in a 1:2 ratio, which solidified at 25 ºC and, therefore, was not evaluated experimentally. The melting point of the selected HES and their individual compounds is presented in Table S3 in Supplementary Material. In addition, the water solubility of the individual HES compounds is listed in Table S4 in the Supplementary Material.

2.2. COSMO-RS model

COSMO-RS (Conductor-like Screening Model-Real Solvents) is a predictive model that relies on the principles of quantum chemistry and statistical thermodynamics. The procedure for the application of COSMO-RS to select HES involved two steps. First, the COSMO files are calculated by optimizing the geometric structure of the water and each HES at specific molar ratios of HBA and HBD using the DMol^3 module in Material Studios 2017 software, the most widely used software for performing density functional theory (DFT) and COSMO calculations [31]. In the present work, the optimization of the structures of the compounds was performed using GGA (VWN-BP) as DFT. Also, the multipolar expansion in the electronic options was set to octupole and the quality fine was chosen for all calculations. The calculations were performed on four parallel cores, and the default values of DMol^3 were used for other options [32]. Second, the generated COSMO files were used in the COSMOthermX 2.1 program to calculate the partition coefficients of OFX in the systems of HES and water at 25 °C.

The calculation of the logarithm partition coefficient of OFX (log-K_{OFX}) between HES and water was determined through the computation of the chemical potentials of the OFX (in HES (μ_{OFX}^{HES}) and in water (μ_{OFX}^{W})) in infinite dilution and in the pure solvents as follows [33]:

$$\log(K_{OFX}) = \log\left[\exp\left(\frac{\mu_{OFX}^{HES} - \mu_{OFX}^{Water}}{RT}\right)\cdot\frac{V_{HES}}{V_{Water}}\right] \quad (1)$$

In addition, the ratio of molar volume of two phases ($\frac{V_{HES}}{V_{Water}}$) was estimated by COSMO-RS according to the volumes of molecules and the temperature (T) was set at 25 °C.

2.3. Liquid-liquid extraction (LLE)

For the extraction of OFX from water, the twelve most promising HES identified in the screening with COSMO-RS were evaluated. Briefly, extractions were conducted for 12 hours at 25 °C and 150 rpm. Afterwards, phases were separated by centrifugation at 10000 rpm for 10 minutes, and OFX in both phases was quantified using UV-spectrophotometry. Fig. 1 provides a summary of the experimental procedure. Further details on the OFX extraction using HES-based LLE are outlined in the Supplementary Material.

The partition coefficient of the OFX (K_{OFX}) was determined according to the following equation:

$$K_{OFX} = \frac{[OFX]_{HES}}{[OFX]_{Water}} \quad (2)$$

where $[OFX]_{HES}$ and $[OFX]_{Water}$ are the concentrations of OFX in the HES and water phases, respectively.

The percentage extraction efficiency of OFX (EE_{OFX} %) is the percentage ratio between the total weight of OFX in the HES-rich phase to that in the total mixture, which was determined according to the following equation:

$$EE_{OFX}\ \% = \left(\frac{w_{OFX}^{HES}}{w_{OFX}^{HES} + w_{OFX}^{water}}\right) \times 100 \quad (3)$$

where w_{OFX}^{HES} and w_{OFX}^{water} are the weight of OFX in the HES and aqueous phases, respectively.

2.4. Optimization of the operating extractions conditions

To study the synergistic or antagonistic effects on the extraction of the operating conditions, the use of an experimental design is helpful. The response surface methodology (RSM) is a robust experimental design tool that uses mathematical and statistical methods to correlate and optimize the unknown function. In a 2^k factorial planning, k represents the number of factors (independent variables) that can contribute to a response y through a polynomial equation as follows:

$$y = \beta_0 + \sum\beta_i X_i + \sum\beta_i\beta_i X_i^2 + \sum_{i<j}\beta_i\beta_j X_i X_j \quad (4)$$

In this equation, β_0, β_i, β_{ii}, and β_{ij} correspond to the adjusted coefficients for the intercept, linear, quadratic, and interaction terms, respectively, while X_i and X_j refer to the operational variables.

A central composite rotatable design (CCRD, 2^3 plus axial) with six replicates at the central point was employed for factorial planning to optimize OFX extraction efficiency. Three key operating variables were evaluated: pH (ranging from 2.0 to 6.0), OFX concentration (ranging

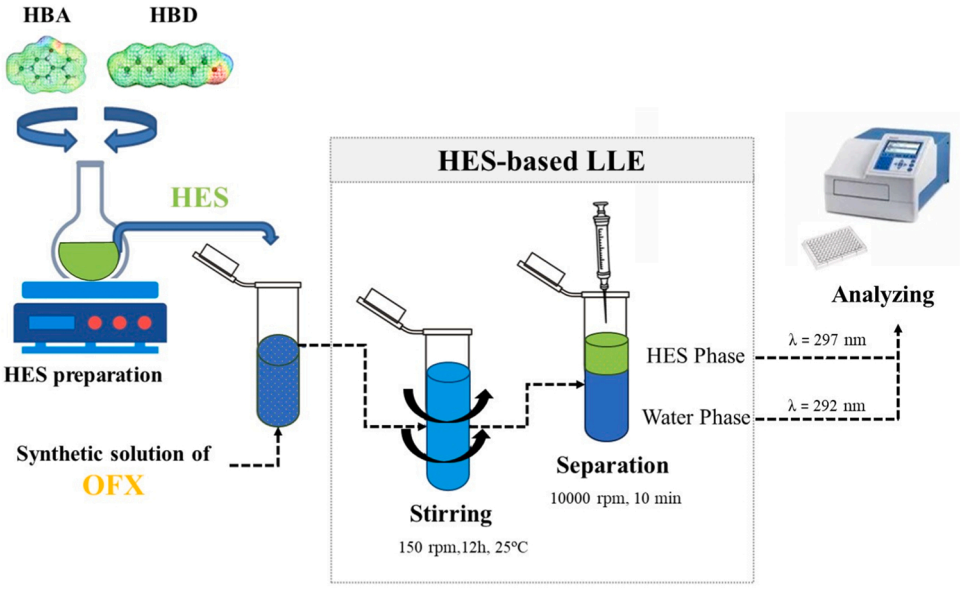

Fig. 1. Schematic representation of the HES-based LLE procedure for the extraction of OFX.

from 0.5 to 2.5 mg/ml), and the HES-water ratio (v/v, ranging from 6:10–21:10). A total of twenty experiments were conducted, including the central point (at zero level), factorial points (at level one, denoted as 1 and −1) and axial points (at level α). Further information on the RSM, such as the actual and coded levels of the parameters considered, can be found in Tables S5 and S6 in the Supplementary Material.

The data was subjected to statistical analysis with a 95% confidence level. The model's suitability was assessed based on the lack of fit, regression coefficient (R^2), and the F-value derived from the analysis of variance (ANOVA). Using these analytical approaches, the interactions between the variables and their effects on OFX extraction efficiency were investigated to determine the most favorable operating conditions. These conditions were then validated experimentally. All statistical analyses and representation of response surfaces were performed using Statsoft Statistica 10.0 software.

3. Results and discussion

3.1. Simulation results

The first step of this work was the selection of HES for the extraction of OFX from water by LLE, using COSMO-RS. For this purpose, the σ-profiles (Fig. 2) were first determined to obtain information about the chemical nature of the compounds, such as polarity and hydrogen bonding ability, which contribute to the understanding of the potential interactions between the solute and the solvents during extraction [34]. Fig. 2 A shows the polarized charge distribution (σ) of OFX and water, where three regions can be identified. The region between $-0.01e/Å^2$ and $+0.01e/Å^2$ is considered non-polar, while the polar regions extend below $-0.01e/Å^2$ and above $+0.01e/Å^2$ and have the potential to form hydrogen bond donor and acceptor, respectively [32]. It is noteworthy that for non-polar compounds, the distribution of the σ-profile is predominantly in the non-polar region, whereas moderately polar compounds have peaks in both the non-polar and polar regions. The σ-profile of OFX, characterized by a significant segment in the non-polar region and a smaller peak in the polar region (see Fig. 2 A), suggests that HES reflecting this pattern are likely to be more effective extractants [35]. In addition, our results suggest that the HES investigated in this study act primarily as pure HBA, as evidenced by a single peak in the positive region (see Fig. 2B). This observation emphasizes a strong interaction potential between OFX and HES, especially since ES act most effectively as either HBA or HBD when their σ profiles do not show peaks in the opposite range, confirming their role as pure acceptors or donors [36]. In particular, fatty acid-based HES are identified as excellent candidates for enhancing the extraction of OFX due to their pronounced peak in the polar region.

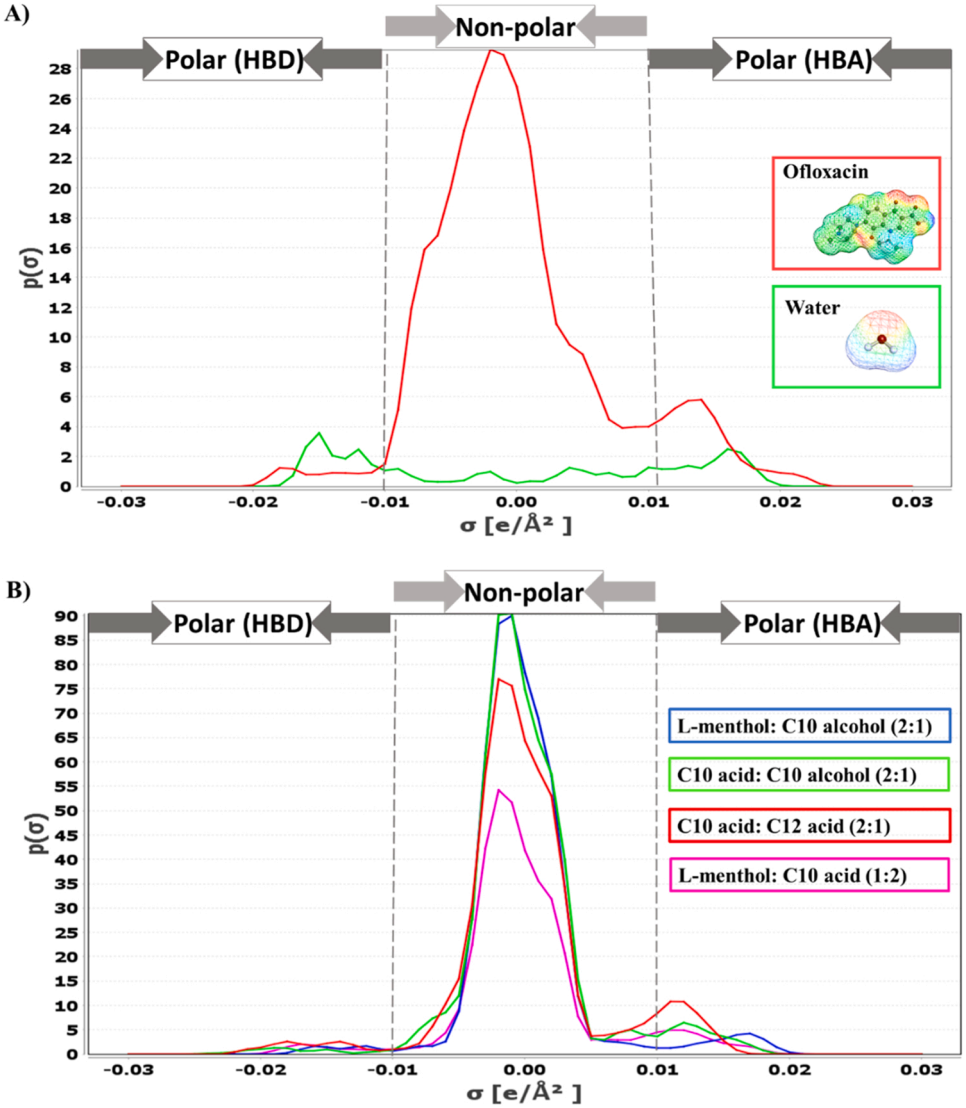

Fig. 2. **(A)** The σ-profiles of water and OFX; **(B)** The σ-profiles of an HES representative of each in each family.

Notice that the structures of the HES were modelled as pseudo-compound; thus, the σ-profile of the HES can be described as the sum of the σ-profiles of its individual compounds weighted by their molar ratio (model HBAHBD). The HES σ-profiles are in agreement with the σ-profiles of their individual compounds (L-menthol, C12 acid, and C10 alcohol), since all of them exhibit favorable characteristics, with C10 acid showing a more pronounced peak in the polar region (Figure S1 in Supplementary Material).

By evaluating the logarithm of partition coefficient of OFX (log (K_{OFX})) it is possible to compare the partition of a given solute in several different LLE under the same conditions. In this case, COSMO-RS was used to predict log (K_{OFX}) between water and twelve HES at three different molar ratios of HBA and HBD (1:2, 1:1, and 2:1) at 25 °C. The results are shown in Fig. 3 (for more details, see Supplementary Material, Table S7).

As shown in Fig. 3, fatty acids HES seem to be indeed the best option to obtain the highest partition coefficients for OFX. The use of the fatty acid: fatty acid-based HES resulted in the highest partition coefficients for OFX among all the studied HES.

This is in line with the studies of Li et al. [20], which highlights the higher efficiency of fatty acid-based solvents compared to menthol-based solvents. Another study [37] reinforces the efficacy of fatty acid-based HES over other HES families in the extraction of ciprofloxacin, another fluoroquinolone. In particular, this study emphasizes that HES formulated with non-ionic components such as fatty acids exhibit better extraction efficiency than HES derived from ionic components such as quaternary ammonium salts. These results emphasize the central role of solvent properties in enhancing intermolecular interactions with the target analyte (OFX/ ciprofloxacin). As Chen et al. [38] stated, the structure and chemical composition of HES play a crucial role in the efficiency of extraction. Building on these findings, our study goes further and investigates the effects of HES composition on extraction efficiency of OFX.

Fig. 3 shows a correlation between log (K_{OFX}) and alkyl chain length and the molar ratio of the components of HES. In general, an increase in the alkyl chain length of the fatty acids and their molar ratio leads to higher log (K_{OFX}) values. For example, the log (K_{OFX}) value in the L-menthol: fatty acid HES changed from 2.36 to 2.61 when the alkyl chain length of the fatty acids increased from C8 to C12 at a constant molar ratio (1:2). These results agree with the observations of Pochivalov et al. [21], and Rodríguez-Llorente et al. [39] who also reported a positive effect on the extraction of antibiotics, such as OFX, with HES based on thymol and fatty acids with longer hydrocarbon chains (from hexanoic acid to nonanoic acid). However, the trend is different for fatty alcohol-based HES. As shown in Fig. 3, an extension in the alkyl chain length of the fatty alcohol results in a decrease in the log (K_{OFX}) in L-menthol: fatty alcohol and fatty acid: fatty alcohol HES. For instance, in C10 acid: fatty alcohol HES, increasing the alkyl chain length of the fatty alcohols from C10 to C12 at a constant molar ratio (2:1) leads to a notable reduction in the log (K_{OFX}) values from 3.51 to 2.36.

Regarding the influence of the molar ratio in L-menthol: C8 acid and C8 acid: C10 alcohol HES, increasing the ratio of C8 acid from (1:1) to (1:2) and from (1:1) to (2:1) resulted in higher log (K_{OFX}) values, specifically an increase from 2.04 to 2.36 for L-menthol: C8 acid and from 1.73 to 2.91 for C8 acid: C10 alcohol. In the case of fatty acid: fatty acid-HES, an increase in the ratio of fatty acid ether in HBA or HBD, in particular (1:2) or (2:1), resulted in higher log (K_{OFX}) values compared to the molar ratio (1:1). This observation can be explained by the fact that an increase in the molar ratio of the fatty acid promotes the formation of hydrogen bonds between the hydroxyl groups of OFX and the carboxyl group of the fatty acid [21]. These results show that the intermolecular interactions are strongly influenced by both the length of the alkyl chain and the molar ratio of the HES components.

In addition to the COSMO-RS, radial distribution function (RDF) also was applied to gain some more insights into the separation of OFX using HES-based LLE. This tool uses a graphical representation to establish a correlation between the distance 'r' and g (r), where 'r' stands for the distance between molecules and neighboring atoms, while g (r) indicates the tendency of different atoms to interact. Strong intermolecular interactions are indicated by higher 'g (r)' values at smaller distances ('r'), which can improve extraction [40,41]. RDF analysis was performed for five HES using Material Studios 2017 software.

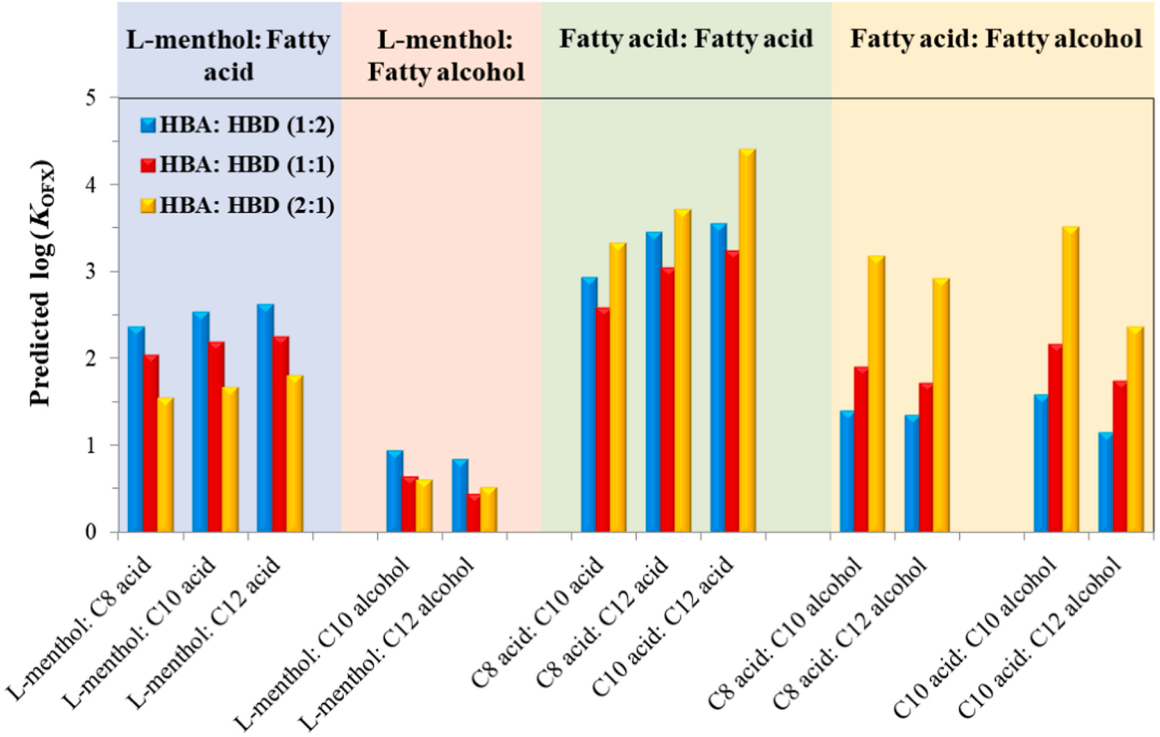

Fig. 3. Predicted log(K_{OFX}) for the HES in different molar ratios (1:1, 1:2 and 2:1), at 25 °C using COSMO-RS.

Specifically, one HES (and the respective composition) within each promising family, L-menthol:C10 acid (1:2), C10 acid: C12 acid (2:1) and C10 acid:C10 alcohol (2:1), were evaluated to assess the effect of specific components. L-menthol:C10 acid (2:1) and C8 acid:C10 acid (2:1) were also investigated to determine the influence of the molar ratio and alkyl chain length, respectively. The results in Table 2 and Figures S2 to S6 in the Supplementary Material show the peak values and the corresponding distances for each HES. Further details on the methodology can be found in the Supplementary Material.

The results show an 'r' distance of 1.09 Å for all HES, indicating a uniform spatial distribution of OFX molecules relative to the HES. This small value of 'r' suggests a strong interaction between HES and OFX, likely due to hydrogen bonding between functional groups [21]. Different g (r) values for each HES indicate different affinities for OFX due to different chemical properties. For example, increasing C10 acid molar ratio in L-menthol:C10 acid resulted in increased interaction with OFX, as indicated by higher g (r) values. A similar trend was observed with increasing alkyl chain length in fatty acids (from C8 to C12 in C8 acid: C10 acid and C10 acid: C12 acid). Furthermore, HES compositions such as L-menthol:C10 acid (1:2), C10 acid:C12 acid (2:1) and C10 acid: C10 alcohol (2:1) exhibited higher g (r) values, indicating improved extraction potential, with slightly better interaction observed with C10 acid:C12 acid HES. These findings are consistent with the COSMO results.

In summary, the COSMO-RS predictions indicate that the most promising HES for the extraction of OFX are those composed of fatty acids with a higher molar ratio of fatty acids and longer alkyl chains, although a balance between the molar ratio and the size of the alkyl chain is required. These results were supported also by RDF. As result, the most effective HES for the experimental extraction of OFX from water were selected from three families: L-menthol: fatty acid (L-menthol: C8 acid (1:2), L-menthol: C10 acid (1:2), L-menthol: C12 acid (1:2)), fatty acid: fatty acid (C8 acid: C10 acid (2:1), C8 acid: C12 acid (2:1), C10 acid: C12 acid (2:1)) and fatty acid: fatty alcohol (C8 acid: C10 alcohol (2:1), C10 acid: C10 alcohol (2:1)).

3.2. Liquid-liquid extraction (LLE)

To further evaluate the suitability of the selected HES for the extraction of OFX, the partition coefficient and extraction efficiency of OFX were determined experimentally. Although L-menthol: C12 acid (1:2) HES in the L-menthol: fatty acid families showed promising results in the extraction of OFX in COSMO-RS, this HES was not selected for further investigation because it is solid at room temperature. In addition, in order to explore a little more the impact of higher molar ratios of fatty acids, novel molar ratios were studied for the most promising HES within each family, *i.e.*, L-menthol: C10 acid (1:3), C10 acid: C12 acid (3:1), and C10 acid: C10 alcohol (3:1).

The chemical and physical properties of the HES used in this study have been previously investigated [32]. Fourier transform infrared spectroscopy (FTIR) confirmed the presence of hydrogen bonding in the HES, even in the presence of water. In addition, the evaluation of water activity showed that HES with longer alkyl chains have higher water stability. The evaluation of thermophysical properties showed that the hydrophobic nature significantly affects the viscosity and density, with HES with longer alkyl chains having higher values. These results emphasize the water stability of HES, which is crucial for the development of efficient, environmentally friendly water-based separation processes. In addition, the melting points of these HES, as indicated in Table S3 of the Supplementary Material, are well below our operating temperature of 25 ºC, which is important to ensure that the solvents remain in a liquid state under the experimental conditions.

Table 2
Radial distribution function (RDF) between HES and OFX.

HES	Molar ratio (HBA:HBD)	g (r)	r (Å)
L-menthol:C10 acid	(1:2)	0.016024	1.09
L-menthol:C10 acid	(2:1)	0.013223	1.09
C8 acid:C10 acid	(2:1)	0.01587	1.09
C10 acid:C12 acid	(2:1)	0.01926	1.09
C10 acid:C10 alcohol	(2:1)	0.016178	1.09

All experiments were performed at constant OFX concentration (1 mg/ml), at 25 °C and HES-water ratio (1:1, v/v) as described in Section 2.4, and without adjusting the pH of the systems. The results of the partition coefficient and extraction efficiency of OFX, along with the initial pH of each system are shown in Fig. 4, and Table S8 in the Supplementary Material.

As expected, the experimental results presented in Fig. 4 show a significant influence of the alkyl chain length on the partition coefficient of OFX, which varies between (2.8 ± 0.1) and (7.4 ± 0.2). The same is true for the extraction efficiency of OFX, although this effect is not so impressive (ranging between (73.5 ± 0.8)% and (88. 02 ± 0.4)%). These effects are particularly pronounced for the HES based on C10 acid. The increase in chain length from C8 to C10, for example for C8 acid: C12 acid to C10 acid: C12 acid, increases the K_{OFX} by over 63% and the EE_{OFX} by 11%. This trend applies to all HES that change from C8 to C10. The changes become less pronounced as the chain length increases further from C10 to C12 (e.g. C8 acid: C10 acid to C8 acid: C12 acid), with an increase of about 20% for K_{OFX} and 4% for EE_{OFX}. This could be related to the pH effect, as the pH increases more with increasing alkyl chain length from C8 to C10 (e.g. fatty acid: fatty acid from 3.92 to 4.40) compared to C10 to C12 (e.g. from 3.80 to 3.92), with higher pH values leading to higher efficiency in the extraction of OFX. These results emphasize the influence of structure and pH on OFX extraction, with the alkyl chain length having the greatest impact. However, they also highlight the role of pH in extraction processes. A more detailed study on the pH effect is carried out in the following section.

Additionally, Fig. 4 shows a decrease in the partition coefficient and in the extraction efficiency of OFX within the three different HES families when the molar ratio of C10 acid increases from 2 to 3, especially for C10 acid: C12 acid (3:1) and C10 acid: C10 alcohol (3:1). This trend can be attributed to the increase in the molar ratio of C10 acid, which likely increases the intermolecular interactions, including hydrogen bonds, van der Waals forces, and electrostatic forces between the HES constituents, thereby decreasing the interactions between the HES and the analytes and affecting the overall extraction efficiency [42]. These results emphasize that while the length of the alkyl chain is a critical factor for the interaction between the compounds, the molar ratio of HBA to HBD is equally important.

The evaluation of both the predicted and measured results show how important it is to consider key factors such as the nature of the compounds and their molar ratio when developing solvents for the extraction of compounds. Another important point to emphasize is that the COSMO-RS simulations reproduce the experimental results at certain pH values corresponding to the neutral form of the drugs. Thus, pH is another critical factor to consider. Our experiments were conducted without pH control, with the pH levels of our systems falling within the range of 3.3–4.6 (see Fig. 4 and Table S8 in the Supplementary Material). Given that the pK_{a1} and pK_{a2} values for OFX are 5.2 and 8.4, respectively (see Figure S7 in the Supplementary Material for further details), the extractions predominantly occurred with 98–70% of the molecule in its positive form, with only a small fraction remaining in the zwitterionic (neutral) form. Thus, these differences between computational and experimental results may be attributed, in part, to this pH-related phenomenon.

In summary, L-menthol:C10 acid (1:2), C10 acid:C10 alcohol (2:1), and C10 acid:C12 acid (2:1) were similar in terms of their efficiency in extracting OFX, with the latter performing slightly better. When selecting the best HES to optimize OFX extraction conditions, it is important to consider not only efficiency but also solvent stability and cost. When comparing L-menthol:C10 acid (1:2) with the HES C10 acid:

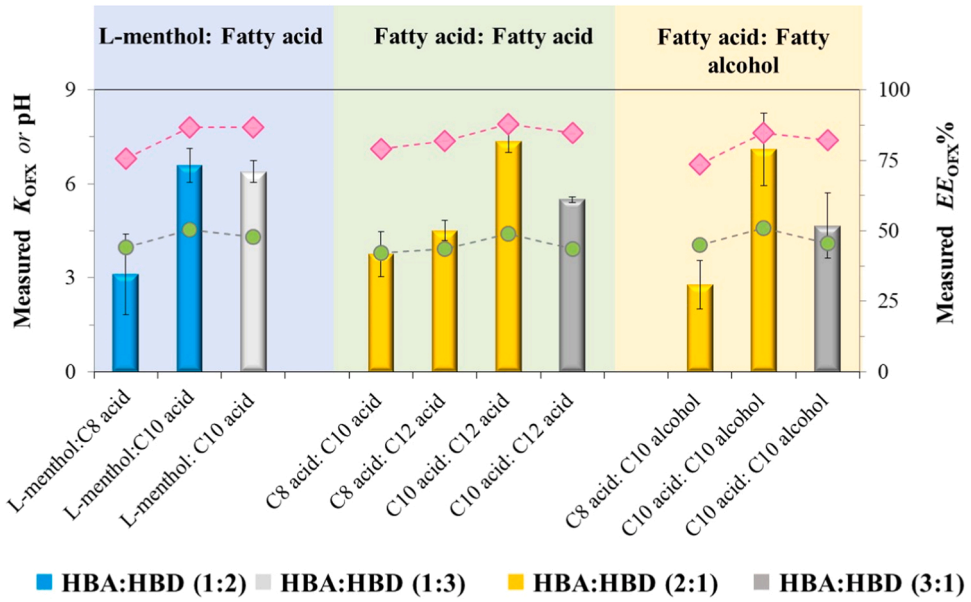

Fig. 4. The measured partition coefficient (bars), extraction efficiency (diamonds) of OFX and pH (circles) for the selected HES at 25 °C.

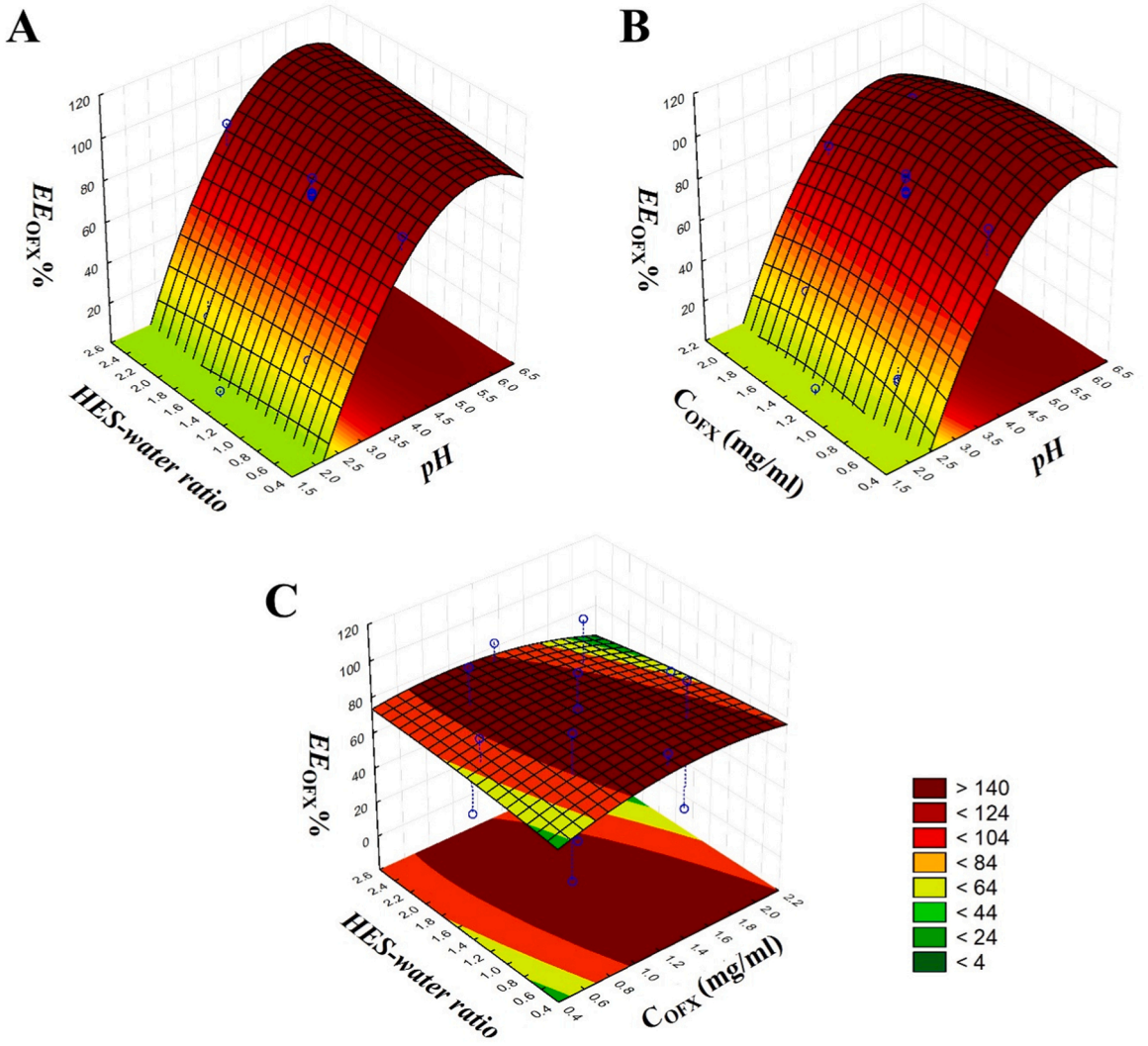

Fig. 5. Surface plots of the extraction efficiency of OFX using C10 acid: C12 acid (2:1) with the combined effects: (**A**) HES-water ratio (V/V) and pH, (**B**) pH and OFX concentration (mg/ml), and (**C**) HES-water ratio (V/V) and OFX concentration.

C10 alcohol and C10 acid:C12 acid (2:1), L-menthol:C10 acid is more expensive due to the higher cost of L-menthol, while C10 acid:C12 acid is slightly cheaper than C10 acid:C10 alcohol. Further details on the prices of the compounds can be found in Table S9 in the Supplementary Material. Additionally, C10 acid:C12 acid (2:1) exhibited greater stability in water [32] and lower solubility in water [37,43] - crucial factors to consider in a water extraction process. Furthermore, it was known that the hydroxyl group (–OH) can undergo esterification reactions with carboxylic acids (–COOH) to form ester bonds [17,44]. This degradation process does not take place when only carboxylic acids are present. Therefore, the C10 acid:C12 acid (2:1) was selected as the HES for the optimization of operating variables in OFX extraction.

3.3. Optimization of the operating extractions conditions

A RSM was applied to optimize the operating conditions to maximize the extraction of OFX. This method establishes a statistical correlation between the independent variables (pH, OFX concentration (C_{OFX}) and HES-water ratio (v/v)), and the response, i.e., the extraction efficiency of OFX (EE_{OFX} %). In addition, previous evaluations of different molar ratios of the selected HES, namely C10 acid to C12 acid (1:2, 1:1, 2:1, 3:1), showed that the 2:1 ratio was the most effective for OFX extraction. Therefore, this ratio was chosen for the RSM experiments. Details of the extraction efficiency measurements for OFX and statistical analyzes can be found in the Supplementary Material (Tables S10–S12, Figures S8–S10) and the respective data are depicted in Fig. 5. The statistical significance of the variables and their interactions was assessed using an analysis of variance (ANOVA). The results were subjected to a statistical analysis with a confidence level 95%. The value of R^2_{adj} obtained for the model was 0.89, indicating a strong correlation between the experimental and calculated responses. This supports the effectiveness of the developed statistical models in providing a reliable and accurate description of the experimental results.

All three variables (pH, OFX concentration, and HES-water ratio) were found to be significant, and their statistically significant effects follow this order: pH >> pH^2 > HES-water ratio^2 ≥ pH x C_{OFX}, ≈ C_{OFX} x HES-water ratio ≈ pH x HES-water ratio ≈ HES-water ratio≈ C_{OFX}, (Figure S8 in the Supplementary Material).

Regarding the influence of pH, the ANOVA results and the Pareto chart (Table S11 and Figure S8 in the Supplementary Material) show that it has a significant influence on the response and outperforms the other variables. The crucial role of pH in OFX extraction is mainly due to the fact that OFX is amphiprotic and has pH-dependent factors such as ionization, polarity and water solubility [45]. Keeping the pH of the solution below the pK_a of the analyte improves its distribution in the organic phase [46], which justifies the choice of a pH range from 2.0 to 6.0 for this study. Since the quadratic effect of pH is the most significant variable and has a negative influence on the response, this means that there is a maximum pH value that leads to optimal extraction efficiency. Our results show that the optimal extraction efficiency for OFX is at a pH of 5–6. This is in agreement with the results of Pochivalov et al. [21], who observed a lower extraction efficiency for fluoroquinolones below pH 5, and Horstkotte and co-workers [45], who found a slight improvement in fluoroquinolone extraction at pH 5–7. Mohammad et al. [47] also reported that OFX extraction is highest at pH 6 and decreases at higher pH values. This improvement in extraction efficiency is attributed to the fact that the molecule changes from a monocharged form to a zwitterionic form in this pH range (OFX pK_{a1} = 5.2 and pK_{a2} = 8.4, see Figure S7 in the Supplementary Material). The low water solubility of the zwitterionic form (pH 5–6) facilitates efficient mass transfer into the HES phase [45], resulting in improved extraction efficiency.

Regarding the HES-water ratio variable, while it is statistically significant, its influence on the response is minimal (see Figure S8 in the Supplementary Material). The quadratic effect, which is the most significant factor, has a negative influence, suggesting that the efficiency of OFX extraction increases with an increase in the HES-water ratio (i.e., an increase in HES volume) and optimal performance is achieved at a threshold of 1.3 (corresponding to a ratio of 13:10), as shown in Figure S10 of the Supplementary Material. Beyond this threshold, an excess of extraction solvent – corresponding to a higher solid-liquid ratio – can have a negative effect on the overall extraction efficiency, which is consistent with the results of previous studies [46,48].

Although the OFX concentration was statistically significant, its effect on the response was minimal, similar to that of the HES-water ratio, as shown by the analysis of variance (ANOVA). Fig. 5C shows that a decrease in the initial concentration of OFX is accompanied by a slight decrease in extraction yield. This tendency could be due to the lower driving force and distribution of the drug at lower concentrations, resulting in a lower extraction of OFX [39].

Analyzing the surface plots reported Fig. 5, the optimal operating conditions using HES C10 acid and C12 acid (2:1) for the extraction efficiency of OFX were as follows: an OFX concentration of 2.5 mg/ml, an HES-water ratio of 1.3, and a pH of 6 (Figure S10 in Supplementary Material). However, it should be noted that a pH of 5.2 was used to prevent the formation of a precipitate at the interface between the two phases. Under these optimized extraction conditions, an average extraction efficiency of (98.8 ± 0.9)% was achieved for OFX, compared to the predicted value of 103% obtained from multiple regression using RSM analysis, resulting in a relative error of 4%. It should be noted that, under these conditions, a partition coefficient of (65 ± 1) was obtained. The close agreement between the experimental and predicted results confirms the validation of the model with a confidence interval of 95%. Furthermore, Figure S10 in the Supplementary Material alongside with Fig. 5 shows that a reduction in the HES-water ratio has no significant effect on extraction efficiency, which emphasizes the minor role of this variable in the extraction process. In particular, when the HES-water ratio is reduced from 1.3 (13:10) to 0.54 (6:10, the lowest evaluated ratio), the predicted extraction efficiency remains constant at 103% (see Figure S10 in Supplementary Material). Therefore, optimal OFX extraction can be achieved even with a lower amount of HES, bringing significant economic and industrial benefits by minimizing material costs and waste without compromising efficiency. This aspect is particularly important from an economic and industrial perspective, as it offers a more sustainable and cost-effective approach to OFX extraction.

A comparison of the OFX extraction method developed in this work with previous approaches can be found in Table 3. Both solid-phase SPE and ionic liquid-based aqueous biphasic system (IL-ABS, a type of LLE) showed lower OFX extraction efficiency compared to HES-based LLE. On the other hand, adsorption and advanced oxidation methods show remarkable efficiency in the extraction of OFX, however, it is difficult to transfer these methods from laboratory scale to large scale and reduce the operating costs. Furthermore, these processes require the use of compounds such as bases and acids, leading to concerns about the environmental impact of these technologies [5]. Although LLME, based on the traditional organic solvents or HES, has high extraction efficiency for OFX extraction (see Table 3), it is not the best technique for processing larger sample volumes, as is the case for wastewater. In addition, equipment designed for lab-scale LLME may not scale seamlessly for industrial use and requires customized solutions to ensure efficiency and consistency [22].

Another important point to consider with solvent-based processes such as LLE, LLME and ABS is the cost of the solvent. Solvents used in our approach and in the literature include ionic liquids (1-ethyl-3-methylimidazolium trifluoromethanesulfonate), HES (consisting of thymol: heptanoic acid, thymol: nonanoic acid, and C10 acid:C12 acid), and an organic solvent (tetrachloroethane) used in ABS, LLME, and LLE, as presented in this study. An estimate of the prices of these solvents and components for laboratory and industrial use can be found in Table S9 in the Supplementary Material. The ionic liquid is significantly more

Table 3
Comparison of the present method with previous approaches for extraction of OFX from water samples.

Extraction method	Absorbent/ catalyst/ solvent	Extraction conditions	Water source	EE_{OFX} (%)	Ref.
Adsorption	N-doped activated carbon	Adsorbent content = 0.2 g/l, [OFX] = 0.2 mg/ml, pH = 8, T = 40 °C	Medical wastewater.	98.3	[49]
	Hydroxyapatite/activated carbon	Adsorbent content = 0.5 g/l, [OFX] = 0.02 mg/ml, pH= 7, T = 50 °C	Synthetic solution	99.2	[50]
Solid-phase extraction (SPE)	Oasis HLB cartridges	Oasis HLB cartridge (6 ml, 200 mg), [OFX] = 3.1×10^{-6} mg/ml, room temperature	Sewage treatment plant	85	[51]
	Oasis HLB cartridges	Oasis HLB cartridges (6 ml, 500 mg), [OFX] = 41×10^{-11} mg/ml, pH=3, room temperature	Piggery wastewater	90.7	[52]
Advanced oxidation process	Neutral photo-fenton	[Fe^{2+}5 = [mg/l, [H_2O_2] = 50 mg/l, UV_{254}, [OFX] = 4.1×10^{-8} mg /ml, pH=7.4, T = 17 °C	Domestic wastewater effluent	100	[53]
	Heterogeneous photo-Fenton	Fe-Mn oxides ratio of 8:3 (wt) = 5 mg/l, [H_2O_2] = 0.14 mg/l, UV_{288}, [OFX] = 0.03 mg/ml, pH=6.8, T = 20 °C	Synthetic solution	98.1	[54]
Liquid-liquid microextraction (LLME)	Thymol: Heptanoic acid (2:1)	HES volume = 150 µL; sample solution volume = 10 ml, [OFX] = 6×10^{-7} mg/ml, pH = 6	Reservoir water	90–93	[20]
			Pond water	86–102	
			Tap water recovery	85–104	
	Thymol: Nonanoic acid (1:1)	HES volume = 100 µL, sample solution volume = 2 ml, [OFX] = 0.1×10^{-1} mg/ml, pH = 6	River water	96–99	[21]
			Lake water	92–99	
	Tetrachloroethane	Tetrachloroethane volume =110 µl sample solution volume = 8.0 ml; methanol volume = 0.5 ml, [OFX] = 0.2 mg/ml, pH = 8.0	Pharmaceutical wastewater	83–102	[54]
Liquid-liquid extraction (LLE)	C10 acid:C12 acid (2:1)	HES-water ratio = 1.3, [OFX] = 2.5 mg/ml, pH = 5.2, T = 25 °C	Synthetic solution	98.8 ± 0.9	This work
Aqueous biphasic system (ABS)	1-ethyl-3-methylimidazolium trifluoromethanesulfonate	ABS composition: aluminum sulfate =15 wt%, IL= 42 wt%, [OFX] = 0.05 mg/ml, pH = 7.2, T = 25 °C	Synthetic solution	91.4	[55]

expensive than the other solvents. The organic solvent (tetrachloroethane) is less expensive than the HES components, but its toxicity is higher. However, the low toxicity of HES should not be generalized and is discussed in more detail in the next section. Considering only the HES, the thymol-based HES are significantly more expensive than the fatty acid-based HES, which is due to the cost of thymol.

Considering all these factors, LLE based on fatty acid-based HES emerges as the most interesting approach due to its efficiency, simplicity, scalability and the economic advantage of using a more environmentally friendly solvent [15,56].

3.4. Discussion

For the development of an efficient and sustainable extraction process it is crucial to consider the saturation of the solvent, its recyclability (including regeneration and reuse) and its stability throughout the process. While these aspects were not directly investigated in our study, valuable insights can be gained from Florindo et al. [37]. They investigated the performance of the same HES composition (C10 acid: C12 acid in a molar ratio of 2:1) over several cycles in the extraction of ciprofloxacin, a fluoroquinolone like ofloxacin, by LLE and evaluated its recyclability. The results showed that HES remained effective for up to four cycles before extraction efficiency decreased from the fifth cycle onwards, indicating saturation of HES. Florindo et al. [37] used activated carbon to recover HES in their approach and showed that it can be reused without loss of extraction efficiency. Crucially, they confirmed the properties of HES after the recovery process with activated carbon and before reuse by ^{1}H NMR analysis and found that its properties remained unchanged. These results highlight the potential of C10 acid: C12 acid (2:1) HES for use in multiple extraction cycles prior to saturation, while emphasizing its reusability and stability during extraction and recovery processes. These results are of particular importance for our extraction process, as they demonstrate the stability of our solvent and the possibility of reusing HES within our framework, thus making an important contribution to the efficiency and sustainability of our process.

Despite the advantages of HES in extraction, another important is its toxicity. Only one study evaluated the effects of fatty acid-based HES, including C10 acid: C8 acid, C10 acid: C12 acid, and C10 acid: tetradecanoic acid. Silva et al. [57] showed that fatty acid-based HES inhibited the growth of the yeast *C. albicans*. However, the results varied depending on the toxicity test used, including minimum inhibitory concentration/minimum inhibitory fungal (MIC/MFC) and diffusion disk. Given the limited research available, analyzing the C10 and C12 acids in HES could offer a viable option for gaining insight into the toxicity of HES, as these acids belong to the same family and have comparable alkyl chain lengths. In this line, an analysis of its individual components, shows that despite their cytotoxicity at high doses, these medium-chain fatty acids are generally considered to have low toxicity at suitable levels [58,59]. In addition, both acids are considered to have low toxicity at appropriate concentrations and are deemed safe by regulatory agencies such as the Food and Drug Administration (FDA) [60]. They are widely used in various industries, from perfumes to food additives. However, caution is advised due to potential skin, eye irritation, and gastrointestinal issues at high doses. While compliance with FDA regulations on C10 and C12 acids may mitigate the problem of HES contamination of drugs, ideally, the active pharmaceutical ingredients should be free of any contamination.

Another crucial aspect to consider is the toxicity of HES in the environment, known as ecotoxicity, particularly concerning aquatic ecosystems, considering the extraction process here developed. Unfortunately, no ecotoxicity tests were carried out for our HES. However, employing the same rationale as previously mentioned, analyzing its individual components suggests that both acids may present a potential risk to aquatic life because they degrade slowly in water [61,62]. It is crucial to handle and dispose of C10 and C12 acids properly to minimize their adverse effects on the environment. Nevertheless, it is worth mentioning that Florindo et al. [37] highlighted that among the studied HES variants, this one resulted in lower water contamination due to its lower water solubility (2 wt%), which is positive from an environmental sustainability point of view.

In summary, our results highlight the critical importance of optimizing operating conditions, including pH, solvent choice and concentration, to improve the efficiency of extraction processes. Achieving an

extraction efficiency of 98.8% ± 0.9 for OFX using HES-based LLE represents a remarkable advance in wastewater treatment, as it significantly mitigates pharmaceutical contamination of wastewater and thus contributes to address the issue of antibiotic resistance in aquatic ecosystems. Among the tested HES, C10 acid: C12 ratio (2:1) emerged as the optimal choice for one-step OFX extraction due to its efficacy, water stability, cost-effectiveness and environmental friendliness. However, to fully realize the potential of HES in industrial applications such as wastewater treatment, comprehensive assessments of their cost-effectiveness, environmental benefits and impact on human and animal health are required.

4. Conclusions

The development of LLE processes based on HES has been shown to be effective in improving the efficiency of separation. For that reason, HES were here used for the removal of OFX from water. To the best of our knowledge, this is the first work on the use of HES-based LLE for the extraction of OFX, coupled with the application of COSMO-RS for an initial rapid and qualitative screening to identify promising HES for OFX extraction from 12 HES at three different molar ratios. Both computational experiments and subsequent experimental tests confirmed that a high molar ratio of fatty acids combined with an increase in their alkyl chain length significantly improved the partition coefficient of OFX, with decanoic acid: dodecanoic acid (2:1), L-menthol: decanoic acid (1:2), and decanoic acid: 1-decanol (2:1), being the most favorable extraction solvents. An experimental design was also applied to study keys factors in the extraction process, using decanoic acid: dodecanoic acid (2:1) as solvent. It was found that pH played a crucial role in the efficiency of OFX extraction, while the ratio OFX concentration had a minor influence. The optimal conditions determined were: an OFX concentration of 2.5 mg/ml, a pH of 5.2 and a HES-water ratio of 1.3, resulting in OFX an OFX extraction efficiency of (98.8 ± 0.9)%. These results highlight the importance of carefully selecting appropriate solvents and establishing critical parameters of extraction to significantly improve the efficiency of the extraction processes. This work not only addresses the removal of OFX as a micropollutant in water streams, but may also be of interest to the pharmaceutical industry, which needs to treat its wastewater prior to discharge.

CRediT authorship contribution statement

Ana M. Ferreira: Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Mahtab Moradi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Samane Zarei Mahmoudabadi:** Writing – review & editing. **Catarina M. S. S. Neves:** Writing – review & editing, Formal analysis, Data curation. **João A.P. Coutinho:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Gholamreza Pazuki:** Writing – review & editing, Supervision, Conceptualization.

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

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2024.113075.

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