Cholinium-based ionic liquids as bioinspired hydrotropes to tackle solubility challenges in drug formulation

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ABSTRACT

Hydrotropy is a well-established strategy to enhance the aqueous solubility of hydrophobic drugs, facilitating their formulation for oral and dermal delivery. However, most hydrotropes studied so far possess toxicity issues and are inefficient, with large amounts being needed to achieve significant solubility increases. Inspired by recent developments in the understanding of the mechanism of hydrotropy that reveal ionic liquids as powerful hydrotropes, in the present work the use of cholinium vanillate, cholinium gallate, and cholinium salicylate to enhance the aqueous solubility of two model drugs, ibuprofen and naproxen, is investigated.

It is shown that cholinium vanillate and cholinium gallate are able to increase the solubility of ibuprofen up to 500-fold, while all three ionic liquids revealed solubility enhancements up to 600-fold in the case of naproxen. Remarkably, cholinium salicylate increases the solubility of ibuprofen up to 6000-fold. The results obtained reveal the exceptional hydrotropic ability of cholinium-based ionic liquids to increase the solubility of hydrophobic drugs, even at diluted concentrations (below 1 mol·kg^{-1}), when compared with conventional hydrotropes. These results are especially relevant in the field of drug formulation due to the bio-based nature of these ionic liquids and their low toxicity profiles. Finally, the solubility mechanism in these novel hydrotropes is shown to depend on synergism between both amphiphilic ions.

1. Introduction

Poor aqueous solubility is a severe obstacle to drug design and formulation since it causes delivery concerns such as erratic absorption and low bioavailability [1,2]. This is especially relevant when dealing with BCS (Biopharmaceutics Classification System) Class II drugs, which are substances with low aqueous solubility but high intestinal permeability [3,4]. Because these drugs already possess high intestinal permeability (high absorption), the main target in their formulation is the enhancement of their aqueous solubility, which may greatly increase their bioavailability. Several methodologies have been proposed to increase the solubility of BCS Class II drugs in water [5], such as the use of solid dispersions [6,7], cyclodextrin complexes [8,9], colloidal formulations [10], salt formation [11], particle size reduction [12], crystal engineering [13], surfactants [14–16], and hydrotropy [17–19].

Hydrotropes are a class of water-soluble compounds capable of greatly increasing the aqueous solubility of hydrophobic solutes, including drugs [17–22]. Besides drug solubilization, hydrotropy is also used in detergent formulation, health care and household applications, and extraction of bioactive compounds [23–25]. Hydrotropes are compounds that possess an amphiphilic structure capable of interacting with both water and apolar moieties. Examples of common hydrotropes include sodium benzoate, sodium salicylate, sodium citrate, urea, caffeine, and nicotinamide. Despite their amphiphilic nature, hydrotropes are not surfactants. While surfactants possess long hydrocarbon chains and self-aggregate above a critical micellar concentration (CMC), hydrotropes are characterized by shorter hydrophobic moieties, leading to a weak tendency to self-aggregate in water and a higher hydrophilic-lipophilic balance [26]. The use of hydrotrope-based formulations circumvents the problem of emulsification usually associated with conventional surfactant solutions. Nevertheless, hydrotropic solubilization is characterized by the relatively high concentrations of hydrotrope needed when compared to the micellization technique, which can be a concern for human administration.

Despite the growing demand for natural resources and bio-based formulations, only a small number of studies have been reported on

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using natural hydrotropes to solubilize hydrophobic drugs. Caffeine, piperazine, tannic acid, and epigallocatechin gallate are examples of naturally available compounds that have shown considerable ability to enhance the solubility of some poorly water soluble drugs [27–29]. In this sense, phenolic compounds are an attractive class of compounds to be tested as hydrotropes due to their abundancy as plant secondary metabolites and well-known antioxidant features [30]. Their applicability is limited, though, due to their poor water solubility. However, the conversion of phenolic acids into cholinium salts has been recently proposed as a powerful strategy to overcome the solubility issue of phenolic acids, with an aqueous solubility enhancement of three orders of magnitude being attained [31]. In addition, these cholinium-based salts present similar or even higher antioxidant and anti-inflammatory activities, as well as comparable cytotoxicity and lower ecotoxicity profiles than their respective phenolic precursors [31,32]. In this context, cholinium-based salts composed of ions derived from natural sources emerge as promising candidates to enhance the aqueous solubility of hydrophobic drugs, although further research is needed to assess their potential to become pharmaceutical excipients.

The recent proposal of naturally-derived, cholinium-based ionic liquids, coupled with the growing understanding of the mechanism of hydrotropy [33–36], which reveal ionic liquids to be superior to traditional sodium-based hydrotropes, calls for a systematic study on the ability of these compounds to increase the aqueous solubility of BCS Class II drugs. Thus, in this work, the ability of cholinium vanillate, cholinium gallate, and cholinium salicylate to increase the solubility of two BCS Class II model-drugs, ibuprofen and naproxen (Fig. 1), is studied. The performance of these hydrotropes is also benchmarked against classical hydrotropes and the dissolution mechanism is discussed in terms of the apolarity of the individual ions composing the hydrotrope.

2. Experimental details

2.1. Chemicals

The substances experimentally used in this work are listed in Table 1, along with their CAS number, supplier, and mass purity. The chemical structure of all compounds studied as hydrotropes are depicted in Fig. 2.

The cholinium-based ionic liquids (cholinium vanillate, cholinium gallate, and cholinium salicylate) were synthesized in this work by following well-established protocols, via neutralization of cholinium hydroxide with the corresponding acid, respectively vanillic, gallic or
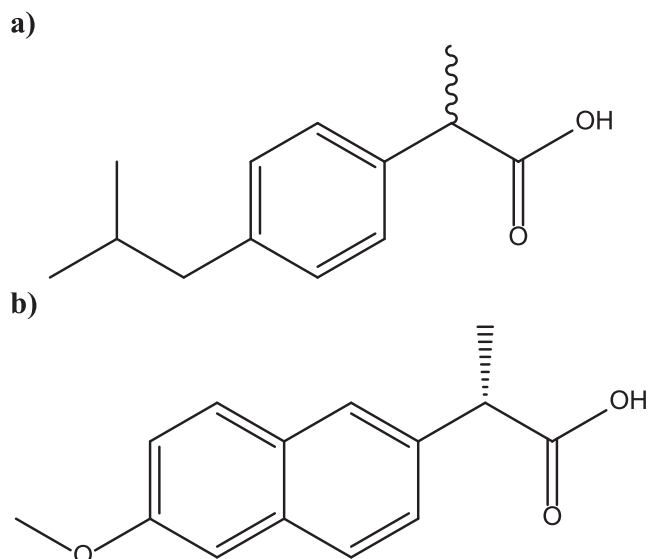
Table 1
List of substances experimentally used in this work, along with their CAS number, supplier and purity.

Compound	CAS Number	Supplier	Purity (wt%)
Ibuprofen	15687–27–1	Sigma-Aldrich	98.0
Naproxen	22204–53–1	Sigma-Aldrich	99.0
Cholinium Vanillate	——	a)	>98
Cholinium Gallate	——	a)	>98
Cholinium Salicylate	2016–36-6	a)	>98
Cholinium Chloride	67–48-1	Sigma-Aldrich	98.0
Benzylcholinium Chloride	7221–40-1	Sigma-Aldrich	97.0
Sodium Benzoate	532–32-1	Panreac	99.0
Sodium Tosylate	657–84-1	TCI	95.0
Urea	57–13-6	Sigma-Aldrich	99.5
Ammonium Acetate	631–61-8	Sigma-Aldrich	99.99
Acetic Acid	64–19-7	Sigma-Aldrich	99.99
Acetonitrile	75–05-8	Fisher Chemical	HPLC Grade

a) Substances synthetized in this work.

salicylic acid [31]. As HPLC-DAD mobile phase, ammonium acetate, acetic acid, acetonitrile, and ultrapure water (treated with a Mili-Q 185 water apparatus) were used. During the filtration steps, syringe filters (0.45 μm; Specanalitica) and regenerated cellulose membrane filters (0.45 μm; Sartorius Stedim Biotech) were applied.

2.2. Solubility curves

The solubility of the two poorly water-soluble drugs under study was measured according to well-established methodologies, previously described in detail [37]. Briefly, each drug (ibuprofen and naproxen) was added in excess amount to each salt aqueous solution or pure water, and was then equilibrated at (303.2 ± 0.5) K, under constant agitation (750 rpm) during 72 h, using an Eppendorf Thermomixer Comfort equipment. Then, all samples were centrifuged at (303.2 ± 0.5) K for 20 min at 4500 rpm, in order to separate the excess undissolved solute from the liquid phase. Samples of the liquid phase were collected and filtered using syringe filters. When necessary, each sample was diluted in acetonitrile:ultrapure water [30:70 (v/v)]. The amount of ibuprofen and naproxen was quantified by HPLC-DAD (HPLC Elite LaChrom, VWR Hitachi, with a diode array detector l-2455), using an analytical method previously developed and validated by our group [38]. DAD was set to measure the amount of ibuprofen and naproxen at 230 nm and 270 nm, respectively, using calibration curves previously established, and the results are reported in Supporting Information. Triplicates were performed for each assay. Note that the aqueous solubilities of ibuprofen and naproxen have been previously reported by us and take the values of 37.5 mg·L^{-1} and 31.9 mg·L^{-1}, respectively [36].

3. Results and discussion

3.1. Cholinium-based ionic liquids

The solubility of ibuprofen and naproxen in aqueous solutions of cholinium vanillate, cholinium gallate, or cholinium salicylate, was measured in this work. The main results are depicted in Fig. 3 and details are reported in Supporting Information. The solubility of the solutes was measured in the entire concentration range of the hydrotrope, from pure water to its aqueous solubility limit.

The ability of cholinium-based ionic liquids to enhance the aqueous solubility of ibuprofen and naproxen is remarkable. Both cholinium vanillate and cholinium gallate are able to increase the solubility of ibuprofen up to 500-fold, while cholinium salicylate is able to enhance its solubility up to 6000-fold. In the case of naproxen, all three ionic liquids reveal solubility enhancements up to 600-fold. In terms of hydrotropy efficiency, cholinium vanillate and cholinium gallate significantly increase the solubility of the anti-inflammatory drugs, showing solubility enhancements of at least 100-fold even at
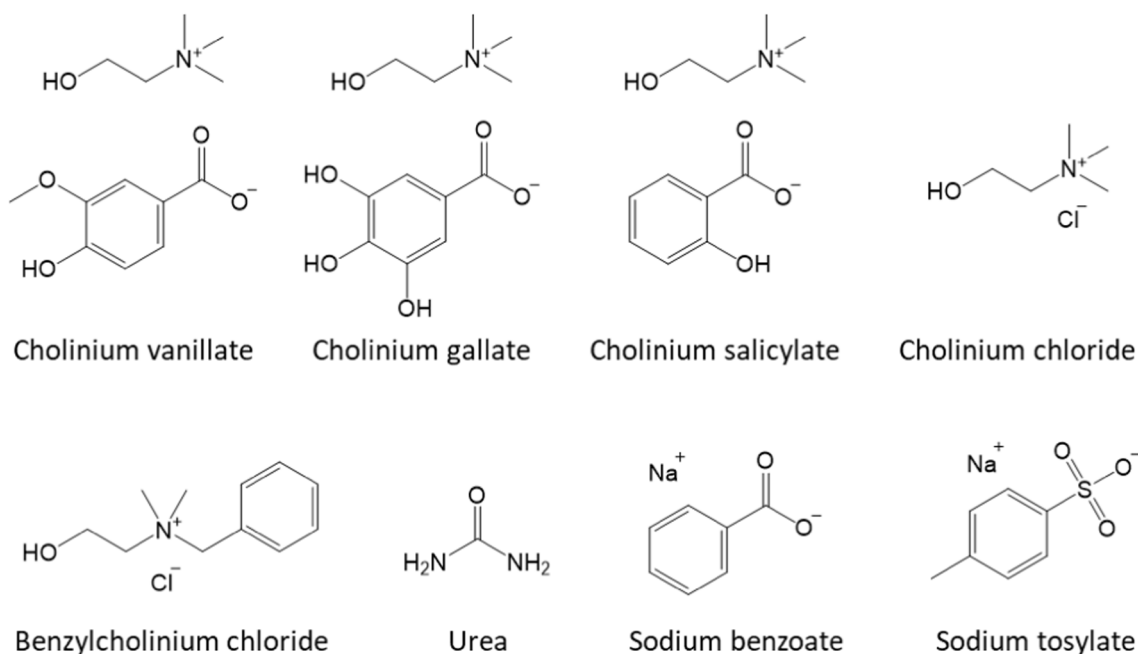

Fig. 1. Chemical structures of a) ibuprofen (racemic) and b) naproxen.

Fig. 2. Chemical structure of the hydrotropes experimentally used in this work.

concentrations below 1 mol·kg^{-1}. This is a particularly important result since the hydrotropic effect is often only effective at high hydrotrope concentrations. In addition, it should be noted, as mentioned in the introduction, that both cholinium vanillate and cholinium gallate present similar cytotoxicity profiles to the respective phenolic acids currently used in the therapeutic, rendering these hydrotropes as valid and valuable candidates in the formulation of pharmaceutical or cosmetic products [31,32].

The shape of the solubility curves depicted in Fig. 3 are significantly different. In particular, naproxen reaches a solubility maximum when cholinium vanillate is used, most likely related to the transition between "ionic liquid in water" to "water in ionic liquid" and a change in the solvation mechanism [39]. A typical hydrotropy solubility curve presents a sigmoidal shape, yet this shape is only observed in the ibuprofen/cholinium salicylate system and, to a lesser extent, in the systems naproxen/cholinium vanillate and naproxen/cholinium gallate. From the perspective of application, the different solubility curve shapes provide freedom of choice of the hydrotrope in terms of optimal hydrotrope concentration. That is, at low hydrotrope concentration cholinium vanillate and cholinium gallate are better choices than cholinium salicylate, while cholinium salicylate is the best hydrotrope at higher concentrations, for the solutes here studied. Fig. 4 illustrates this point by comparing the solubility curves of the three hydrotropes in the dilute region (below 2 mol·kg^{-1}).

The ability of the studied cholinium-based ionic liquids to enhance the aqueous solubility of ibuprofen and naproxen is now benchmarked against classical hydrotropes, namely urea, sodium tosylate, and sodium benzoate. The solubility of ibuprofen in aqueous sodium benzoate or urea was measured in this work, while its solubility in aqueous sodium tosylate was taken from the literature and complemented with novel data here measured [37]. The solubility of naproxen in aqueous sodium tosylate or urea was measured in this work. These results are depicted in Fig. 5 and reported in Supporting Information. As with the previous results, the solubility of the solute was measured in the entire available concentration range of the hydrotrope, from pure water to its aqueous solubility limit.

Fig. 5 clearly demonstrates the superiority of the studied cholinium-based ionic liquids over classical hydrotropes in increasing the aqueous solubility of ibuprofen and naproxen. This is not the first time, though,

that ionic liquids are shown to be excellent hydrotropes for ibuprofen and naproxen [36,37,40]. The molecular mechanism that allows them to outperform conventional hydrotropes is discussed in the next section.

3.2. Dissolution mechanism

According to recent studies, hydrotropy occurs due to the aggregation of apolar moieties of the hydrotrope around the solute [33,35,41,42]. This aggregation is loosely driven by the hydrophobic effect, in which the minimization of water-solute contacts maximizes the extent of water hydrogen bonding. Contrary to the aggregation of neutral hydrotrope species around hydrophobic solutes, the aggregation of ions is constricted by the increase in the local charge of the resulting cluster [36]. In other words, a synergistic effect arises when ionic liquids are used as hydrotropes because both ions are amphiphilic and, thus, both ions aggregate around the solute, minimizing the local charge of the resulting cluster. This phenomenon is clearly seen in the results of this work. The ions of the cholinium-based ionic liquids here studied are, individually, not particularly more apolar than the tosylate anion. Nevertheless, the difference in hydrotropy efficiency between sodium tosylate, a prototypical hydrotrope, and any cholinium-based ionic liquid here studied is enormous.

The astonishing ability of cholinium salicylate, the best hydrotrope studied in this work, to increase the solubility of ibuprofen can thus be understood in light of the synergistic effect introduced in the previous paragraph. In order to better showcase this effect, the solubility of ibuprofen in aqueous cholinium salicylate is now compared against its solubility in aqueous cholinium chloride (Sintra et al. [37] and this work) and aqueous sodium salicylate (Singh et al. [43]). The novel data measured in this work is reported in Supporting Information and the three solubility curves are depicted in Fig. 6.

Fig. 6 clearly demonstrates the existence of a synergistic effect when a salt with two amphiphilic ions is used as a hydrotrope instead of one amphiphilic ion and one very hydrophilic counterion. The solubility enhancement of ibuprofen in aqueous cholinium salicylate is much larger than the sum of its solubility enhancement in cholinium salicylate and cholinium chloride. The difference is so large that the vertical axis of Fig. 6 needs to be depicted in a logarithm scale. This difference in the extent of hydrotropy has been previously explained in the literature
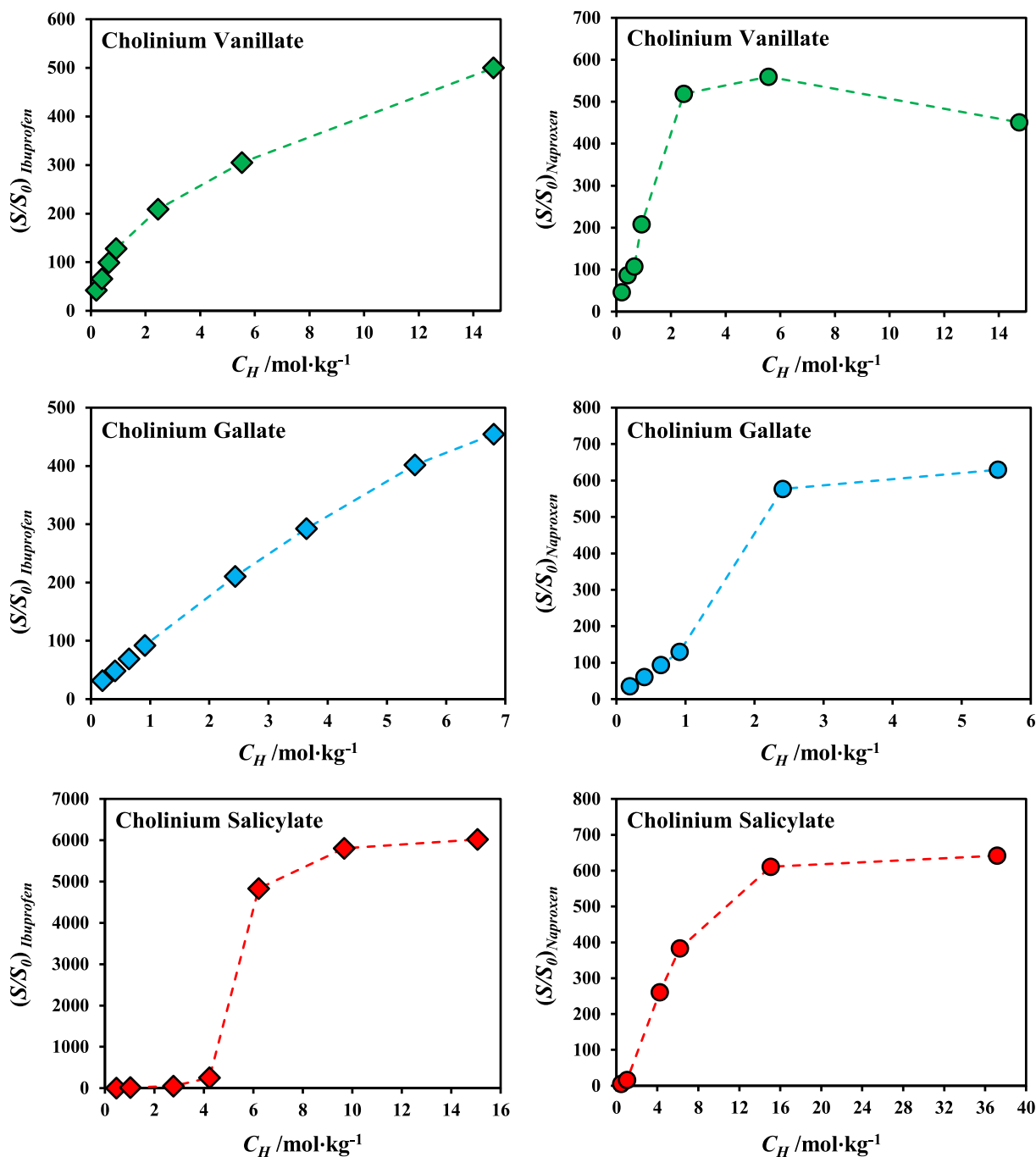
Fig. 3. Solubility enhancement of ibuprofen (left) and naproxen (right) in aqueous solutions of cholinium-based ionic liquids, as a function of hydrotrope molal concentration, at (303.2 ± 0.5) K. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.

[36]. In brief, the cholinium-based ionic liquids used in this work possess two bulky ions that do not form strong solvation structures with water. Thus, both ions can be driven to aggregate around the solute through their apolar moieties, and there is no counterion with strong interactions with water limiting the extent of solute-hydrotrope aggregation through charge neutrality.

Besides using densely charged ions, another common fault of conventional hydrotropy is to assume that the presence of aromatic rings is crucial for the formation of solute-hydrotrope aggregates. In fact, hydrotropy is often justified by the presence of a phenyl group in the hydrotrope structure, with π-π interactions being proposed by various authors as the driving force of hydrotropy [44–46], even though this has

been previously shown to be incorrect [37,40,47,48]. Nevertheless, to probe this hypothesis, the solubility of ibuprofen in aqueous benzyl-cholinium chloride was measured in this work and compared with the solubility curve of ibuprofen in aqueous cholinium chloride. These results are reported in Supporting Information and depicted in Fig. 7.

Fig. 7 shows that benzylcholinium chloride is indeed a better solubility enhancer for ibuprofen than cholinium chloride. Thus, the replacement of a methyl group by a benzyl group in the cholinium cation is favorable for hydrotropy as it increases the size of the apolar moiety of the hydrotrope. However, the magnitude of the solubility enhancement of benzylcholinium chloride is quite inferior to that of the ionic liquids studied in this work. The addition of the benzyl group is benefic only
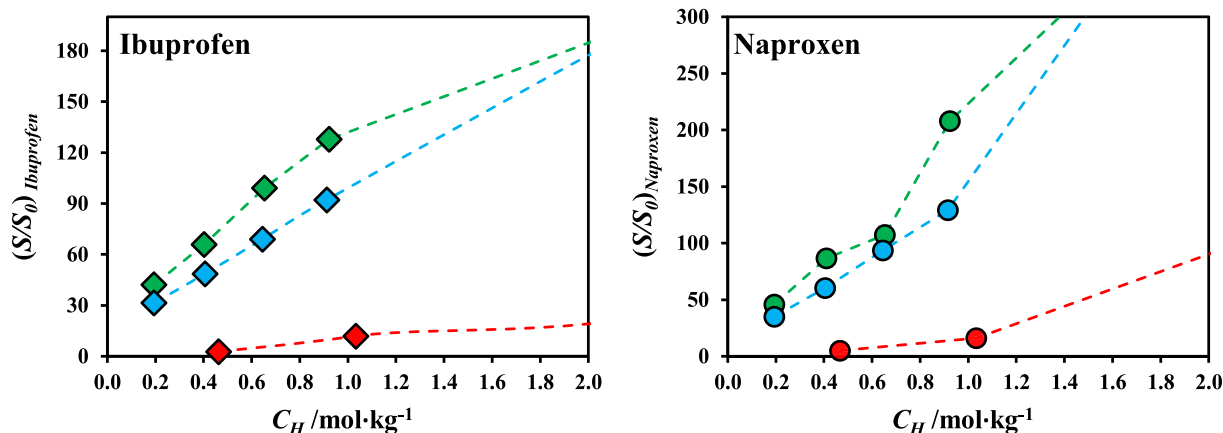
Fig. 4. Solubility enhancement of ibuprofen (left) and naproxen (right) in the dilute region of aqueous solutions of cholinium vanillate (◆,●), cholinium gallate (◆,●), or cholinium salicylate (◆,●), as a function of hydrotrope molal concentration, at (303.2 ± 0.5) K. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.
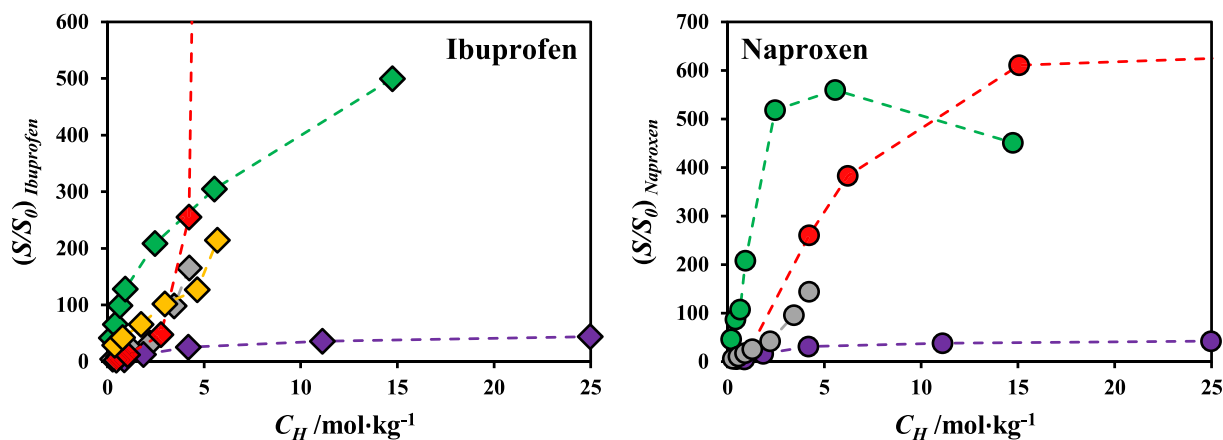

Fig. 5. Solubility enhancement of ibuprofen (left) and naproxen (right) in aqueous solutions of cholinium vanillate (◆,●), cholinium salicylate (◆,●), sodium benzoate (◆), sodium tosylate (◆[37],●), and urea (◆,●), as a function of hydrotrope molal concentration, at (303.2 ± 0.5) K. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.

because it increases the apolarity of the cation, but the effect is much smaller when compared to switching the chloride counterion for a bulky anion.

4. Conclusions

In this work, the ability of cholinium-based ionic liquids to act as hydrotropes and enhance the solubility of the BCS Class II drugs, ibuprofen and naproxen, was investigated. The ionic liquids experimentally used (cholinium vanillate, cholinium gallate, and cholinium salicylate) present similar antioxidant and anti-inflammatory activities to their phenolic precursors, as well as comparable cytotoxicity and lower ecotoxicity profiles, making them attractive choices for further drug formulation research.

Cholinium vanillate and cholinium gallate were able to increase the solubility of ibuprofen up to 500-fold, while cholinium salicylate

increased the solubility of ibuprofen up to 6000-fold. All three ionic liquids revealed solubility enhancements up to 600-fold in the case of naproxen. Because the solubility curves of the drugs in these hydrotropes presented different shapes, they widen the choice of hydrotrope concentration for a specific solubility enhancement objective. That is, cholinium vanillate and cholinium gallate were shown to be the best hydrotropes at low hydrotrope concentration, while cholinium salicylate is the best choice for larger hydrotrope concentrations. The hydrotropic ability of the ionic liquids was compared to common hydrotropes, namely sodium tosylate, sodium benzoate, and urea, showing these novel hydrotropes to be far better than the conventional ones.

Finally, a synergistic effect was demonstrated by comparing the solubility enhancement of ibuprofen in aqueous cholinium salicylate against its solubility enhancement in aqueous cholinium chloride or sodium salicylate. This reasoning reinforces the remarkable hydrotropic
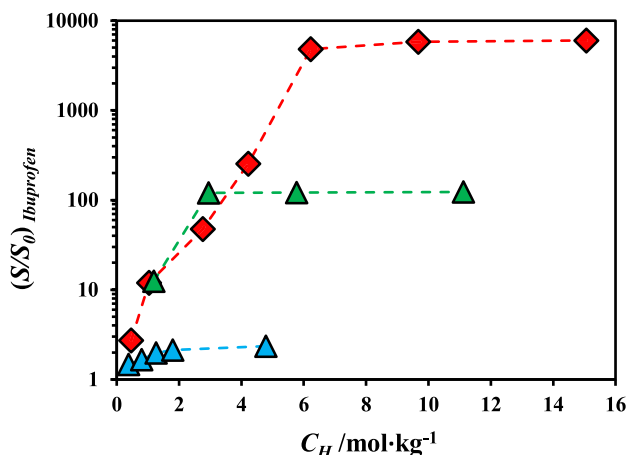
Fig. 6. Solubility enhancement of ibuprofen in aqueous solutions of cholinium salicylate (⬥), sodium salicylate (▲ [43]), or cholinium chloride (▲ [37]), as a function of hydrotrope molal concentration, at (303.2 ± 0.5) K. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.
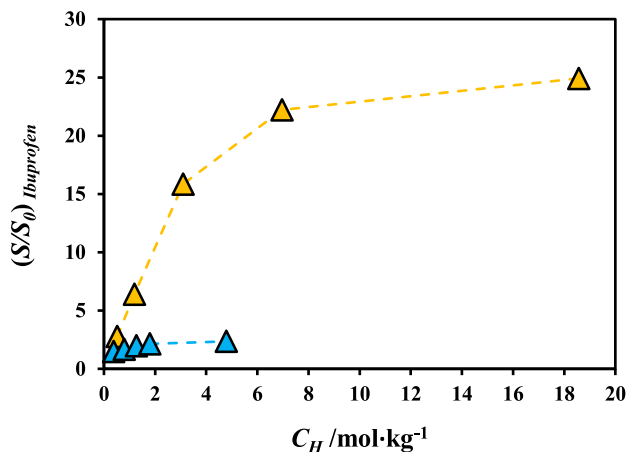

Fig. 7. Solubility enhancement of ibuprofen in aqueous solutions of cholinium chloride (▲ [37]) or benzylcholinium chloride (▲), as a function of hydro-trope molal concentration, at (303.2 ± 0.5) K. S and S_0 represent the solubility of the drug in the aqueous solution of the hydrotrope and in water, respectively. Lines are guides for the eye.

ability of ionic liquids and paves the way for the design of novel and more effective hydrotropes, where conventional counterions such as sodium or chloride are replaced by bulkier ions with dispersed charge.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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