Green Solvents as Hydrotropes to Enhance the Solubility of Acetaminophen

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"Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar.
Mas o mar seria menor se lhe faltasse uma gota"

Madre Teresa de Calcutá

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Abstract

Solubility, the ability to dissolve a solute in a solvent, is crucial in pharmaceutical research, influencing drug formulation and bioavailability. Poorly water-soluble drugs, such as acetaminophen (ACP), a world-wide used drug as painkiller and antipyretic, often present challenges. The addition of hydrotropes to aqueous solutions is one of the strategies used to enhance the solubility of those solutes in water. This study compares the effect of various hydrotrope types (organic compounds, ionic liquids, deep eutectic solvents and organic or inorganic salts) at different concentrations. New solubility data in aqueous solutions of [BMIm][Ac], ChBr, ChCl, NaBS, NaCapry, NaSCN, NaSal, Na_2SO_4, NaTOS, NH_4SCN, $(NH_4)_2SO_4$, urea, ethanol, 1,2-propanediol, glycerol and acetone were measured at 298.2 K by the shake-flask method coupled to UV-Vis spectroscopy or gravimetry as analytical techniques. A critical comparison with literature data was also carried out. NaTOS, NaSal and [BMIm][Ac] stood out as hydrotropes with better performance, by enhancing the ACP solubility at lower hydrotropic concentrations.

Statistical analysis of the hydrotrope polarity assessed using the COSMO-RS model showed a good positive correlation with the apolar factor, at a hydrotrope concentration of 0.10 (weight fraction). At the same hydrotrope concentration, in the studied organic solvents (ethanol, 1,2-propanediol, glycerol and acetone) a strong negative correlation is observed between their hydrogen donor character and the acetaminophen solubility, and an evident negative correlation between the hydrogen bond parameter and the ACP solubility was observed for systems containing ionic liquids.

It is necessary to investigate these correlations for other hydrotrope concentrations, and temperatures, attempting to find heuristics that allow the analysis of the drug solubility increase in a predictive way.

Finally, it was possible to identify hydrotropes capable of enhancing the solubility of acetaminophen, with potential application in other drugs formulations.

Keywords: Solubility enhancement; Hydrotropes; computational modelling; acetaminophen;

Resumo

A solubilidade, a capacidade do soluto para se dissolver num solvente, é crucial na investigação farmacêutica, influenciando a formulação e a biodisponibilidade do medicamento. Os fármacos pouco solúveis em água, como o acetaminofeno (ACP), um fármaco mundialmente utilizado como analgésico e antipirético, apresentam frequentemente desafios. A adição de hidrótropos a soluções aquosas é uma das estratégias utilizadas para aumentar a solubilidade desses solutos em água. Este estudo compara o efeito de vários tipos de hidrótropos (compostos orgânicos, líquidos iónicos, solventes eutécticos profundos e sais orgânicos ou inorgânicos) em diferentes concentrações. Foram medidos novos dados de solubilidade em soluções aquosas de [BMIm][Ac], ChBr, ChCl, NaBS, NaCapry, NaSCN, NaSal, Na_2SO_4, NaTOS, NH_4SCN, $(NH_4)_2SO_4$, ureia, etanol, 1,2-propanodiol, glicerol e acetona a 298,2 K pelo método do frasco agitado acoplado à espetroscopia UV-Vis ou gravimetria como técnicas analíticas. Foi também efectuada uma comparação crítica com dados da literatura.

NaTOS, NaSal e [BMIm][Ac] destacaram-se como hidrótropos com melhor desempenho, aumentando a solubilidade do ACP em concentrações hidrotrópicas mais baixas.

A análise estatística da polaridade do hidrótropo, avaliada pelo modelo COSMO-RS, mostrou uma boa correlação positiva com o fator apolar, a uma concentração de hidrótropo de 0,10 (fração mássica). Para a mesma concentração de hidrótropos, nos solventes orgânicos estudados (etanol, 1,2-propanodiol, glicerol e acetona), observa-se uma forte correlação negativa entre o seu carácter dador de hidrogénio e a solubilidade do acetaminofeno, e uma evidente correlação negativa entre o parâmetro de ligação de hidrogénio e a solubilidade do ACP para os sistemas que contêm líquidos iónicos.

É necessário investigar estas correlações para outras concentrações de hidrótropos, e temperaturas, tentando encontrar heurísticas que permitam analisar o aumento da solubilidade do fármaco de forma preditiva.

Finalmente, foi possível identificar hidrótropos capazes de aumentar a solubilidade do acetaminofeno, com potencial aplicação em formulações de outros fármacos.

Palavras-chave: Aumento de solubilidade; hidrótropos; modelagem computacional; acetaminofeno;

TABLE OF CONTENTS

LIST OF FIGURES vii

LIST OF TABLES ix

1 SCOPE AND OBJECTIVES 1

2 INTRODUCTION 3

2.1 Solubility Definition 3

2.2 Solubility Measurement 3

2.3 Solubility Enhancement Techniques: Hydrotropy 5

2.4 Acetaminophen: A Summary 12

2.5 COSMO-RS modelling 17

3 MATERIALS AND METHODS 18

3.1 Chemicals 18

3.2 ACP solubility determination 21

3.3 Water content and pH measurements 22

3.4 Thermodynamics modelling 23

4 RESULTS AND DISCUSSION 24

4.1 Hydrotrope solutions' pH 24

4.2 Solubility of acetaminophen in water 25

4.3 Solubility data in different hydrotropes 26

4.4 Polarity surface area data analysis 43

5 CONCLUSIONS AND FUTURE WORK 47

6 REFERENCES 48

Appendix A. pH data 58

Appendix B. Solubility data. 60

Appendix C. Sigma-profile data 62

LIST OF FIGURES

Figure 1. Hydrotropy main mechanisms, adapted from Paul et al. (2021). 8
Figure 2. Hydrotropic mechanism proposed by Abranches and his coworkers (2020), where the interaction hydrotrope-solute vary according to the hydrotrope apolarity. Adapted from Abranches and his coworkers (2020). 11
Figure 3. Acetaminophen chemical structure. 12
Figure 4. Graphical representation of acetaminophen solubility in water from literature, in **Table 1:** (a) acetaminophen solubility [g/gwater] as function of temperature [K], and (b) Natural logarithm of the solubility in mole fraction as function of $1/T$. 13
Figure 5. σ-profile of water calculated with COSMO*thermX* with BP_TZVP_21.ctd parametrization. 18
Figure 6. Chemical structures of the hydrotropes used in this work, grouped in chemical classes. 21
Figure 7. Acetaminophen UV-Vis spectrum at $10^3 x_1$ = 1.3943E-6 drug concentration. 22
Figure 8. Top: ACP speciation curves as a function of pH (adapted from Chemicalize, 2023); Bottom: Acetaminophen ionic species. 24
Figure 9. Experimental data for ACP solubility in pure water: (a) acetaminophen solubility ($10^3 x_1$) as function of temperature [K] and (b) Natural logarithm of the solubility in mole fraction as function of $1/T$. 25
Figure 10. Summary of the ACP relative solubility in all the tested hydrotropic systems as a function of the hydrotrope concentration in mass fraction. 27
Figure 11. Effect of alcohols on ACP solubility in aqueous solutions at 298.2 K: (a) all hydrotrope concentration range; (b) close up at $0 \leq w_{hydrotrope} \leq 0.3$ region. 29
Figure 12. Water, ACP, and alcohols sigma profiles. 30
Figure 13. Acetaminophen solubility in hydrotropic systems containing choline-based salts and [BMIm][Ac], at 298.2 K. 32
Figure 14. ACP, water, choline-based salts and [BMIm][Ac] sigma profiles. 32
Figure 15. Effect of the IL on ACP solubility in aqueous solutions at 298.2 K. 33
Figure 16. ACP, water, and ILs sigma profiles. 35
Figure 17. Acetaminophen solubility in hydrotropic systems containing salts, at 298.2 K. 36
Figure 18. Acetaminophen solubility in hydrotropic systems containing: (a) sodium and ammonium sulphates; (b) sodium tosylate and salicylate; (c) sodium and ammonium

thiocyanates; (d) sodium benzene sulphonate and caprylate. 37
Figure 19. ACP, water, and traditional salts sigma profile. 39
Figure 20. Experimental solubility of acetaminophen at 298.2 K in aqueous solutions of acetone or urea. 40
Figure 21. Water, ACP, acetone and urea sigma profiles. 41
Figure 22. Comparison between ternary solutions of ACP/NaBen/water: (a) before magnetic stirring (b) after stirring with precipitation. 42
Figure 23. UV-Vis spectra of the nicotinamide system: (a) comparison between pure nicotinamide, acetaminophen and NA+ACP; (b) NA+ACP after NA baseline correction. 43
Figure 24. Correlation between apolar factor and acetaminophen's solubility at hydrotrope mass fraction of 0.1: (a) adjusted correlation, (b) comparison between experimental and predicted solubilities within a prediction interval of 95%. Red marker indicates the outlier [BMIm][Ac]. 44
Figure 25. Linear regressions for ACP solubility at whydrotrope = 0.1 vs DF: (a) linear regression of ACP solubility in organic solvents vs DF; (b) comparison between the predicted solubility values and the experimental data obtained for organic solvents; (c) linear regression of ACP solubility in miscellaneous vs DF; (d) comparison between the predicted solubility values and the experimental data obtained for miscellaneous. 45
Figure 26. Adjusted model excluding [BMIm][Ac]: (a) ACP solubility at hydrotrope mass fraction of 0.1 vs DF with linear adjustment; (b) comparison between model predicted data and experimental points. 46

LIST OF TABLES

Table 1. Solubility definitions schemes according to the U.S. Pharmacopeia. 5
Table 2. Drugs Biochemical Classification System provided by U.S. Food and Drug Administration. 6
Table 3. Main solubility enhancement techniques. 6
Table 4. Compilation on the solubility of acetaminophen in water at different temperatures. 13
Table 5. Solubility enhancement of acetaminophen: summary of literature data. 14
Table 6. Hydrotropes used to enhance the solubility of acetaminophen. 19
Table 7. Experimental solubility (in mole fraction) of acetaminophen in pure water, at different temperatures and at atmospheric pressure. The correspondent standard deviation is presented between brackets. 25
Table 8. ACP, and alcohols characteristic factors of the different regions (Donor - DF, Acceptor - AcF and Apolar – AF) calculated from the sigma profiles. 30
Table 9. Choline-based salts and [BMIm][Ac] computed characteristic factors. 32
Table 10. Computed characteristic factors for the ILs discussed in this work. 35
Table 11. Computed characteristic factors for the selected salts used in this work. 39
Table 12. Computed characteristic factors for ACP, acetone and urea. 41

Appendices

Table A. 1. Ternary solutions containing acetaminophen, hydrotrope and water measured pH at 298.2K and hydrotrope mass fraction of 0.2. 58
Table A. 2. Acetaminophen speciation data as function of solution pH 58
Table B. 1. Acetaminophen measured solubility aqueous solubility at 298.2K in different hydrotropic systems. 60
Table C. 1. Computed sigma-profile for hydrotropes' molecules used in this work 62
Table C. 2. Computed sigma-profile for hydrotropes used to enhance ACP solubility at literature and used for comparison purposes. 64

LIST OF ABREVIATIONS

ACP	Acetaminophen
AcF	Acceptor factor
AF	Apolar factor
BCS	Biopharmaceutics classification system
COSMO-RS	Conductor-like Screening Model for Real Solvents
DES	Deep eutectic solvent
DF	Donor factor
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
IL	Ionic Liquids
KF	Karl-Fischer
MHC	Minimum hydrotrope concentration
NaBen	Sodium benzoate
NaBS	Sodium benzene sulphonate
NaCapry	Sodium caprylate
NADES	Natural deep eutectic solvents
NaSal	Sodium salicylate
NaTOS	Sodium tosylate
NMP	*N*-methyl pyrrolidone

List of symbols

P	Property of the system
K	Equilibrium constant
M	Molar mass [kg.mol^{-1}]
m	Molality [kg.mol^{-1}]
S	Solubility in aqueous solution with hydrotrope
S_0	Solubility in pure water
w	Weight fraction
x	Mole fraction

List of Greek symbols

ε	Equilibrium parameter

$p(\sigma)$	Sigma-profile
σ	Charge density [e.Å^{-2}]

1 SCOPE AND OBJECTIVES

Solubility plays a key role in many aspects of our daily life and is also of utmost importance in many industries. In the pharmaceutical area, for instance, solubility is one of the most fundamental parameters since it rules the concentration of the drug in the organism to obtain a pharmacological response and gives information for its crystallization. All the drugs are classified according to the Biopharmaceutics Classification System (BCS), an empirical system provided by the U.S. Food and Drug Administration to predict intestinal drug absorption based on solubility and intestinal permeability. The system classifies the drugs into four different classes: high soluble and high permeable (I), low soluble and high permeable (II), high soluble and low permeable (III), and low soluble and low permeable (IV) (Savjani, 2012). It was reported that up to 40% of drug candidate failures are due to biopharmaceutical properties, in which poor water solubility plays a role (Lipper, 1999; Prentis et al., 1988). Furthermore, more than 70% of the commercialized drugs show a very low solubility in water, leading to poor bioavailability (Shekhawat & Pokharkar, 2017), since the compounds are ineffectively absorbed in the site of administration. This is identified as a key part of elevated clinical failure due to poor pharmacokinetics (Di & Kerns, 2003).

Acetaminophen (ACP), commercially presented as paracetamol, is a very well-known compound, firstly introduced in medicine as an antipyretic and analgesic by Von Mering in 1893. Since then, its use has been widely spread and nowadays is a standard treatment for fever and pain relief in all age groups (Bosch et al., 2006; Graham et al., 2013). Chemically, ACP is an acylated aromatic amide and falls into the BCS Class III (Kalantzi et al., 2006). In the past years, ACP has been the subject of several research studies aiming to achieve improved solubility in aqueous systems (Hajebrahimi & Roosta, 2020; Mehrdad et al., 2017; Mehrdad & Miri, 2016a, 2016b; Shekaari et al., 2018; Soltanpour & Jouyban, 2011; Warmińska et al., 2021).

To overcome low solubility issues and increase drugs bioavailability, several techniques have been developed over the past decades; including co-solvency, complexation, cryogenic techniques, crystal engineering, micellar solubilization, microemulsion, pH adjustment, particle-size reduction, supercritical fluid process, solid dispersion and hydrotropy (Savjani, 2012; Patil et al., 2017). The last stands as the most promising technique in comparison with others, if non-toxic, non-flammable, eco-friendly hydrotropes are selected, allowing fast progress (Dhapte & Mehta, 2015). Hydrotropes have achieved solubility

enhancements over 1000-folds for water-poorly soluble drugs such as rapamycin (Simamora et al., 2001).

Mathematical models are often used to predict drug solubility, drawing a new horizon by providing reliable screening data in drug development, and overcoming time and money in expensive laboratory experiments, with COSMO-RS being one of the most powerful tools able to be applied in this kind of analysis.

This work aims to investigate the solubility enhancement of acetaminophen using different hydrotrope types, at different concentrations, and statistically evaluate possible correlations between hydrotropes polarity factors and drug solubility.

2 INTRODUCTION

2.1 Solubility Definition

Solubility is the ability of a substance called solute, to dissolve in another substance called solvent, forming a homogeneous solution of a solute in a solvent. Those can be solids, liquids, or gases. This property depends on the nature of the solvent utilized, as well as on the temperature and pressure of the system (Savjani, 2012). Solubility can also be defined as the maximum measured concentration of the solute in a specific solvent, where its concentration in solution does not increase by the addition of solute (Lachman et al., 1986). IUPAC (1997) defines solubility as the analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a solvent. Solubility may be expressed in terms of molality, mole fraction, or molar concentration. Solubility values may range from extremely small values, such as the solubility of copper chloride in water (Kale et al., 1979), which is considered water-insoluble, to infinitely soluble mixtures, as the case of ethanol in water, considered a fully miscible system (Savjani, 2012).

2.2 Solubility Measurement

One of the key elements of a new compound discovery is the measurement of its solubility in several solvents since poorly soluble solutes in certain solvents may lead to severe process or clinical failures (Alsenz and Kansy, 2007). Many different methods have been proposed to determine the solubility of a compound in a solvent. Among the experimental ones, there are two main groups (Bard et al., 2008):

- Thermodynamic methods, that measure the concentration of the solute in equilibrium with the solid phase due to an excess amount of material. The shake-flask method is usually employed as the standard way to prepare the saturated solution, whose composition can be found by different analytical methods;
- Kinetic methods, based on the precipitation, or disappearance of the last crystal of a solution containing the compound after a dilution or temperature change.

Kinetic solubilities are strongly dependent on time, and the values are likely to be overpredicted due to the degree of supersaturation that may occur. On the other hand, thermodynamic methods are easier to measure and are frequently taken as the compound ‘true’ solubility. However, these values depend on several experimental factors, such as polymorphism, compound purity, stability in solution, temperature, mixing conditions, among

many others. Thus, on traditional solubility assays in the pharmaceutical industry, kinetic measurement is often employed at drug discovery stages, while thermodynamic solubility measurements are used at development steps (Alsenz & Kansy, 2007).

The solubility experimental measurement methods can be also classified as direct and indirect (Cohen-Adad and Cohen-Adad, 2004). Direct methods encompass the solubility measurement by analytical methods – involving the chemical analysis of both liquid and solid phases in equilibrium – or through synthetic methods, where the variation of a property in a saturated solution of known bulk composition is measured.

The analytical direct methods involve the chemical characterization of the phases in equilibrium under isobaric and isothermal conditions. A sample is prepared with weighted components in a flask containing a stirrer that is maintained under agitation with controlled temperature until the solid-liquid equilibrium is reached. The method proceeds with the separation of liquid and solid phases using decantation or filtration.

Analytical methods are then applied to determine the composition of the liquid saturated solution, whilst solid phases must be treated before further analysis once it is permeated with saturated liquid, and its composition may differ from the composition of crystals. The authors recommend drying the solid residues by low-pressure filtration when possible, and if the solid phase is not soluble in volatile liquids, which are miscible with the liquid phase, it must be rinsed with volatile solvent and then dried before being analysed. The characterization may occur by chemical analysis *via* X-ray spectra or differential scanning calorimetry.

In synthetic direct methods the chemical analysis is not performed. Instead, the solubility is obtained by measuring a property of the system (P), which is initially measured at well-known solution compositions, and thereafter an equilibrium parameter (ε) is modified, and the variation of property P versus the equilibrium parameter is analysed in a curve of $P = f(\epsilon)$ type. The choice of which system property will be used for solubility determination may vary according to the compounds in equilibrium, temperature range, and solubility magnitude. These properties may be electrical conductivity, refractive index, UV-Vis or IR absorption, osmotic pressure, and pH, among others.

On the other hand, in the indirect methods the solubility is obtained as a derivate of the solubility product, and is used to determine the solubility of slightly soluble compounds (Cohen-Adad and Cohen-Adad, 2004). One example is the determination of the solubility of silver cyanate in water by progressive mixing solutions of sodium cyanate with silver nitrate

and evaluating the electrical conductivity against the concentration of silver nitrate for a given concentration of sodium cyanate. A break in the curve points the saturation point.

2.3 Solubility Enhancement Techniques: Hydrotropy

Solubility is a crucial factor in the pharmaceutical industry, playing a vital role in drug design, human pharmacokinetics, and consequently safety. It is thus closely linked to the development of efficient and safe drug formulations (Yang et al., 2020). Solubility impacts oral absorption and dissolution in the gastrointestinal system, potentially limiting them (Augustijns et al., 2014). Even when absorption is not solubility-limited, it remains a relevant parameter. Supersaturation, for instance, can lead to drug precipitation and negatively *in vivo* oral adsorption (Barrett et al., 2022). This is quite significant because over 40% of novel drug candidates fail due to biopharmaceutical properties, mainly poor water solubility (Lipper, 1999; Prentis et al., 1988).

In **Tables 1** and **2**, the solubility definitions schemes proposed by the United States Pharmacopeia and the drugs biochemical classification according to the BCS are presented, respectively. The latter is an experimental system provided by the U.S Food and Drug Administration that allows to predict qualitatively the intestinal drug absorption, based on the solubility and intestinal permeability.

Table 1. Solubility definitions schemes according to the United States Pharmacopeia (2007).

Solubility definition	**Parts of solvent required for one part of solute**	**Solubility Range ($mg \cdot mL^{-1}$)**	**Solubility Assigned ($mg \cdot mL^{-1}$)**
Very soluble	<1	>1000	1000
Freely soluble	1 to 10	100-1000	100
Soluble	10 to 30	33-100	33
Sparingly soluble	30 to 100	10-33	10
Slightly soluble	100 to 1000	1-10	1
Very slightly soluble	1000 to 10,000	0.1-1	0.1
Practically insoluble	>10,000	<0.1	0.01

Table 2. Drugs Biochemical Classification System provided by U.S. Food and Drug Administration (2021).

Class	Solubility	Permeability	Absorption Pattern	Rate limiting step in absorption	Drug example
I	High	High	Well absorbed	Gastric emptying	Acetylsalicylic acid
II	Low	High	Variable	Dissolution	Clonazepam
III	High	Low	Variable	Permeability	Acetaminophen
IV	Low	Low	Poorly absorbed	Case by case	Amphotericin

The problem of pharmaceuticals' low solubility may be overtaken using techniques to improve the drug solubility in aqueous systems, which may vary from physical to chemical modifications in the solution media (Savjani et al., 2012). **Table 3** provides an overview of the main techniques employed nowadays, as well as their advantages and disadvantages. Notably, hydrotropy stands out for its utilization of water-soluble molecules in the formulations that may possess non-toxic nature, capable of significantly enhancing drug solubility in water (Booth et al., 2012).

Table 3. Main solubility enhancement techniques.

Technique	Modification Nature	Enhancement mechanism	Advantages	Disadvantages
Inclusion Complex Formation (Saokham et al., 2018)	Chemical	Insertion of nonpolar drug molecule or drug region into the cavity of another molecule or group of molecules (hosts)	Possibility of changing the physicochemical drug properties, possibility of natural hosts usage	Dependence of drug molecule size and host complexation capacity to improve drug solubility
Cryogenic Techniques (Jakubowska & Lulek, 2021)	Physical	Nano sized drug particles with high porosity	Increasement in solubility with pure drug particle usage, flexibility	High costs, need of complementary techniques such lyophilization to obtain the drug particles
Hydrotrophy (Booth et al.,	Chemical	Uncertain, but probably involves	Non-flammable, huge flexibility, high	Knowledge of preferential drug-

Technique	Modification Nature	Enhancement mechanism	Advantages	Disadvantages
2015; Savjani et al., 2012)		complexation with weak interaction between hydrotrope and solute	solubility enhancement	hydrotrope interaction dependence, need for higher hydrotrope concentrations
Micellar Solubilization (Savjani et al., 2012)	Chemical	Micelles formed by surfactants self-aggregation which entraps drug molecule	Low-cost, well-defined methodology and data	Micelle stability difficulties
Nanosuspension (Savjani et al., 2012)	Physical	Nano sized drug particles stabilized by surfactants	Allows the solubilization of drugs both insoluble in oils and water	Difficulties in the suspension stability
Particle Size Reduction (Savjani et al., 2012)	Physical	Increase at surface area ratio by milling and gridding	Economic, reproducibility	May induce drug degradation due to physical stress
Solid dispersion (Savjani et al., 2012)	Physical	Usage of a hydrophilic matrix combined with a dispersed hydrophobic drug	Increases absorption, dissolution, and therapeutic efficacy in the dosage form	High preparation costs, may induce drug degradation due to physical and thermal stress
Supercritical fluid process (Misra & Pathak, 2020)	Physical	Creation of drug nano particles by recrystallization after supercritical fluid process	Non-toxicity, high flexibility and eco-friendly	Produced particle characteristics sensitive to operation parameters, complex nucleation phenomenon

The term hydrotropy was first coined by the German chemist Carl Neuberg, in 1916, as a peculiar effect observed in salt compounds able to solubilize water-insoluble substances. The original hydrotropic compounds investigated by Neuberg include salts of benzoic, benzyl sulfonic, 1-naphtoic, 1-naphthalene sulfonic, thiophene, carboxylic, 2-furoic, phenylacetic acids and their derivatives, and also aromatic fatty acids, demonstrating a solubility enhancement from 7 to 100 times in comparison with that in water, as the original Neuberg publication translated by Mehringer & Kunz (2021) reports. The effect was observed while the

chemist was working with cattle urine in a trial to extract a dye solution, biliverdin, with pentanol. The prepared aqueous solution containing the dye was miscible with the alcohol (Neuberg & Hildesheimer, 1910). In its paper, Neuberg also pointed out the apparent optimum number of carbon atoms in the hydrotropes to be in a range of 5 to 6. Due to the limitations at that time, it was not possible to completely understand the mechanism involved in hydrotropy, and in Neuberg's words "It remains difficult for now to deduce the underlying laws from the wealth of the experimental data.".

Such laws and mechanisms are still in discussion nowadays, being far from a conclusion, even due to the ambiguity of the term "hydrotrope". There are however, three main theories for the mechanism of hydrotropic solubilization, namely: (i) self-aggregation of the hydrotropes, (ii) disruption of water molecules structure caused by the hydrotropes, and (iii) formation of a complex between the hydrotrope and the solute (Booth et al., 2012a; Namdev et al., 2022) – **Figure 1**.

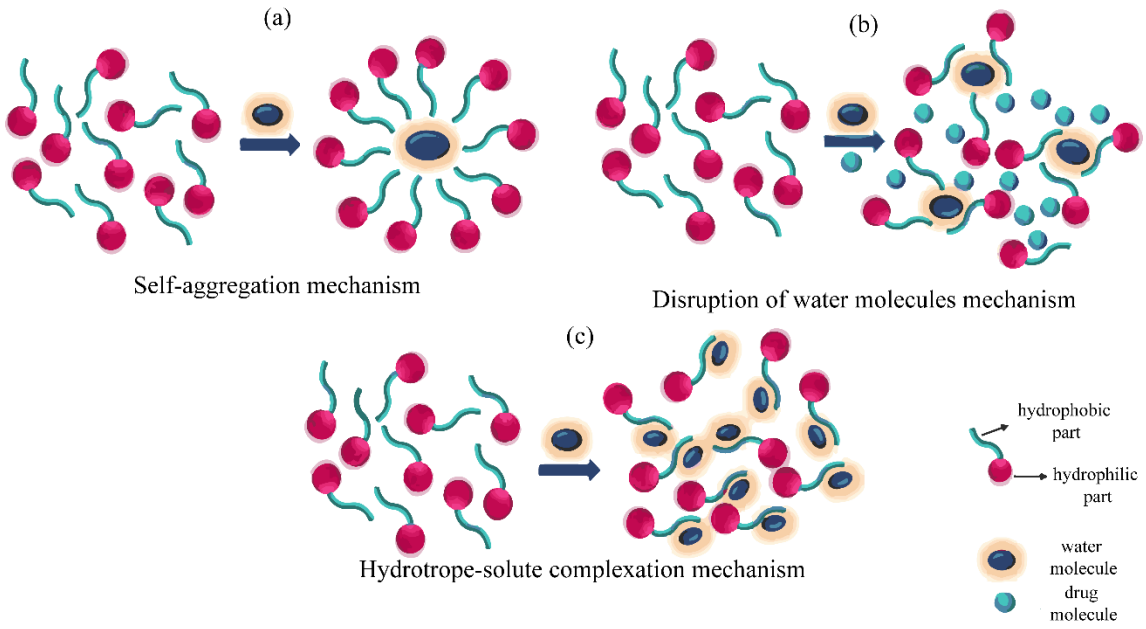


Figure 1. Hydrotropy main mechanisms, adapted from Paul et al. (2021).

The hydrotropes' self-aggregation is explained by the formation of planar and open-layer assemblies, in contrast with surfactant micelles, which are dense spheroid structures and show long hydrocarbons chains (Padiyar et al., 2020). According to Coffman & Kildsig (1996), this theory may be described as occurring stepwise through monomer addition, leading to formation of dimers, whereas higher-order aggregates (such as trimers) are formed by the addition of monomers to dimers, that already exist in solution. The process is likely to occur in

equilibrium, with each association step having its own equilibrium constant (the so-called association constants):

$$2A_1 \overset{k_2}{\rightleftharpoons} A_2 \quad (1)$$

$$A_1 + A_2 \overset{k_3}{\rightleftharpoons} A_3 \quad (2)$$

$$A_1 + A_{n-1} \overset{k_n}{\rightleftharpoons} A_n \quad (3)$$

where A_1 refers to a monomer, A_2 to a dimer molecule, and so on. The association constants k_n are defined as:

$$k_n = \frac{[A_n]}{[A_1][A_{n-1}]} \quad (4)$$

with $n \geq 2$. Coffman (1996) evaluated the association constants both with osmotic pressure and light-scattering assays for nicotinamide, concluding that both methods are applicable, and pointing out the aggregation number for aggregates as being composed of more than three nicotinamide molecules.

The self-aggregation theory was also reinforced by Kim et al. (2010) in a study combining Coffman osmometric method (1996) and a Gibbs-Duhem equation treatment (Ts'o & Chan, 1964) that relates the molar osmotic coefficient to the activity coefficient. The experimental results point to a better solubilization capacity of *N*,*N*-dimethylbenzamide compared to *N*,*N*-diethylnicotinamide, explained by Kim and coworkers (2010) as a result of differences in self-aggregation properties due to the presence of an aromatic ring in *N*,*N*-dimethylbenzamide, that favours the hydrotropic effect – **Figure 1a**.

On turn, the disruption of water molecules theory – **Figure 1b**, can be drawn from studies using nicotinamide and urea as hydrotropic agents on riboflavin solutions (Coffman & Kildsig, 1996a). In contrast to earlier studies with nicotinamide (Hussain et al., 1993), which suggested a complexation phenomenon, Coffman and Kildsig (1996b) have presented strong evidence to the contrary. They employed fluorescence quenching and UV-Vis spectrophotometry assays, revealing no support for the complex formation between the hydrotrope and the hydrophobic molecule. This was evidenced by the absence of significant changes in fluorescence, and the absence of new peaks in the UV-Vis spectrum. Thus, they have concluded that the hydrophobic molecule solubility enhancement caused by the addition of an hydrotrope in an aqueous solution is due to the solvent-hydrotrope interaction and not solvent-solute interaction. The study has exploited the effect of nicotinamide and urea not only

on aqueous solutions, but also on methanol and DMSO solutions. It was noticed that the hydrotropic effect only occurred in solvents that present both the hydrogen bond acceptor and donor characters, allowing intermolecular biddings, or "icebergs" formation. As the hydrotrope performs like a chaotropic agent, it would lead to a structure-breaking effect, weakening the hydrophobic effect of water on the solute (Frank & Franks, 1968).

Finally, the theory of complex formation – **Figure 1c** – is illustrated through the Sanghvi et al. (2006) studies. This theory proposes that the hydrotropes, above a minimum hydrotrope concentration (MHC), induce a stack-type aggregation with hydrophobic molecules as operationally defined by Saleh et al. (1983). A complex is formed between the hydrotrope and the hydrophobic molecule to minimize their exposure to water, once the complexation is explained to occur between the planar hydrophobic regions of hydrotrope and hydrophobic solute (Sanghvi et al., 2007). Nevertheless, the work highlights that it is difficult to verify the existence of complexes in dissolved states, once the interpretation of shifts in UV or IR spectra may be confusing, and studies in the solid state to determine the complex presence may not be possible if their complexes are not stable upon the evaporation of the solvent.

To verify if the hydrotropic mechanism increases drug solubility through complexation or by the above theories, Sanghvi and his coworkers (2012) studied eleven water-poorly soluble drugs using nicotinamide as hydrotrope. Solubility, surface tension, and conductivity measurements were conducted to verify the nature of the phenomena. In conclusion, they noticed that all the studied drugs formed complexes with nicotinamide. At lower hydrotrope concentrations, 1:1 complex were found, whereas, at concentrations over 10% (m/v), 1:2 complexes took place. Booth et al. (2012) also refutes the two first theories and reformulates the third one in the light of the Fluctuation Theory of Solution, a rigorous statistical thermodynamic approach. Such conclusions were obtained based on the experimental data collected using sodium benzoate, or sodium salicylate as hydrotropes, and butyl acetate or benzyl benzoate as solutes. The results obtained by the authors point out two main driving forces to the solubilization through hydrotrope addition to the solution: solute-hydrotrope binding and water activity depression (Booth et al., 2012). However, this work was focused on small hydrotropic molecules using high concentrations of hydrotrope (over 3 M).

Recently Abranches et al. (2020) investigated the hydrotrope accumulation around the solute using proton nuclear magnetic resonance (H-NMR). Their premise is that the hydrotrope accumulates around the solute due to a strong hydrophobic interaction between the hydrotrope and solute molecules, where the hydrophobic moieties interact with each other. The statistical

thermodynamics that support this study predicts that the chemical shifts of the protons of a given molecule dissolved in water may change due to the presence of another substance. Bearing the above in mind, the paper hypothesizes that if the hydrotropic agent aggregation around the solute is induced by itself, then the proton's chemical shift at the apolar regions of the hydrotrope should decrease. The experiments were conducted with gallic and syringic acids as solutes and monoalkylglycerol ethers, namely: 3-methoxypropane-1,2-diol, 3-ethoxypropane-1,2-diol, 3-propoxypropane-1,2-diol, 3-butoxypropane-1,2-diol, 3-pentoxypropane-1,2-diol, as hydrotropes. The results obtained from H-NMR demonstrate that the chemical shift of these protons diminishes proportionally to the enhancement of solute concentrations, while the hydrotrope's carbons in regions with higher polarity exhibited shift peaks in NMR spectra lesser than the apolar ones. Calculations using the predictive COSMO-RS model allowed to conclude that the apolarity of solute and hydrotrope is the driving force, leading to a maximum aggregation of a hydrotropic agent around the solute when they have the similar apolarity.

According to Abranches and coworkers, it is then evident that the experimental results demonstrate the hydrotrope accumulation around the solute and not a possible hydrotropic effect due to the interaction of hydrotrope-solvent – **Figure 2.**

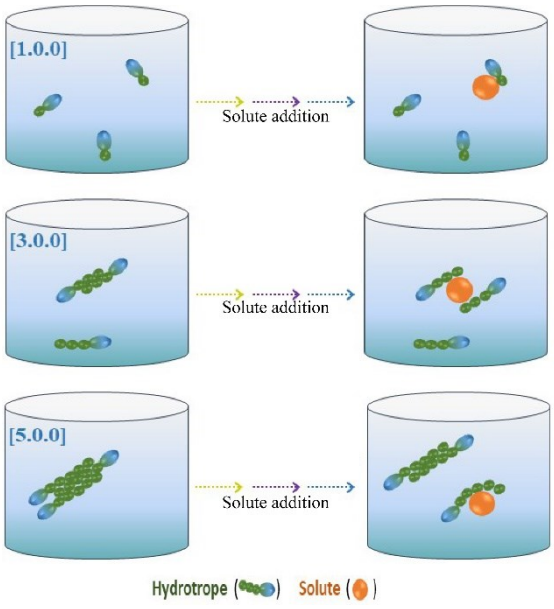


Figure 2. Hydrotropic mechanism proposed by Abranches and his coworkers (2020), where the interaction hydrotrope-solute vary according to the hydrotrope apolarity. Adapted from Abranches and coworkers (2020).

2.4 Acetaminophen: A Summary

N-Arylamides are molecules prevalently encountered in pharmaceuticals, resulting from a wide variety of amidation methods, through palladium and copper catalysis, or through cross-coupling reactions utilizing aryl boronic derivatives under oxidative conditions. The *N*-acetyl-*p*-aminophenol (**Figure 3**), commonly known as paracetamol or acetaminophen, is one of the most well-known representatives of this class of compounds (Joncour et al., 2014).

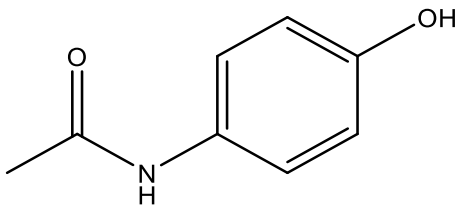


Figure 3. Acetaminophen chemical structure.

Acetaminophen was first synthetized two centuries ago by the unintentional reaction of *p*-nitrophenol with tin glacial acetic acid, as described by Morse (1878). Five years later, the German pharmaceutical von Mering (1893) introduced it to human medicine as an antipyretic. Though, it was left aside in face to the interest in phenacetin antipyretics' properties at the time, which initially gained more popularity and held it in the following decades (Prescott, 2000).

Nevertheless, phenacetin clinical usage declined due to occurrence of serious side effects, such as haemolytic anaemia and methaemoglobin formation, which turned the attention to acetaminophen (Ayoub, 2021). Consequently, a new rediscover of acetaminophen occurred between 1948 and 1949. ACP was then proposed as one of the principal active metabolites of phenacetin and acetanilide, and its analgesic properties were demonstrated by elevating the resistance to pain caused by radiant heat in female volunteers (Prescott, 2000).

Nowadays, ACP is one of the most widely consumed non-prescription drugs in the world, being inexpensive. It counts with a global production of over 100,000 tons per year, with an estimated cost of production of around 4.00 € per kg (Joncour et al., 2014). Acetaminophen has a low molar mass (M = 151.17 g·mol^{-1}), and is a weak acid, pK_a = 9.46, being essentially unionized at physiological pH values (Craig, 1990). Additionally, it shows solubility values in water of around 14 g·L^{-1} at 298.15 K (Yalkowsky et al., 2016), being classified as a Class III BCS compound (Lindenberg et al., 2004). The main water-solubility data available in the literature are summarized in **Table 4** and depicted in **Figure 4**.

Table 4. Compilation on the solubility of acetaminophen in water at different temperatures.

Solubility range ($g_{ACP}/kg_{solvent}$)	Temperature range (K)	Solubility at 298 K (g/kg water)	Reference
7.21 – 17.39	273.15 – 303.15	14.90	(Granberg & Rasmuson, 1999)
13.45 – 27.78	298.15 – 333.15	13.45	(Shakeel et al., 2013)
12.76 – 26.48	293.15 – 313.15	15.64	(Mehrdad & Miri, 2016a)
12.77 – 26.51	293.15 – 313.15	15.55	(Jiménez & Martínez, 2006)
11.06 – 27.53	288.15 – 323.15	14.40	(Yalkowsky et al., 2016)
13.35 – 30.31	293.15 – 318.15	15.46	(Shekaari et al., 2018a)

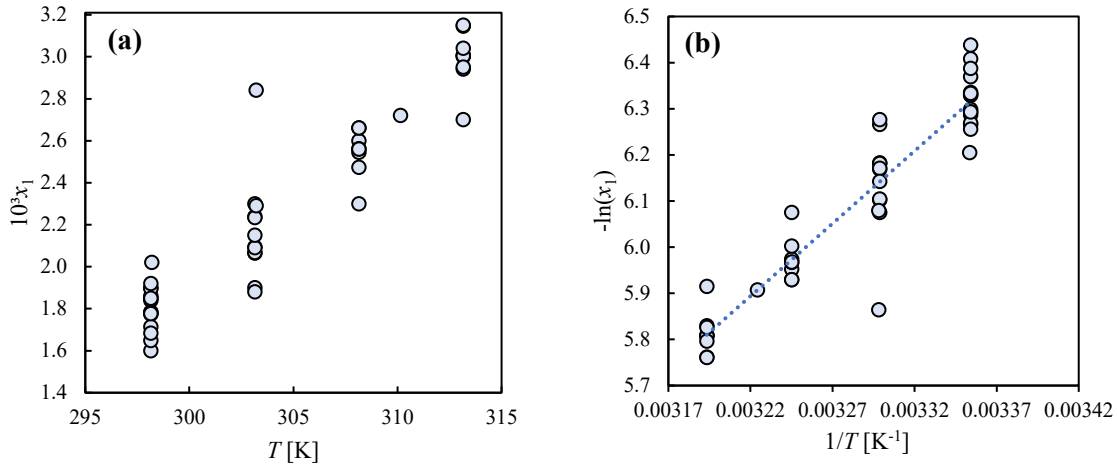


Figure 4. Graphical representation of acetaminophen solubility in water from literature, in Table 1: (a) acetaminophen solubility [g/g_{water}] as function of temperature [K], and (b) Natural logarithm of the solubility in mole fraction as function of $1/T$.

Figure 4 shows that the solubility increases with temperature, though a small data dispersion is observed in each temperature. In general, the natural logarithm of the solubility as a function of the inverse of temperature shows a consistent linear trend – Figure 2b. Nonetheless, data at higher temperatures require further evaluation, since less experimental data are available.

Additionally, several studies were performed in the last decades aiming to achieve a higher ACP solubility in aqueous solution by adding a cosolvent or hydrotrope. **Table 5** presents a summary of the experimental data found in the literature, including the maximum relative solubility enhancement. The relative solubility is, in this study, defined as the ratio between the solubility in the aqueous solution with cosolvent/hydrotrope (S) and the solubility in pure water (S_0), using the units in mole fraction.

Table 5. Solubility enhancement of acetaminophen: summary of literature data.

Cosolvent/ hydrotrope	Hydrotrope concentration range	Temperature range [K]	Maximum enhancement of S/S_0	Reference
Sodium gentisate	0.2 – 0.4 (m/m)	298.15	5.38	Hamza and Paruta (1985)
Sodium salicylate	0.2 – 0.4 (m/m)	298.15	9.56	
Sodium glycinate	0.2 – 0.4 (m/m)	298.15	11.4	
Nicotinamide	0.2 – 0.4 (m/m)	298.15	22.85	
Ethanol	0.0 – 0.95 (v/v)	293.15 – 313.15	35.44	Bustamante et al. (1995)
Dioxane	0.0 – 1.0 (v/v)	293.15 – 313.15	55.30	Bustamante et al. (1998)
Acetone	0.0 – 1.0 (m/m)	268 – 303	49.46	(Granberg & Rasmuson, 2000)
Acetone + toluene	66.5/3.5 – 92.15/4.85 (m/m)	268 – 303	49.18	
Isopropanol	0.0 – 1.0 (m/m)	278 – 313	25.61	(Hojjati & Rohani, 2006)
PEG-600 + *N*-methyl pyrrolidone (NMP)	0.0/0.0 – 1.0/0.0 and 0.0/0.0 – 0.0/1.0 (m/m)	298.15	212.82	Soltanpour & Jouyban (2011)
Methanol	0.0 – 1.0 (m/m)	298.15	32.76	(Muñoz et al., 2016)
[BMIm]Br	0.0 – 0.15 (m/m)	293.15 – 313.15	26.05	Mehrdad & Miri, (2016a)
[HMIm]Br	0.0 – 0.15 (m/m)	293.15 – 313.15	29.31	Mehrdad & Miri, (2016b)
ChCl/urea (1:2)	0.0 – 0.9 (m/m)	293.15 – 318.15	27.04	Shekaari et al. (2018)
ChCl/oxalic acid (1:1)	0.0 – 0.9 (m/m)	293.15 – 318.15	28.63	
ChCl/malonic acid (1:1)	0.0 – 0.9 (m/m)	293.15 – 318.15	39.04	
1-Propanol	0.0 – 1.0 (m/m)	293.2 – 313.2	22.38	(Pourkarim et al., 2020)
Urea	3E-2 – 11.99E-2 (mole fraction)	293.15 – 323.15	3.15	Hajebrahimi & Roosta (2020)
Malonic acid	1.34E-2 – 5.37E-2 (mole fraction)	293.15 – 323.15	3.18	
L-Malic acid	1.34E-2 – 6.71E-2 (mole fraction)	293.15 – 323.15	3.51	

ChCl	1.29E-2 – 6.56E-2 (mole fraction)	293.15 – 323.15	5.79	(Warmińska et al., 2021)
ChCl/malic acid (1:1)	0.05 – 0.2 (m/m)	293.15 – 313.15	2.63	
ChCl/tartaric acid (1:1)	0.05 – 0.2 (m/m)	293.15 – 313.15	2.31	
ChCl/1,2-propanediol (1:2)	0.05 – 0.2 (m/m)	293.15 – 313.15	1.86	

Hamza and Paruta's report from 1985 is here identified as the very first study of ACP solubility increase through hydrotropic agents. They analysed the drug solubility enhancement and the dielectric constants of aqueous systems containing sodium gentisate, sodium salicylate, sodium glycinate, and nicotinamide at 25°C. The results for solutions with 40% (m/v) of hydrotrope demonstrate an increase in the solubility in the range of 5.38 to 11-fold for the sodium salts and up to 22-fold for the organic molecule. Electrical studies conducted using an oscillometer revealed an interesting behaviour in the nicotinamide-acetaminophen-water system, in which the dielectric constant was observed to be close to pure-water data. The presence of the drug in the aqueous solution was expected to result in lower values for this property.

Besides, the use of ethanol, an amphiprotic solvent, as cosolvent was reported as being capable of increasing the acetaminophen solubility in order of 35-fold the corresponding value in water, presenting a small maximum in the region rich in alcohol – at 0.95 (v/v) of ethanol in solution, viewed as a possible effect of stronger solvent-cosolvent interactions; the entropy increase was pointed here as the main contributor for the solubility enhancement (Bustamante et al., 1995). In the same study, the influence of an amphiprotic-aprotic system in the drug solubility, namely ethanol-ethyl acetate, was checked and an enthalpic-driven dissolution phenomena was demonstrated, with a lower heat of solution, as opposed to ethanol-water. Still, ACP solubility is lower in ethanol-ethyl acetate than in ethanol-water mixture.

Three years later, the same group analysed the effect of enthalpy-entropy compensation in solubility phenomena for ACP, nalidixic acid, or acetanilide in dioxane-water mixtures (Bustamante et al., 1998). The work demonstrated a maximum increase in ACP solubility of 55.3 times the value in pure water, presenting a maximum like the observed in the ethanol-water mixture, but in the region of 0.85 (v/v) of dioxane.

Soltanpour and Jouyban (2011) studied the effect of N-methyl pyrrolidone (NMP) and polyethylene glycol (PEG-600) as cosolvents in aqueous systems to enhance ACP solubility,

obtaining increments in solubility of 113-fold for the first system and over 212-fold for the second, over the drug solubility in pure water.

In 2016, ionic liquids (IL) were the focus of Mehrdad & Miri reports' who analysed the solubility in aqueous mixtures of 1-buty-3-methyl imidazolium bromide ([BMIm]Br) and 1-hexyl-3-methyl imidazolium bromide ([HMIm]Br). Solubility and thermodynamics studies performed with [BMIm]Br resulted in a solubility enhancement of 26-fold, compared to pure water, using a solution containing a IL's weight fraction of 0.15. Thermodynamic calculations pointed to the enthalpy as the main contributor to the standard Gibbs energy of the solution formed. Similar results were observed with [HMIm]Br, showing a solubility enhancement of 29-fold at the same concentration of IL of the former work, being again enthalpy the main contributor to the standard Gibbs energy of the solution. Parallel results were obtained by Mehrdad et al. (2017) with 1-hexyl-4-methylpyridinium bromide aqueous system, where thermodynamics showed that the solubilization of ACP is always an endothermic process.

Shekaari et al. (2018) proposed aqueous systems containing Deep Eutectic Solvents (DES) prepared by mixing choline chloride (ChCl) as hydrogen bond acceptor (HBA) and urea, oxalic acid, or malonic acid as hydrogen bond donors (HBD). The highest solubility increase was obtained with an aqueous solution of the equimolar mixture ChCl/malonic acid (1:1), in order of 39-fold to that of pure water solubility, whereas the DES containing urea exhibited lower solubility enhancement, closer to ChCl/oxalic acid (1:1). The studies also demonstrated that the solubility of ACP increases with a decrease in the standard molar Gibbs free energy of the mixture process. Activity coefficients for ACP in all three studied systems were also calculated based on the Wilson thermodynamic model. An analogous study was conducted by Hajebrahimi & Roosta (2020), where DES were prepared with ChCl plus urea, L-malic acid, or malonic acid. Urea based systems demonstrated the lowest solubility increase, while the drug exhibited the maximum solubility in ChCl mixture solutions. Malonic acid and choline chloride stood out again among the NADES.

Finally, Warmińska et al. (2021) also applied NADES as hydrotrope, namely ChCl as HBA and 1,2-propanediol (1:2), L-tartaric acid (1:1), or L-malic acid (1:1) as HBD. Authors investigated the potential occurrence of ACP incubation in NADES on its polymorphic form by the analysis of the drug powder before and after the solubility with the aid of DSC and image analysis. No significant alteration in the crystal morphology was identified, and the higher solubility enhancement was demonstrated for the ChCl/L-tartaric acid (2.63-fold). The

study also reported the standard partial molar volumes and the density of solutions for each system.

In sum, acetaminophen is an inexpensive, world-wide consumed drug with relevant pharmacological properties, and largely used to treat several different diseases. It is therefore a very convenient model molecule to evaluate mechanisms of solubility enhancement. Additionally, it has been the subject of numerous studies recently, allowing comparisons and a more comprehensive analysis of the results. It also provides a solid database to establish connections between thermodynamic properties, and solubility, maintaining the unionized molecular form in a wide range of pH.

2.5 COSMO-RS modelling

Three decades ago, the conductor-like screening model, abbreviated as COSMO, was presented by Klamt & Schüürmann (1993) which became very popular since then, especially in computational chemistry. COSMO may be considered a variation of the apparent surface charge dielectric continuum models (ASMs), and works as follows: constructing a cavity to separate the solute from the dielectric continuum, representing dielectric polarization through surface charges, calculating energy gains due to continuum polarization, iteratively adjusting electron density and polarization charges in quantum chemical programs, allowing solvation energy gradient calculations for solute geometry optimization, and achieving quantitative agreement with experimental solvation energies by supplementing electrostatic solvation energy with non-dielectric and cavity-formation energy components (Klamt, 2018).

Thereafter, COSMO-RS appears, merging the COSMO model to a statistical thermodynamic treatment of interacting surfaces, allowing the analysis of realistic solvation, and fundamentally addresses solute and solvent with equal emphasis, employing a quantum chemical framework alongside statistical thermodynamics, thereby departing from a mere dielectric field depiction of the solvent. This approach facilitates the coherent treatment of thermodynamic mixtures across diverse temperatures, allowing several engineering applications that ranges from phase equilibrium predictions to pharmaceutical research on formulation and drug development. Since 1999 the COSMO-RS model is implemented at COSMO*therm* (Klamt, 2018).

One of the key-concepts of COSMO-RS is the σ-profile, that represent the probable distribution of molecular surface segments based on their specific charge densities. It refers to a crucial set of parameters that describe the distribution of atomic charges and polarizabilities

across the surface of a molecule, capturing the detailed electrostatic and polar interactions between a solute molecule and the surrounding solvent molecules. σ-profiles provide a representation of the solute's surface properties in terms of charge and polarizability, enabling accurate modelling of solute-solvent interactions. These profiles enable a refined understanding of the intermolecular forces and interactions in solvation processes, contributing to improved accuracy in the estimation of thermodynamic properties across a range of temperatures (Mullins et al., 2006). **Figure 5** shows the sigma profile for the water molecule.

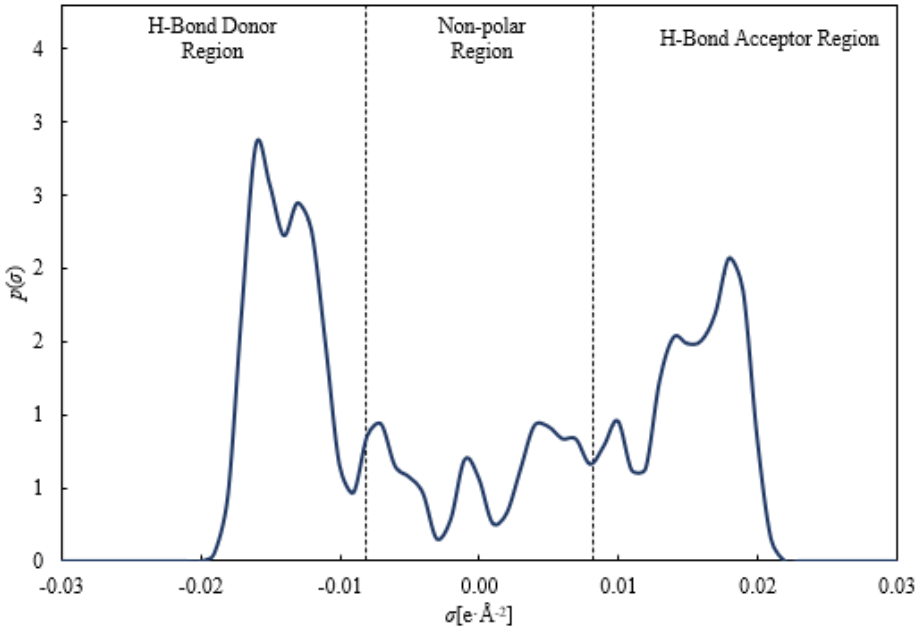


Figure 5. σ-profile of water calculated with COSMO*therm*X with BP_TZVP_21.ctd parametrization.

In a recent pharmaceutical study, COSMO-RS was combined with the solvatochromic parameters of the hydrotropic solutions, showing that their apolarity affects the increase of artemisinin solubility in aqueous solutions of ionic liquids. At higher hydrotrope concentration, the solubility is dominated by the hydrotrope lower hydrogen-bond acceptor character (Sales et al., 2022).

3 MATERIALS AND METHODS

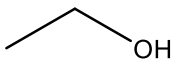
3.1 Chemicals

The ACP used in this work was provided by Thermo scientific with a purity of 98%. The hydrotropes names, as well as their source and purity, are listed in **Table 6**, while their structures are depicted in **Figure 6**. All compounds were used as received, without further purification.

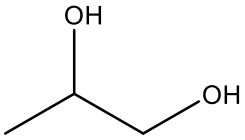
Table 6. Hydrotropes used to enhance the solubility of acetaminophen.

Hydrotrope	Supplier	CAS	Purity [%]	Water content [mg/g]
1-butyl-3-methylimidazolium acetate ([BMIm][Ac])	Iolitec	284049-75-8	≥ 98.0	6.06
1,2-propanediol	Sigma-Aldrich	57-55-6	≥ 99.5	-
Acetone	Fischer Scientific	67-64-1	≥ 99.8	-
Ammonium sulphate ($(NH_4)_2SO_4$)	PanReac	7783-20-2	≥ 99	-
Ammonium thiocyanate (NH_4SCN)	Acros Organics	1762-95-4	≥ 99	5.14
Choline bromide (ChBr)	TCI	1927-06-6	≥ 98	8.26
Choline chloride (ChCl)	Acros Organics	67-48-1	≥ 99	4.22
Ethanol	Fischer Scientific	64-17-5	≥ 99.8	-
Glycerol	Sigma-Aldrich	56-81-5	≥ 99.5	-
Sodium benzene sulphonate (NaBS)	Acros Organics	515-42-4	≥ 98	-
Sodium caprylate (NaCapry)	Acros Organics	1984-06-1	≥ 98	-
Sodium salicylate (NaSal)	Sigma-Aldrich	54-21-7	≥ 99.5	-
Sodium sulphate (Na_2SO_4)	Alfa Aesar	7757-82-6	≥ 99	-
Sodium thiocyanate (NaSCN)	Acros Organics	540-72-7	≥ 98	5.77
Sodium tosylate (NaTOS)	TCI	540-63-6	≥ 90	-
Urea	PanReac	57-13-6	≥ 99.5	0.15

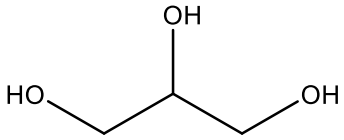
Alcohols



Ethanol

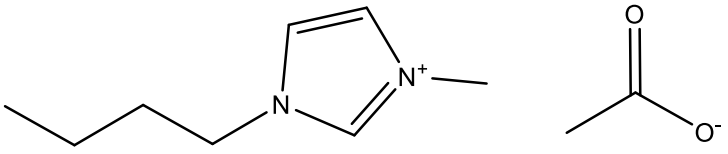


1,2-propanediol

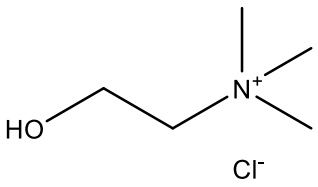


Glycerol

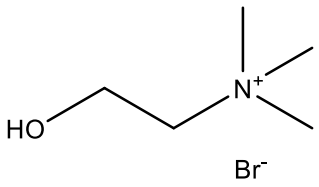
Choline based salts and Ionic Liquids



1-butyl-3-methylimidazolium acetate

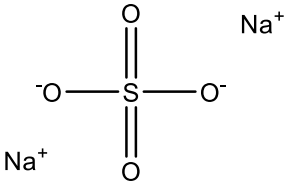


Choline chloride

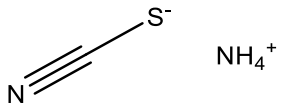


Choline bromide

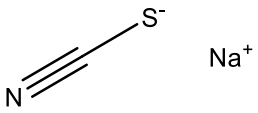
Salts



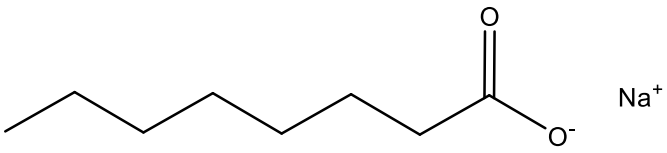
Sodium sulphate



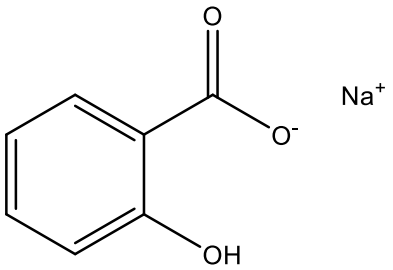
Ammonium thiocyanate



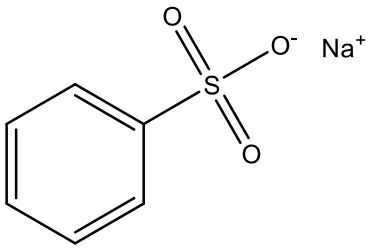
Sodium thiocyanate



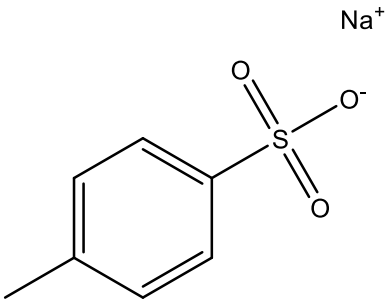
Sodium caprylate



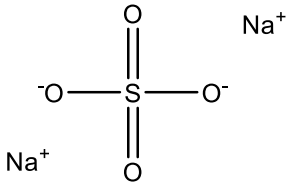
Sodium salicylate



Sodium benzene sulphonate



Sodium tosylate



Sodium sulphate

Others

Figure 6. Chemical structures of the hydrotropes used in this work, grouped in chemical classes.

3.2 ACP solubility determination

Solubility of ACP was experimentally determined using the shake-flask method, in which an excess of ACP powder was mixed with approximately 5 mL of pure water or aqueous solutions of hydrotropes. Those were previously prepared by weighting each hydrotrope and ultra-pure water, according with the desired mass fraction, using a Denver Instruments TP-214 balance with readability of 0.1 mg, repeatability ≤± 0.1 mg and linearity ≤± 0.2 mg. The binary (ACP + water) or ternary (ACP + water + hydrotrope) systems were agitated at 298.2 ± 0.5 K for at least 24 hours using an Eppendorf Thermomixer C, followed by a 12-hour period of rest. Subsequently, a liquid sample of approximately 0.04 - 1.5 mL was collected from the equilibrium flask using a plastic syringe (kept at the same temperature) and filtered through a 45 μm Branchia SFNY-145-100 nylon filter to a previously weighted vial. Two different techniques were employed to determine the solubility of the drug: UV-Vis Spectroscopy, using a PG Instruments T70, or gravimetry.

The technique employed was chosen based on the characteristics of the hydrotropic solutions, as well as their interactions with the ACP. Hydrotropes like acetone, ammonium thiocyanate, sodium salicylate, sodium thiocyanate, and sodium tosylate, exhibit absorbance within the UV-Vis absorption range of ACP, posing a challenge for accurate measurement. To address this issue, gravimetry was used instead. In such cases, samples of approximately 1.5 g were taken from the equilibrium flask and placed in previously weighted flasks. Those were then dried on a stove until a constant mass was achieved. Gravimetry was found to be an effective method for measuring the solubility of ACP in systems containing [BMIm][Ac], acetone, NH_4SCN, NaCapry, NaBS, NaTOS, NaSal, and NaSCN.

For the remaining compounds, the solubility of ACP was determined using UV-Vis detection at the specific wavelength of 244.5 nm – **Figure 7**. In this case, the collected samples were diluted with water or water + hydrotrope (with the same concentration used for the equilibrium preparation).

A calibration curve was previously established, by diluting a mother solution of ACP and water/ethanol mixed solvents ($w_{ethanol}$ = 0.05) up to 1000 times with a water/hydrotrope solution.

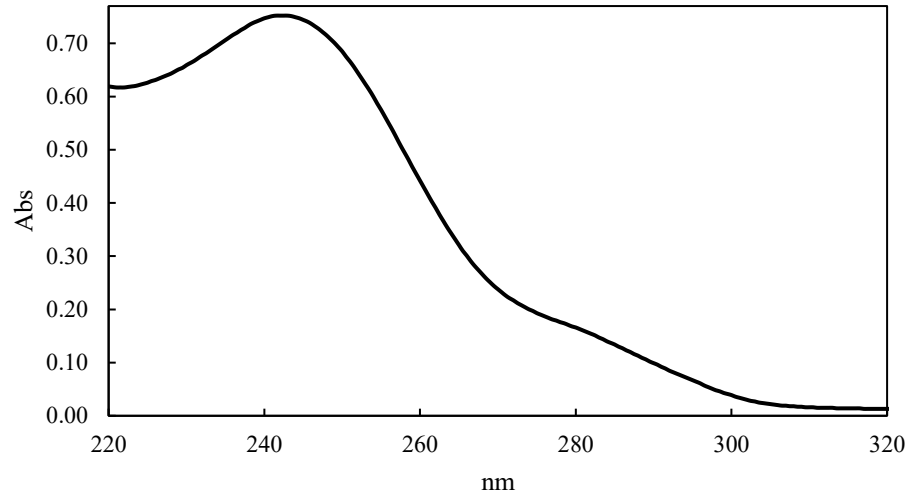


Figure 7. Acetaminophen UV-Vis spectrum at $10^3 x_1$ = 1.3943E-6 drug concentration.

The experimental solubility of ACP in different hydrotropes and at different concentrations, was calculated using the following equation:

$$x_1 = \frac{\frac{m_1}{MM_1}}{\left(\frac{m_1}{MM_1} + \frac{m_2}{MM_2} + \frac{m_3}{MM_3}\right)} \quad (9)$$

where subindexes 1, 2 and 3 indicates ACP, hydrotrope and water, respectively.

3.3 Water content and pH measurements

The water content of the hydrotropes was determined by weighting approximately 0.004 g on a Kern ABT 100-5M balance (reproducibility of 5.10^{-4} g, readability of 1.10^{-4}), following by dissolution in ethanol. Subsequently, the water content of the pure ethanol, and the mixtures was assessed through Karl Fischer (KF) coulometric titration using a Metrohm 831 KF Coulometer. This procedure was replicated five times to ensure a statistically significant mean value.

Equation 9 summarizes the KF reaction taking place within the equipment, which enables the determination of the water content:

$$H_2O + I_2 + [RNH]SO_3CH_3 + 2\ RN \leftrightarrow [RNH]SO_4CH_3 + 2\ [RNH]I \quad (10)$$

In the reaction, iodine is directly generated within the electrolyte via electrochemical processes (*831 KF Coulometer - Instructions for use*, 2003). The obtained values for water-content were taken into account for the solubility calculations.

pH determinations were conducted using a Hanna Instruments Edge bench meter equipped with a pH/temperature digital probe, exhibiting a precision of ± 0.01 for pH measurements at 298.2 K. Measurements were performed in duplicate.

3.4 Thermodynamics modelling

The σ-profile of the pure hydrotropes was computed with the COSMO*therm* software with the BP_TZVP_21.ctd parametrization. The molecules structural information was taken from the COSMOtherm TZVP database. As several hydrotropes present more than one conformer, a weighted average using the COSMO*therm* "normalized weight factor" was used.

Thereafter, an adaption of the procedure proposed by Abranches et al. (2020) and later used by Sales et al. (2022), was applied. It consists of using the sigma-profiles to estimate the Apolar Factor (AF), the polar Donnor Factor (DF) and polar Acceptor Factors (AcF), by using:

$$AF = \int_{-0.008}^{0.008} p(\sigma)(0.008 - |\sigma|)d\,\sigma \tag{11}$$

$$DF\ and\ AcF = \int_{0.008}^{|\sigma|} p(\sigma)(|\sigma| - 0.008)d\,\sigma \tag{12}$$

Those equations allow for the quantification of the surface area of the different regions of the molecules. Integrals were determined using Origin 2023b. In the original work, the integral is computed using |0.0082|, however, we were not able to achieve such limit, and |0.008| was used instead in Equations 11 and 12.

4 RESULTS AND DISCUSSION

4.1 Hydrotrope solutions' pH

Acetaminophen exists in different chemical forms depending on the pH of the surrounding environment. As can be seen in **Figure 8**, at acidic conditions it exists in its neutral form, but as the pH becomes more basic, ACP shifts into its anionic form, which is more soluble in water. The strongest acid peak is observed at a pKa of 9.5.

The pH values of the hydrotropic systems investigated in this work ranged from 4.8 (NaTOS) to 9.4 (NaCapry), with half of the hydrotropes falling within the pH range of 5 to 6. As a result, we can deduce that in those cases the primary factor responsible for enhancing the drug's solubility in this study is not the pH of the solution. The particular solution of NaCapry is an exception, and in fact, it exhibits a solubility peak for acetaminophen, a phenomenon that is going to be discussed in the next sections. However, it is likely that this phenomenon linked both with the concentration of the hydrotrope and the occurrence of speciation. Experimental data are available in the Appendix A.

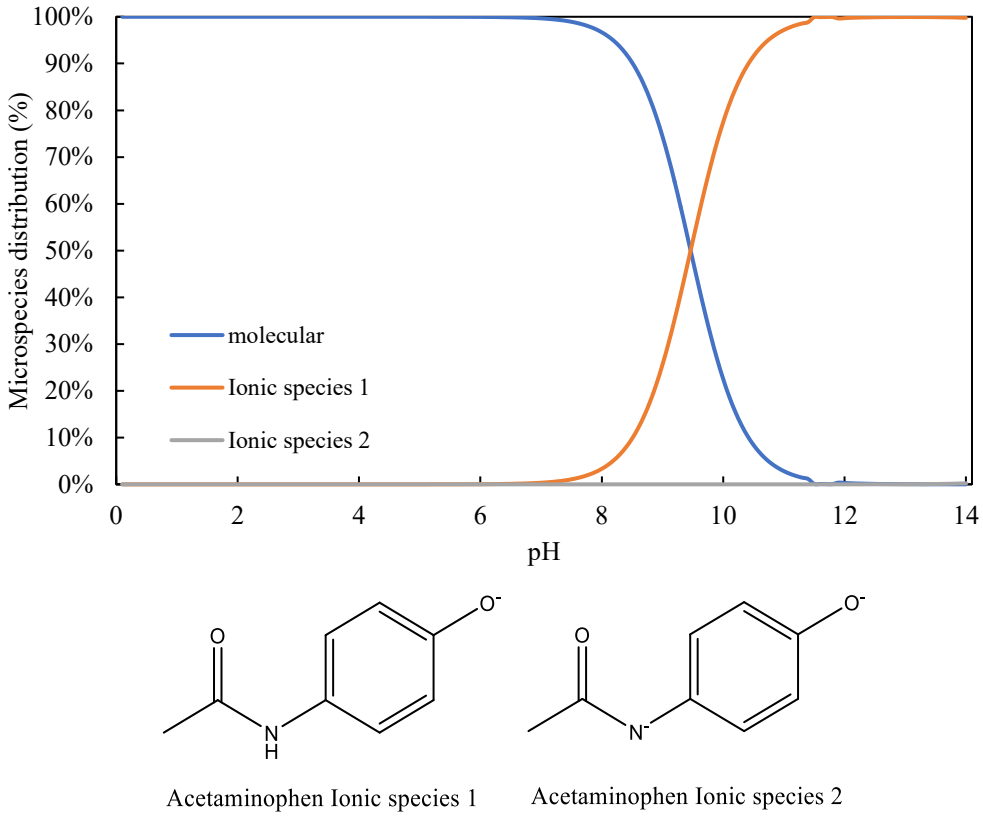


Figure 8. Top: ACP speciation curves as a function of pH (adapted from Chemicalize, 2023); Bottom: Acetaminophen ionic species.

4.2 Solubility of acetaminophen in water

The solubility of acetaminophen in pure water was measured using spectrophotometry as the analytical technique, at different temperatures. Results are listed in **Table 7** and displayed in **Figure 9,** along with experimental values from literature. The main goal here was to validate the experimental methodology employed, by comparing the results with data from literature. To compare our data to literature data an average absolute deviation (AAD) was calculated using the equation below, where n is the number of samples at a given temperature:

$$AAD = \frac{\sum_{i=1}^{n}\left(S_{i,this\ work} - \bar{S}_{literature}\right)}{n} \quad (13)$$

Table 7. Experimental solubility (in mole fraction) of acetaminophen in pure water, at different temperatures and at atmospheric pressure. The correspondent standard deviation is presented between brackets.

Temperature [K]	10^3x_1 (this work)		10^3x_1 (literature average)		AAD[10^3x_1]
293.2	1.5211	(0.0753)	1.52	(0.14)	0.05
298.2	1.7478	(0.0368)	1.81	(0.11)	0.07
303.2	2.0337	(0.0308)	2.12	(0.14)	0.09
313.2	2.7743	(0.0380)	3.00	(0.13)	0.24

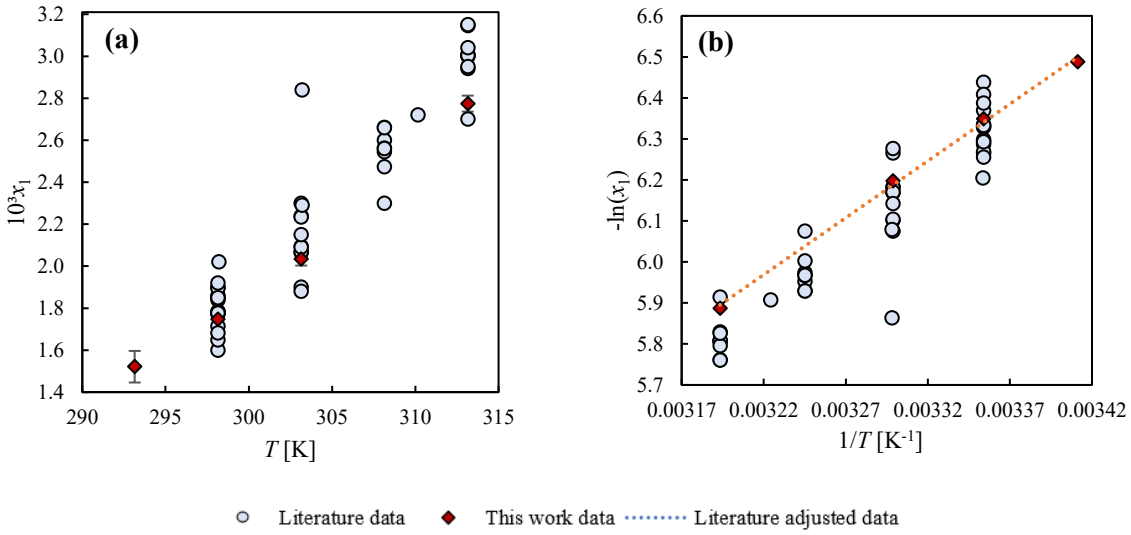


Figure 9. Experimental data for ACP solubility in pure water: (a) acetaminophen solubility (10^3x_1) as function of temperature [K] and (b) Natural logarithm of the solubility in mole fraction as function of $1/T$.

Overall, the data measured in this work are in good agreement with those from literature, with some differences observed at higher temperatures. This may be due to the occurrence of experimental errors during the measurements – particularly frequent at high temperatures, differences in the equipment used, laboratory conditions, or drug purity.

The solubility of ACP in pure water measured at 298.2 K was used as default solubility to calculate the relative solubility in the next sections.

4.3 Solubility data in different hydrotropes

Various types of hydrotropes were applied in this work, ranging from organic solvents to ionic liquids. This approach allowed to examine the behaviour of each hydrotrope class, discerning differences within the same class and between distinct classes. The identified classes encompass alcohols, choline-based salts, ILs, conventional salts, and others (hydrotropes not belonging to any of the aforementioned categories).

To validate the methodology and corroborate existing literature data, acetone, ethanol, urea and sodium salicylate (NaSal) were selected (Hamza & Paruta, 1985; Bustamente et al., 1995; Granberg & Rasmuson, 2000; Hajebrahimi & Roosta, 2020). Furthermore, well-stablished hydrotropes were also selected, namely 1,2-propanediol, glycerol, NaCapry, NaBS, and NaTOS. Interestingly, these hydrotropes have not yet been extensively studied in aqueous systems with ACP (González et al., 2000; Varade et al., 2004; Kamble et al., 2015; Sela et al., 2017; Soni & Sharma, 2021; Silva et al., 2023). To investigate ion-specific effects on ACP, Na_2SO_4, NaSCN, NH_4SCN, and $(NH_4)_2SO_4$ were included, based on their relevance in Hofmeister series studies of proteins (salting-in and salting-out effects) and hydrotropic investigations (Hyde et al., 2017; Kang et al., 2020; Sales et al., 2022). Finally, [BMIm][Ac] was selected to represent ILs, facilitating the comparison with existing literature data on ILs hydrotropy (listed on **Table 5**).

At this point, it is important to highlight that the maximum UV absorption peak of acetaminophen, which is typically around 243 nm (as depicted in **Figure 7**), can shift its position in the presence of some hydrotropes. This phenomenon was observed and reported by Hamza & Paruta in 1985, where they noted that sodium gentisate, sodium salicylate and nicotinamide induced shifts in the drug's peak to wavelengths of 229 nm, 257 nm and 292, respectively. In the case of nicotinamide, the shift was attributed to a complexation process, whereas for sodium gentisate, and sodium salicylate, a different mechanism based in purely electronical interactions with the drug was proposed.

Figure 10 provides a comprehensive overview of S/S_0 (acetaminophen solubility S divided by its solubility in pure water S_0) for all the hydrotropes experimentally tested. In all systems, the solubility of acetaminophen increases with an increase in hydrotrope concentration, except for systems containing sulphate ions (SO_4^{2-}), where a decrease in the drug's solubility is observed. Due to solubility limits, most hydrotropes were tested up to a maximum mass fraction (w_2) of 0.4 for urea and 0.2 for the remaining compounds. For aqueous solutions of ethanol, data were collected through the entire concentration range.

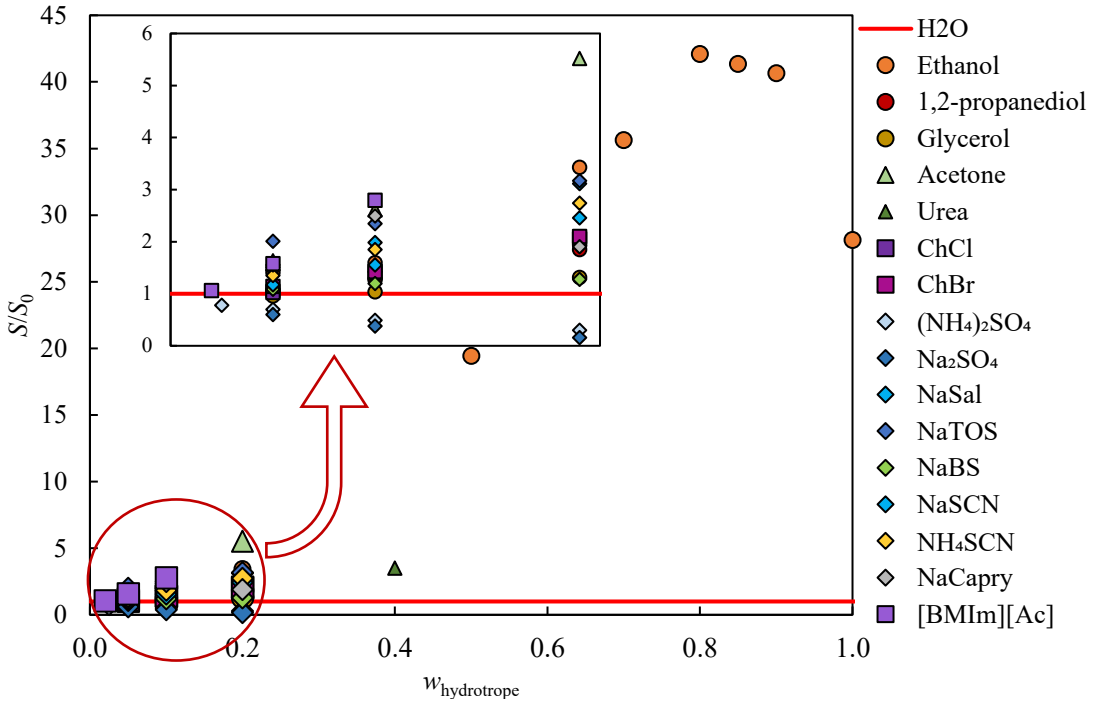


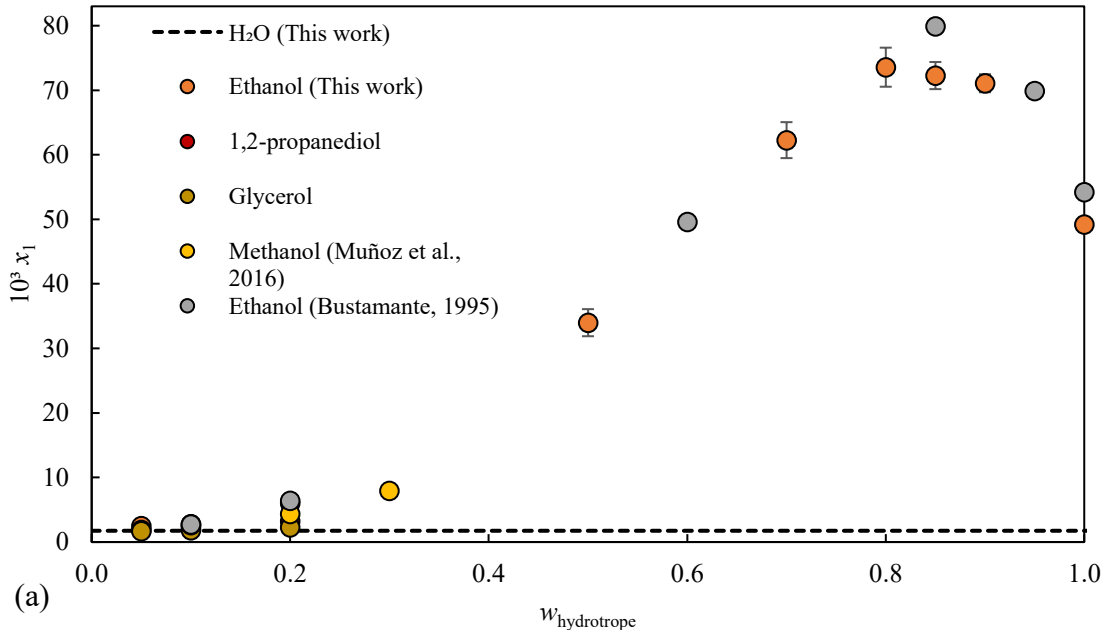
Figure 10. Summary of the ACP relative solubility in all the tested hydrotropic systems as a function of the hydrotrope concentration in mass fraction.

In the next sections, the solubility enhancement of ACP within different hydrotropes classes will be further analysed. Additionally, COSMO-RS will be employed to calculate the hydrotropes' σ-profiles, with the aim of determining the characteristic factors (DF, AF, and AcF) calculated from Equations 11 and 12, to further exploit the influence of the molecular charge density on drug solubility. This approach aligns with the findings of Abranches and co-workers, who found that the hydrotropic capability tends to increase as the apolarity of the hydrotrope approaches the apolarity of the solute, particularly in the lower hydrotrope concentration range. The maximum performance in enhancing solubility is thus achieved when

both the solute and hydrotrope have the same apolarity (Abranches et al., 2020; Sales et al., 2022).

Alcohols

Acetaminophen solubility was measured in aqueous solutions of three different alcohols, namely ethanol, 1,2-propanediol and glycerol. As none of them displays UV-Vis absorbance in the range of interest, spectrophotometry was the analytical technique applied in these solubility experiments. **Figure 11** displays the experimental data obtained, along with data from literature (the data tables are in Appendix B. In addition, methanol data reported by Muñoz et al. (2016) were also included to investigate the impact of alcohol alkyl chain length in drug solubility enhancement.



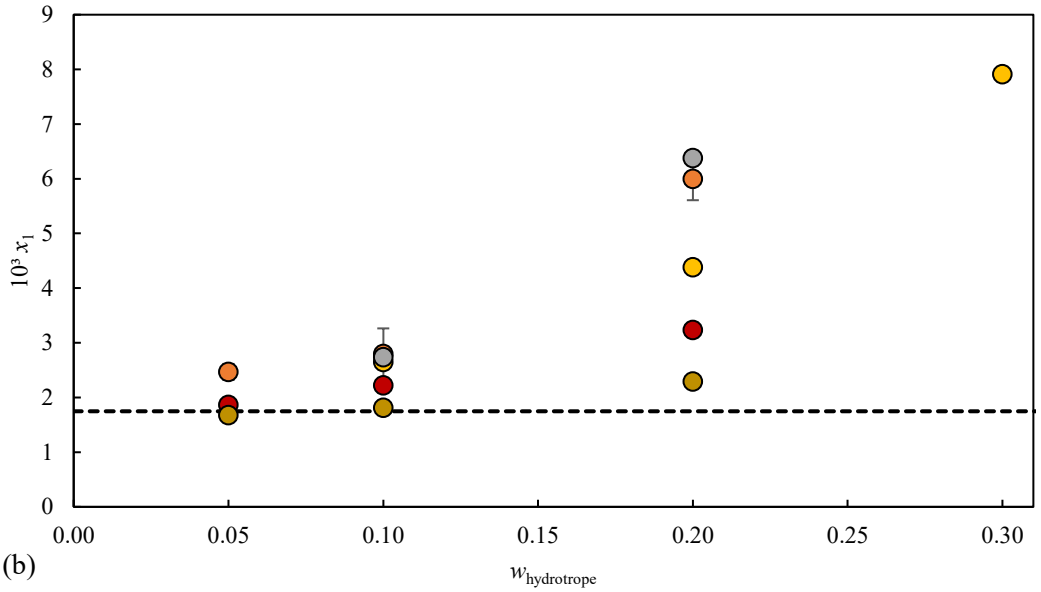


Figure 11. Effect of alcohols on ACP solubility in aqueous solutions at 298.2 K: (a) all hydrotrope concentration range; (b) close up at $0 \leq w_{hydrotrope} \leq 0.3$ region.

Among the alcohols, ethanol stands out for exhibiting a higher ACP solubility enhancement in the measured hydrotrope concentration range. This enhancement is particularly prominent within the region of $w_{ethanol}$ = 0.8 to 1.0. Notably, the solubility in pure ethanol (10^3x_1 = 49.2) is significantly lower than that in ethanol/water at $w_{ethanol}$ = 0.8 (10^3x_1 = 73.6). These findings suggest that the drug dissolution process is more favourable with a low water content ($0<w_{water}\leq0.2$), due to the solute-organic solvent interactions. Bustamante (1995) indicates that this result may be correlated with stronger water-ethanol interactions at this maximum region and the solubility enhancement is mainly due to an entropy increase.

When increasing the number of hydroxyl groups of the alcohol and the alkyl chain (from ethanol to glycerol), it is possible to see that the solubility of ACP decreases. Moreover, by increasing the length of the alcohol alkyl chain length from methanol to ethanol, the solubility of ACP increases.

In the existing literature, the data from Bustamante et al. (1995) is the only available reference for the set of alcohols investigated in this study. Our experimental data closely matched Bustamante's findings at lower ethanol concentrations, with diverging more at concentrations above $w_{ethanol}$ = 0.8. Such differences may be attributed to experimental challenges in measuring the drug solubility, arising from the rapid evaporation of the solvent in compositions with higher concentrations of the ethanol. Another possible reason might be the difference in experimental conditions of both assays (temperature, solvent and solute purity, stirring rate, among others) which can also have an impact on the solid phase.

To assist the interpretation of the experimental results, the COSMO-RS σ-profiles of alcohol-based hydrotropes (**Figure 12**), and the donor (DF), apolar (AF) and acceptor (AcF) factors were calculated (**Table 8**).

Table 8. ACP, and alcohols characteristic factors of the different regions (Donor - DF, Acceptor - AcF and Apolar – AF) calculated from the sigma profiles.

Compound	DF	AF	AcF
Acetaminophen	1.24	5.71	1.33
Methanol	0.48	2.19	0.89
Ethanol	0.53	3.17	0.74
1,2-propanediol	0.72	3.75	1.32
Glycerol	0.93	2.86	1.67

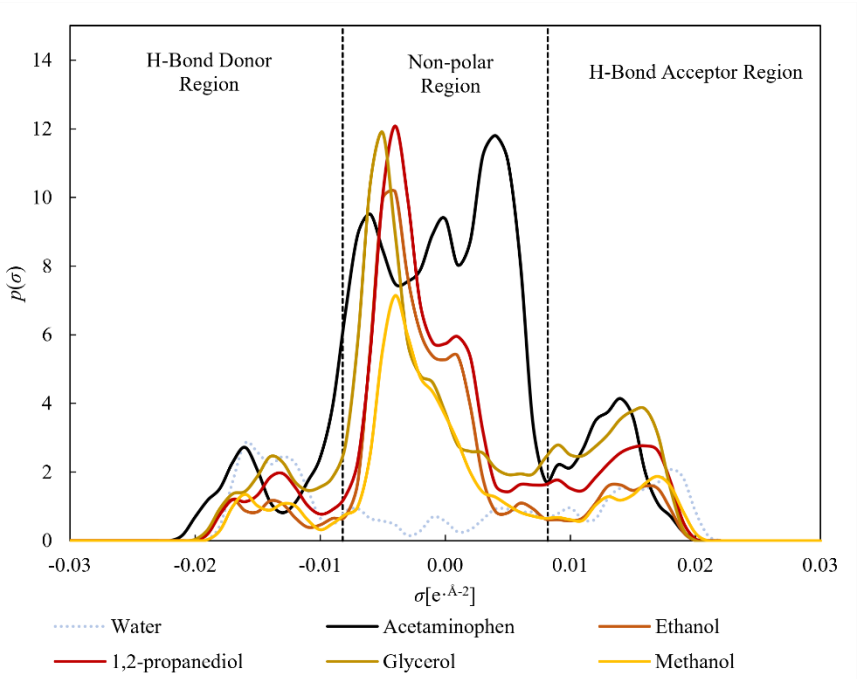


Figure 12. Water, ACP, and alcohols sigma profiles.

From the characteristic factors, it can be noticed a loss on the hydrotropic capability of alcohols as the alkyl chain length increased, as well as a increase in the DF value. Methanol is an exception, since despite having the shortest alkyl chain and the lowest DF value among the analysed alcohols, it exhibited a lower solubility enhancement for the drug compared to ethanol. Some possible explanations could involve stronger methanol-water interactions due to

methanol polarity and higher dielectric constant, leading to the formation of stronger hydrogen bonds with water, which could in turn influence drug dissolution.

Choline-based salts & Ionic Liquids

Acetaminophen solubility data in systems containing choline-based salts and [BMIm][Ac] are shown in **Figure 13** (full data are available in Appendix B). Nonsignificant anion effects were noticed among the choline salts, with the system containing ChBr presenting a slightly higher ACP solubility difference in relation to ChCl (10^3x_1 = 3.68 against 3.59 for ChBr and ChCl, respectively, at $w_{\text{hydrotrope}}$ = 0.2). The scenario changes when comparing choline-based salts to the IL [BMIm][Ac], that shows a significant higher ACP's solubility enhancement for all concentration ranges investigated. The same results as the salt were achieved at lower hydrotrope concentration (10^3x_1 = 1.86 for w_{IL} = 0.02 against 10^3x_1 = 1.80 and 2.0 for ChCl and ChBr at $w_{\text{hydrotrope}}$ = 0.05, respectively). At an hydrotrope concentration of $w_{\text{hydrotrope}}$ = 0.1, [BMIm][Ac] hydrotropic capability of increasing ACP solubility is almost 2-folds higher than choline-based salts. It is important to highlight that [BMIm][Ac] is highly hygroscopic, making its solubility measurement quite challenging.

When analysing the values computed from the σ-profiles (**Table 9** and **Figure 14**) for the three investigated compounds, it is possible to realize that the IL presents a DF value (1.28) lower than ChCl and ChBr (both with 1.66). Moreover, the DF value for [BMIm][Ac] is slightly higher than the value of ACP (1.24), demonstrating a trend of drug solubility increase with DF value decrease.

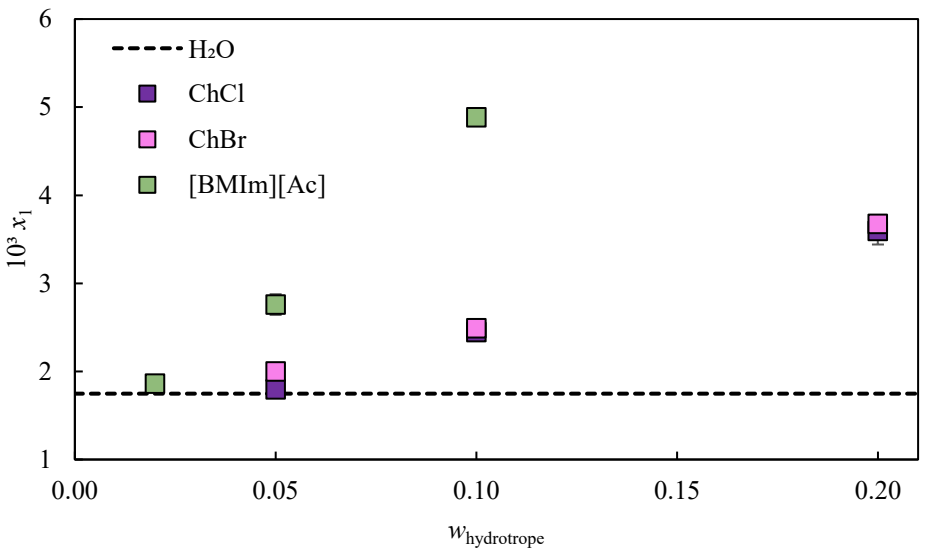


Figure 13. Acetaminophen solubility in hydrotropic systems containing choline-based salts and [BMIm][Ac], at 298.2 K.

Table 9. Choline-based salts and [BMIm][Ac] computed characteristic factors.

Compound	DF	AF	AcF
Acetaminophen	1.24	5.71	1.33
[BMIm][Ac]	1.28	8.60	5.78
ChCl	1.66	1.90	6.07
ChBr	1.66	1.90	5.60

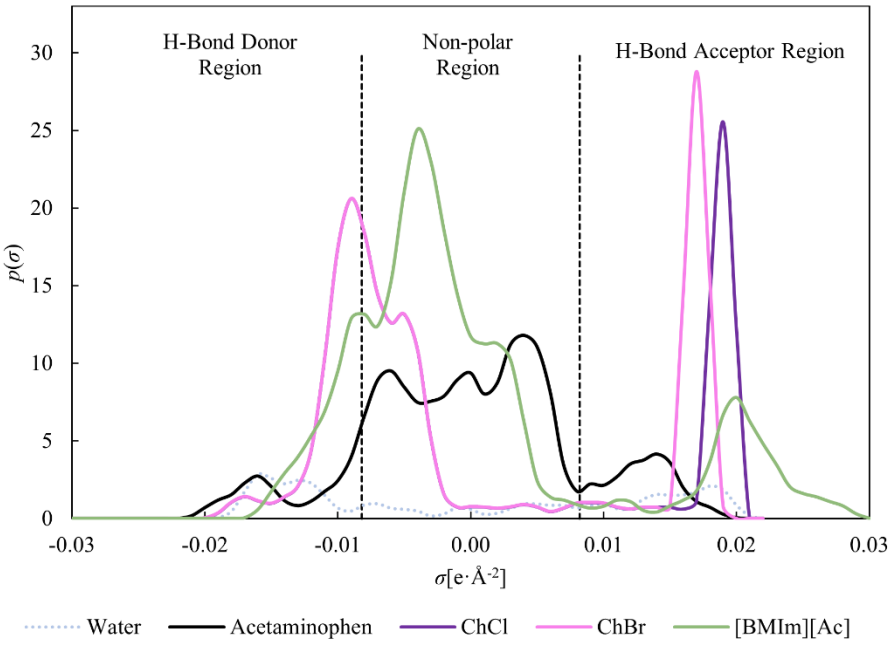


Figure 14. ACP, water, choline-based salts and [BMIm][Ac] sigma profiles.

For a better understanding of the ILs behaviour as hydrotropes, the experimental data obtained for [BMIm][Ac] were further compared with other IL-based hydrotropic systems from literature (Mehrdad et al., 2017, 2020; Mehrdad & Miri, 2016a, 2016b). Data are summarized in **Figure 15** and show that the ILs hydrotropic capability increases as the alkyl-chain length of the cation increases, similar to what was observed for methanol and ethanol. Moreover, the results suggest that the presence of nitrogen atoms in the molecular structure of these ILs leads to a decrease on the acetaminophen solubility, once the pyridinium-based ILs demonstrated a higher drug solubility enhancement over the imidazolium ones.

In general, 1-octyl-4-methylpyridinium bromide ([OMPyr]Br) exhibited the best results among the ILs, achieving the highest drug solubility (value of $10^3 x_1 = 5.41$ at $w_{[OMPyr]Br} = 0.07$). In sequence, 1-octyl-3-methylimidazolium bromide ([OMIm]Br) achieved a significant drug solubility of $10^3 x_1 = 4.94$ at $w_{[OMIm]Br} = 0.07$ and an overall ACP solubility of $10^3 x_1 = 10.15$ at a hydrotrope concentration of 0.15. The least favorable results for drug solubility enhancement were obtained with more polar 1-butyl-3-methylimidazolium bromide ([BMIm]Br) and [BMIm][Ac] (this work).

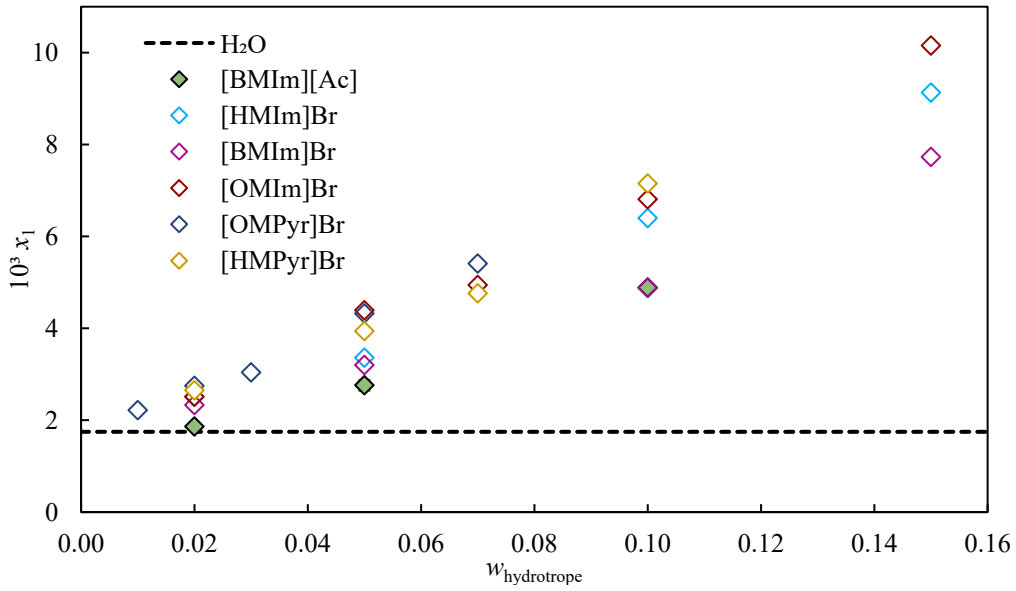


Figure 15. Effect of the IL on ACP solubility in aqueous solutions at 298.2 K.

Overall, all authors concluded that the main driving force of the drug solubility process are the hydrophobic interactions between acetaminophen and the alkyl chain of the IL (Mehrdad et al., 2017, 2020; Mehrdad & Miri, 2016a, 2016b). Moreover, all these studies reported that the process is driven by enthalpic effects.

Additionally, Shekaari and coworkers investigated the ACP thermodynamic properties in the aqueous solutions of ILs (Shekaari et al., 2017 and Shekaari et al., 2021). On a first paper, authors investigated the drug's thermodynamic properties through density studies on mixtures containing ACP+[HMIm]Br or [HMIm]Cl, and water at temperatures ranging from 293.15 to 308.15 K (Shekaari et al., 2017). Later, they focused on amino acids-based ILs, namely [Ch][Gly], [Ch][L-Ala], and [Ch][L-Val] (Shekaari et al., 2021). Both studies demonstrated that acetaminophen behaves as structure-breaker in ternary solutions containing ILs, and that such behaviour tends to decrease when increasing the IL concentration. Moreover, it was found that solute-solvent interactions between ACP and ILs are dominated by non-polar interactions and polar ion-polar. Such interactions are dependent on the size and polarity of the anion, becoming stronger at larger and more polar anions. These findings could explain the highest solubility in aqueous solutions of [BMIm]Br over [BMIm][Ac] at some hydrotrope concentrations discussed above. Furthermore, both studies indicates that the V_{ϕ}^{0} values are positive for all solutions studied in both works, as well as the molar isentropic compressibility (the variation of solution compressibility as function of concentration), indicating attractive interactions between ACP and the ILs. It was also found that these properties are temperature and hydrotrope concentration dependent.

Table 10 presents the computed characteristic factors for the ILs analysed, with the correspondent σ-profiles shown in **Figure 16**. Data show that ILs with larger alkyl chains display higher AF values, and consequently lead to a higher ACP solubility. The same was observed for choline-based salts (**Table 9**). These results could corroborate Mehrdad and coworkers' conclusions that acetaminophen interactions are stronger with the alkyl chain of ionic liquids, and this phenomenon leads to drug solubility increasement (2016a, 2016b). By the other side, such set of data do not follow the theory of Coutinho and co-workers (Sales et al. (2022)), as higher solubility enhancements are here achieved by hydrotropes presenting AF values close to ACP. In addition, for ILs and choline-based salts, acetaminophen solubility tends to increase with the DF value decrement, as shown at both **Table 9** and **10**.

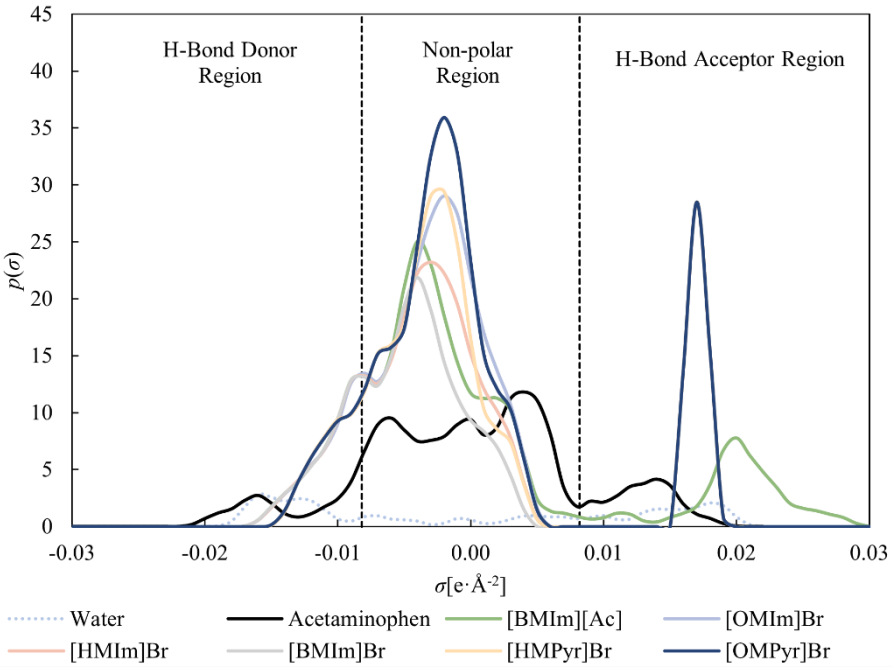


Figure 16. ACP, water, and ILs sigma profiles.

Table 10. Computed characteristic factors for the ILs discussed in this work.

Compound	DF	AF	AcF
Acetaminophen	1.24	5.71	1.33
[OMPyr]Br	1.06	12.49	5.31
[OMIm]Br	1.27	11.52	5.31
[HMPyr]Br	1.05	9.99	5.31
[HMIm]Br	1.28	8.96	5.31
[BMIm]Br	1.28	6.52	5.31
[BMIm][Ac]	1.28	8.60	5.78

Salts

Both sodium and ammonium-based salts were analysed to assess their hydrotropic capabilities to increase the solubility of ACP in water. Experimental results are displayed in **Figure 17**. In general, ammonium salts demonstrated a higher ACP solubility enhancement compared to sodium salts, for the thiocyanate anion, and a lower salting out effect when considering the sulphate salts.

The highest overall drug solubility enhancement was achieved with NaTOS ($10^3 x_1$ = 5.55) and NaSal ($10^3 x_1$ = 5.45), both at a hydrotrope mass fraction of 0.20. In most cases, a consistent increase in acetaminophen solubility with increasing salt concentration was observed, with exception of NaCapry, which exhibited a maximum in solubility, and sulphates salts that induced a salting-out effect.

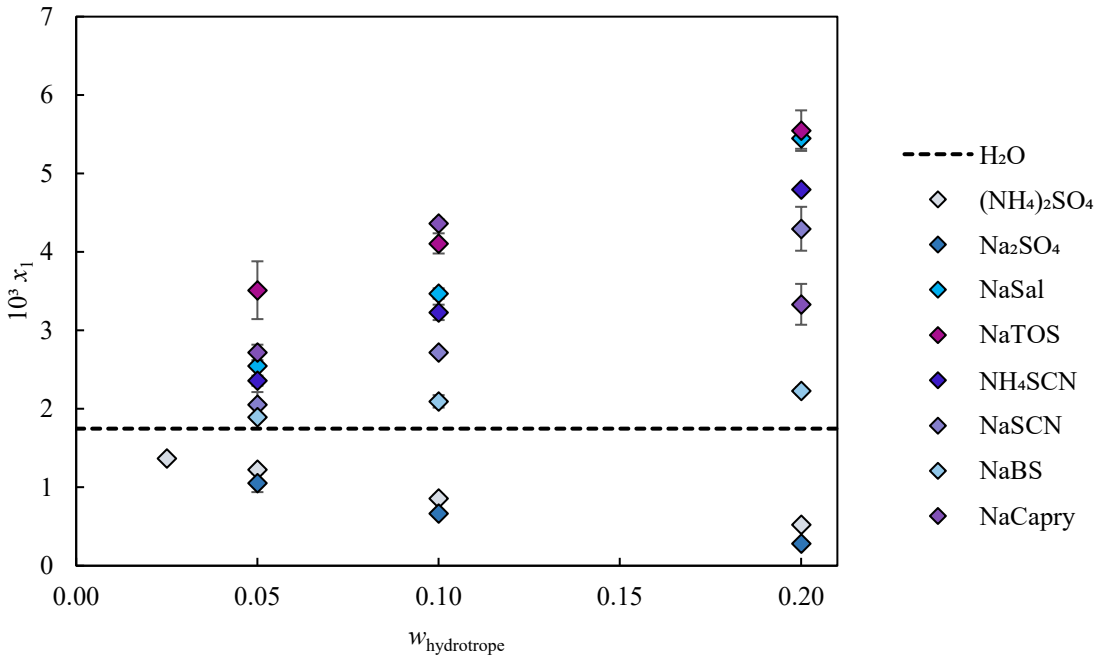
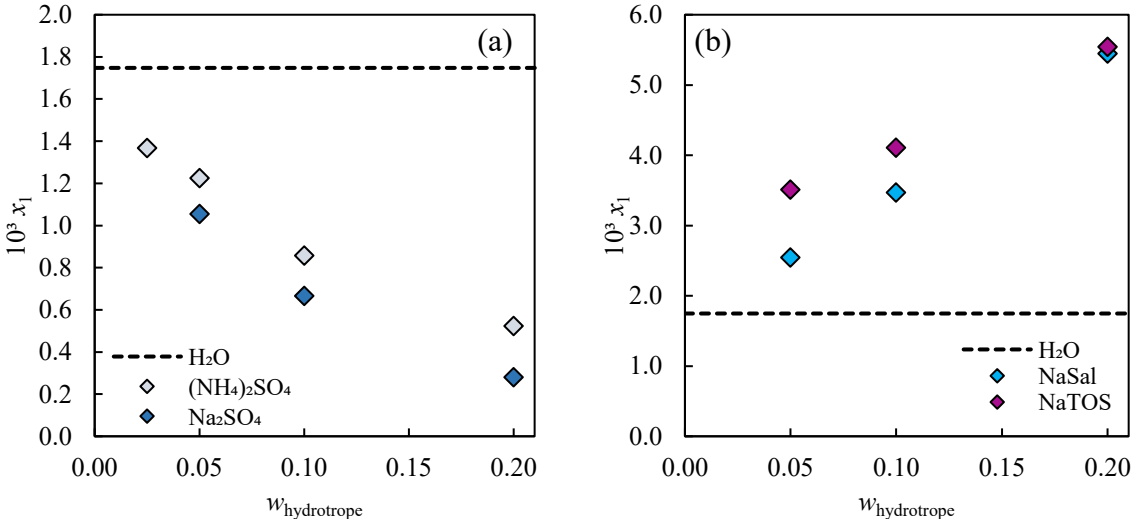


Figure 17. Acetaminophen solubility in hydrotropic systems containing salts, at 298.2 K.

For a better interpretation and discussion of the experimental results obtained, **Figure 18** presents the salts divided according to their chemical structure. **Figure 19** shows the σ-profile for each salt, with the exception of sodium benzene sulphonate and caprylate that were not available at COSMO*therm* database. **Table 11** summarizes the characteristic factors calculated from the σ-profiles.



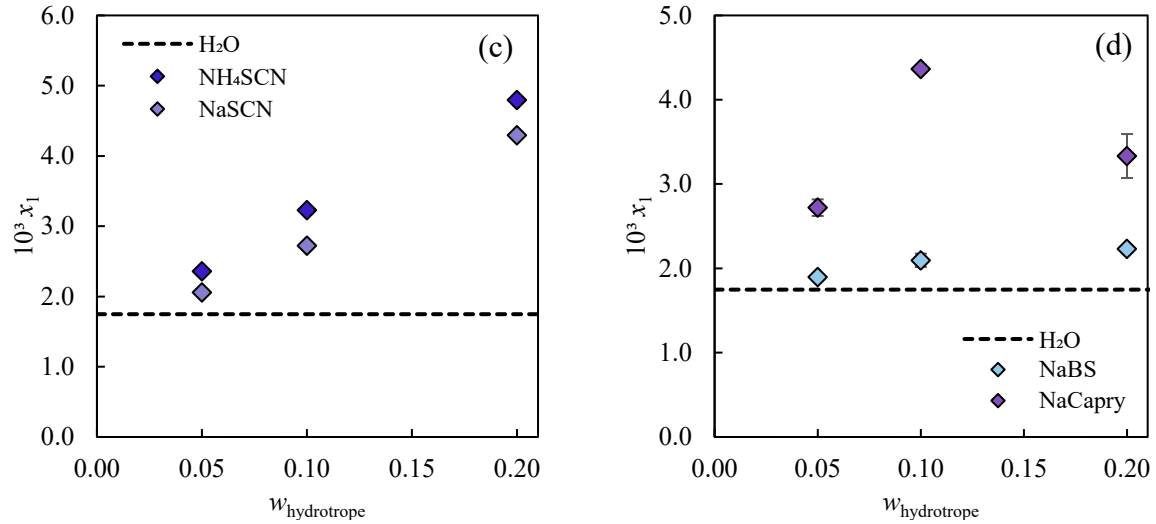


Figure 18. Acetaminophen solubility in hydrotropic systems containing: (a) sodium and ammonium sulphates; (b) sodium tosylate and salicylate; (c) sodium and ammonium thiocyanates; (d) sodium benzene sulphonate and caprylate.

As expected, according to experimental studies on salting-out strategies for organic compounds (Hyde et al., 2017), sulfate salts demonstrate a strong salting-out effect that increases with salt concentration – **Figure 18a**. Hyde and coworkers' (2017) study demonstrate that the salting-out effect depends on ion-specific effects, and it may be influenced by ion's effective charge density and polarizability. Thus, $(NH_4)_2SO_4$ shows a lower salting-out effect than Na_2SO_4, which might be explained by the lower charge density of the ammonium cation. Another plausible explanation for the comparatively lower ACP salting-out effect in the presence of $(NH_4)_2SO_4$ is linked to the presence of hydrogen atoms in this molecule, which can interact with acetaminophen and with water through the formation of hydrogen-bonds, thereby attenuating the precipitation of the drug.

Upon analysing Hofmeister's series, it becomes evident that SCN^- salts, known as chaotropic agents, induce a salting-in effect. This observation is further validated by the experimental results displayed in **Figure 18c**. Both sodium and ammonium thiocyanate demonstrated an increase in the solubility of ACP as the salt concentration increased. Specifically, values of approximately $10^3x_1 = 4.80$ and 4.30 were achieved for $(NH_4)_2SCN$ and NaSCN, respectively, at $w_{hydrotrope}$ of 0.2. The higher solubility of ACP observed in the NH_4SCN system can be attributed to the presence of hydrogen atoms, similar to the situation with ammonium sulphate, where the hydrogens atoms interact with the hydroxyl groups of the drug through hydrogen-bonds. Nevertheless, NaSCN is more commonly reported as a hydrotrope for drug systems, and it was already studied as hydrotrope using the COSMO-RS

model (Ikeda et al., 2005), and successfully tested in experimental studies involving aromatic drugs such as *p*-aminoacetophenone (Dhinakaran et al., 2012) and modafinil (Thimmasetty et al., 2020).

Among all salts, NaTOS exhibited the best result, increasing the solubility of ACP 3.17-fold (**Figure 18b**). When analysing the characteristic factors presented in **Table 11**, NaTOS is the only hydrotrope among those tested that shows an apolar factor similar enough to ACP, corroborating Sales' observations (2022). Notably, when comparing the solubility of acetaminophen in solutions containing NaTOS or NaSal as hydrotropes, it becomes apparent that they converge to nearly identical values at $w_{\text{hydrotrope}} = 0.2$.

The experimental data obtained for NaSal ($10^3 x_1 = 5.45$ at $w_{\text{hydrotrope}} = 0.2$) is below the reported in literature by Hamza & Paruta (1985) ($10^3 x_1 = 8.63$ at $w_{\text{hydrotrope}} = 0.2$), where the authors analysed hydrotrope concentrations of 20, 30 and 40%. The substantial difference of approximately 58% observed between the two results can be attributed to the choice of an inappropriate technique for quantifying ACP by the authors, which was UV-Vis spectrometry. This method might not be appropriate due to the overlap of the absorption peaks of sodium tosylate and ACP which introduce quantification errors. In this work, gravimetry was chosen instead. In fact, Hamza's work reported a shift in the peak positions of both ACP and NaSal in the UV spectra, while there was no change in the absorption values of these compounds. Such finding, combined with NMR studies, provided evidence that there was no formation of complexes or chemical bonds between the solute and the hydrotrope.

Solutions containing NaCapry or NaBS led to ACP solubilities of $10^3 x_1$ equal to 4.37 for NaCapry at $w_{\text{hydrotrope}} = 0.1$ and 2.23 for NaBS at $w_{\text{hydrotrope}} = 0.2$ (**Figure 18d**). But, while NaBS demonstrates a low hydrotropic capability even at higher hydrotrope concentration, the solubility of ACP in NaCapry solutions exhibited a non-linear relationship with the hydrotrope concentration. A maximum in the ACP solubility can be seen at $w_{\text{hydrotrope}} = 0.1$, and it subsequently decreased at higher concentrations. A possible explanation for this phenomenon would be related to the high pH of the solution reported in Appendix A. Somasundaran et al. (1984) elucidated that anionic surfactants can undergo precipitation phenomena in solutions containing specific ions due to intricate surfactant-ion interactions. The solution's pH rises with the NaCapry concentration. This pH elevation causes the ionization of the acetaminophen molecule, giving rise to the presence of ionic drug species in the solution. These ionic drug species may interact with NaCapry, culminating in its precipitation. Consequently, this interplay engenders a diminution in the solubility of acetaminophen, as the compound no

longer exists in bulk form to facilitate interaction with the drug. Further studies should be carried out to analyse the solid phase.

Analysing **Table 11**, a consistent trend is observed: the ACP solubility increases with the decrease in DF values when comparing inorganic salts (i.e., NaSCN and NH_4SCN, $(NH_4)_2SO_4$ and Na_2SO_4). An exception occurs with the pair of organic salts NaTOS and NaSal, where NaTOS shows an AF value very similar to acetaminophen, as discussed earlier.

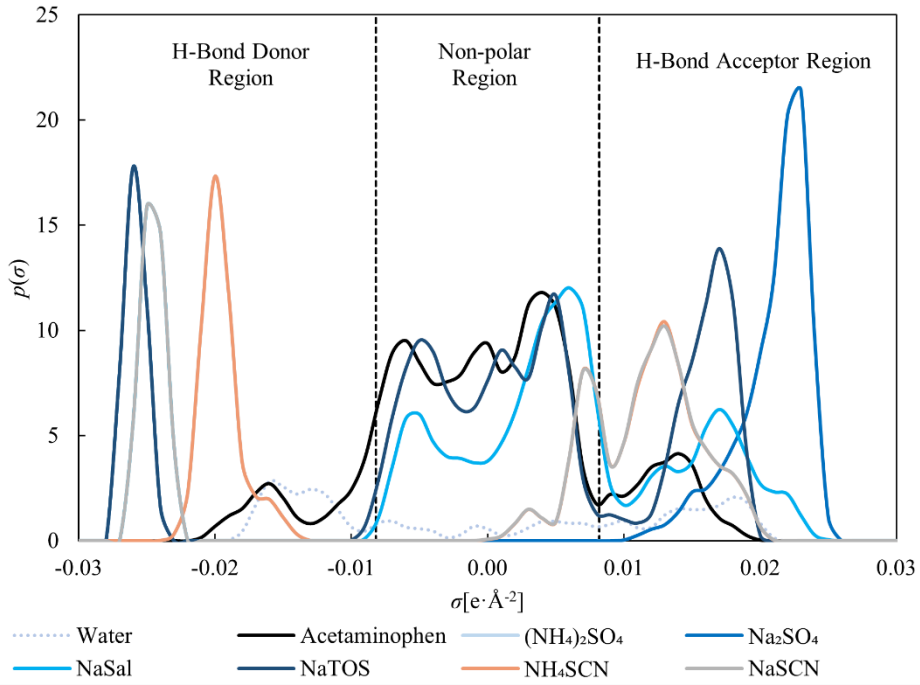


Figure 19. ACP, water, and traditional salts sigma profile.

Table 11. Computed characteristic factors for the selected salts used in this work.

Compound	DF	AF	AcF
Acetaminophen	1.24	5.71	1.33
NaTOS	6.91	5.11	5.06
NaSal	6.74	3.72	4.02
NH_4SCN	5.90	0.37	3.44
NaSCN	6.76	0.37	3.44
$(NH_4)_2SO_4$	5.90	0.00	12.37
Na_2SO_4	6.90	0.00	1.24

Others

Acetone and urea exhibit unique structures, which do not fit into the previously discussed categories. Therefore, the results for these compounds will be analysed separately in **Figure 20**. Acetone demonstrated the highest ACP solubility enhancement, achieving a value of $10^3x_1 = 9.65$ at $w_{acetone} = 0.2$. This result is almost 169% higher than that obtained with urea at the same hydrotrope concentration ($10^3x_1 = 3.59$). Interestingly, the relationship between drug solubility and acetone concentration appears to be non-linear, whereas for urea a linear trend is observed, at least at lower hydrotrope concentrations.

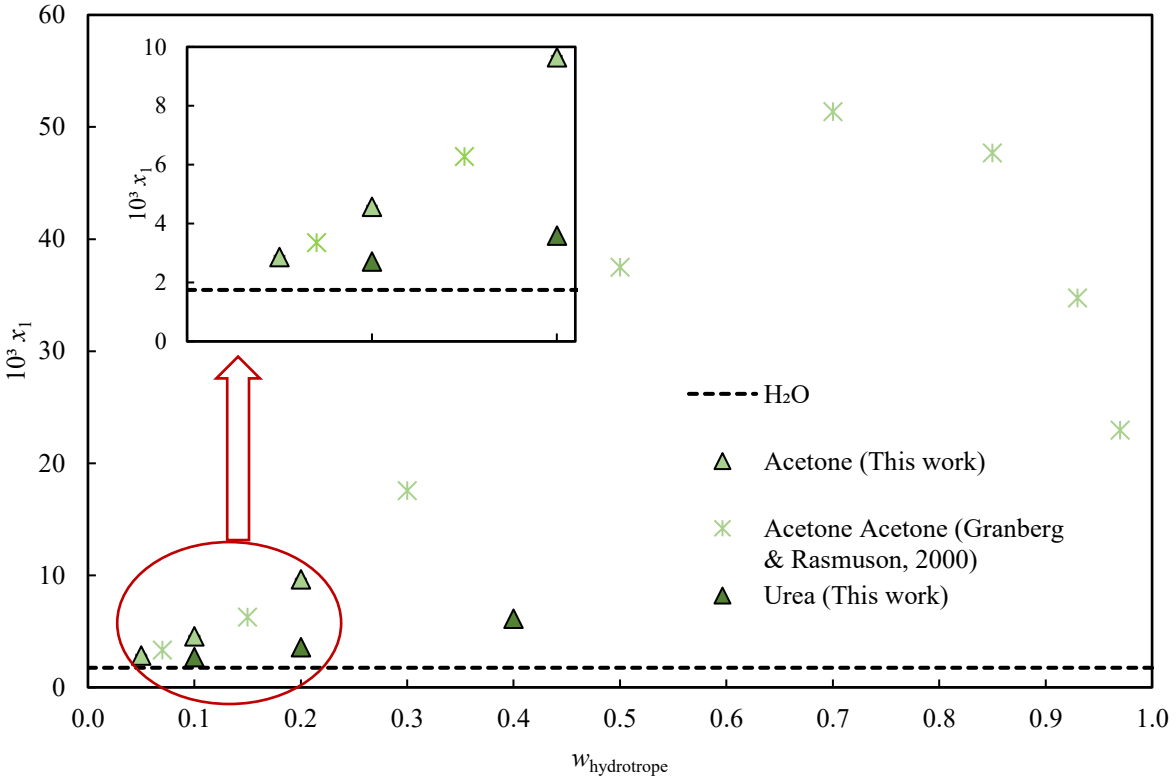


Figure 20. Experimental solubility of acetaminophen at 298.2 K in aqueous solutions of acetone or urea.

Literature data for ACP solubility in acetone at 298.15 K (Granberg & Rasmuson, 2000) demonstrates a behaviour similar to that of ethanol, with a solubility peak occurring in the region of $w_{hydrotrope} = 0.7$ ($10^3x_1 \approx 51.4$). The drug has a lower solubility in pure acetone ($10^3x_1 \approx 23$). **Figure 20** provides a comparison between the data available for this system, showing good agreement between both datasets.

Table 12 and **Figure 21** show the σ-profile and computed characteristic factors for both hydrotropes. As can be seen, the drug solubility increases for lower hydrotrope DF value.

Furthermore, acetone has an apolar charge density area more similar to that of paracetamol than that of urea.

Table 12. Computed characteristic factors for ACP, acetone and urea.

Compound	DF	AF	AcF
Acetaminophen	1.24	5.71	1.33
Acetone	4.73E-3	3.67	0.92
Urea	1.63	1.35	1.79

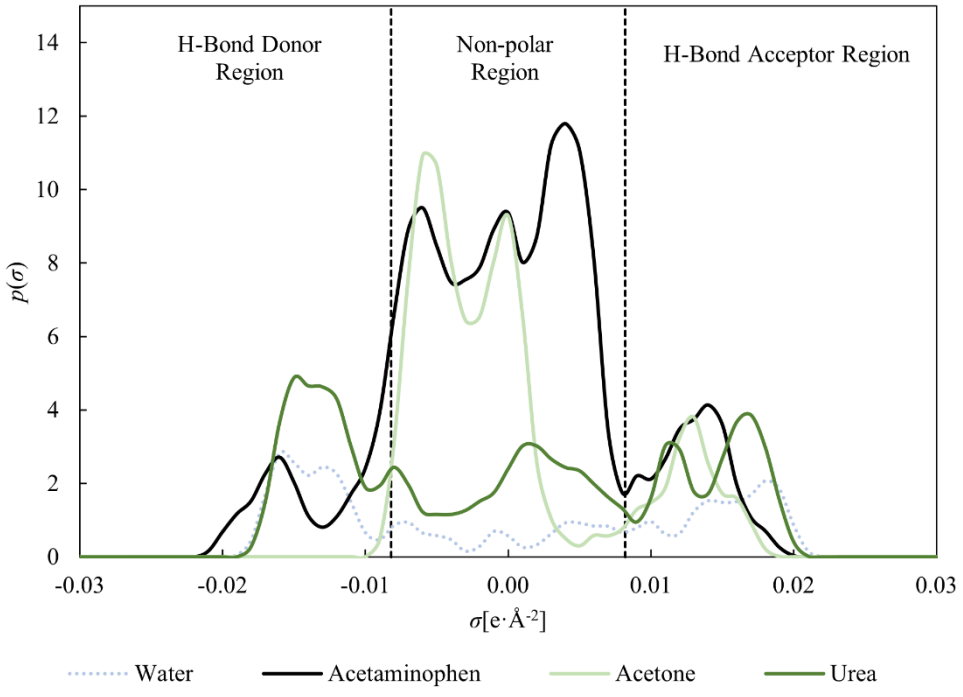


Figure 21. Water, ACP, acetone and urea sigma profiles.

In addition to the previously discussed systems, two additional systems involving sodium benzoate (NaBen) and nicotinamide (NA) were examined, yielding unexpected outcomes. Firstly, NaBen exhibited a robust salting-out effect on ACP, resulting in the visible precipitation of solid during stirring. While this compound has been noted for its efficacy as a hydrotrope in enhancing the solubility of nifedipine (Jain et al., 1988), lumefantrine (Agrawal & Kasturi, 2018), and albendazole (Joshi et al., 2022), the observed behaviour was unforeseen and unreported in the context of ACP. **Figure 22** illustrates a sample of the ternary system comprising ACP/NaBen/water before and after magnetic stirring. Consequently, we faced challenges in quantifying the extent of the salting-out effect, as the compound's UV-Vis

absorbance spectra overlaps with that of acetaminophen, and gravimetry does not allow for the calculation of the mass of precipitated solute. Once again, further studies should be carried out to analyse the solid phase.

(a) **(b)**

Figure 22. Comparison between ternary solutions of ACP/NaBen/water: (a) before magnetic stirring (b) after stirring with precipitation.

In the case of nicotinamide, a shift in absorbance peaks for both NA and ACP in UV-Vis spectrometry, as shown in **Figure 23**, was observed. This phenomenon was previously reported by Hamza & Paruta (1985), who correlated it with complexation between the hydrotrope and the drug. Indeed, nicotinamide has been reported as a complexation agent for increasing the solubility of drugs, even up to 4000-fold (Sanghvi et al., 2007), and the formation of 1:1 or 1:2 complexes between the hydrotrope and the drug has been observed (Das & Paul, 2017). However, these complexes are still unknown and, as far as we know, have not been characterized yet. Such results demand further investigation with appropriated equipment and methods. Spectroscopy cannot provide precise measurements due to baseline instability, and the gravimetric technique faces limitations as the hydrotropes decompose at temperatures exceeding 340 K in laboratory stove. Moreover, distinguishing the extent of acetaminophen complexation with NA in the solution and analysing the solid phase was out of the scope of this work.

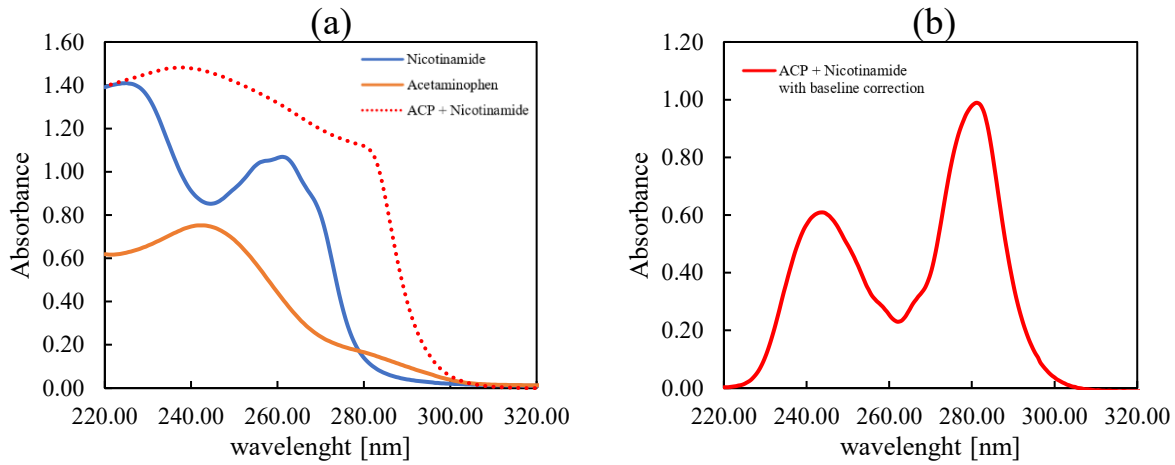


Figure 23. UV-Vis spectra of the nicotinamide system: (a) comparison between pure nicotinamide, acetaminophen and NA+ACP; (b) NA+ACP after NA baseline correction.

4.4 Polarity surface area data analysis

In this section, a statistical analysis to explore the correlation between the computed factors related to hydrotropes' polar/apolar surface area and the experimental solubility data is conducted. This analysis follows the guidelines proposed by Sales et al. (2022) and Abranches et al. (2020).

The variables directly linked to the hydrotropes charge density (i.e., DF, AF and AcF) were calculated following the previously described procedure, using the σ-profile data obtained from COSMO-RS. For sodium benzene sulphonate and sodium caprylate the structures were not available, precluding the calculation of the characteristic factors. Thereafter, data were subjected to a multiple regression analysis employing *Minitab*® 21.4 in order to: (a) determine if there is a correlation between any of three characteristic factors (Y) and acetaminophen solubility (X), considering a significance level of $\alpha = 0.1$; (b) if (a) is true, to identify which variables are relevant to the mathematical model. For this analysis, ACP solubility data at hydrotrope concentrations of 0.1 were chosen.

The analysis revealed a strong correlation between the X and Y variables, returning a p-value equal to 0.001. Also, it shows that, considering all hydrotropes data obtained in the present work and literature data above-mentioned, the AF value can be significantly correlated with the solubility of the drug, with an R^2 value of 74.8%. The correlation was positive, suggesting that solubility tends to increase with the increase of AF. These findings differ from the observations made by Sales and coworker's, who noted that solubility tends to increase as AF values of hydrotropes approach the solute's value (Sales et al. 2022). To validate the model,

a prediction interval of 95% was used, and **Figure 24** displays both the correlation and prediction data plots.

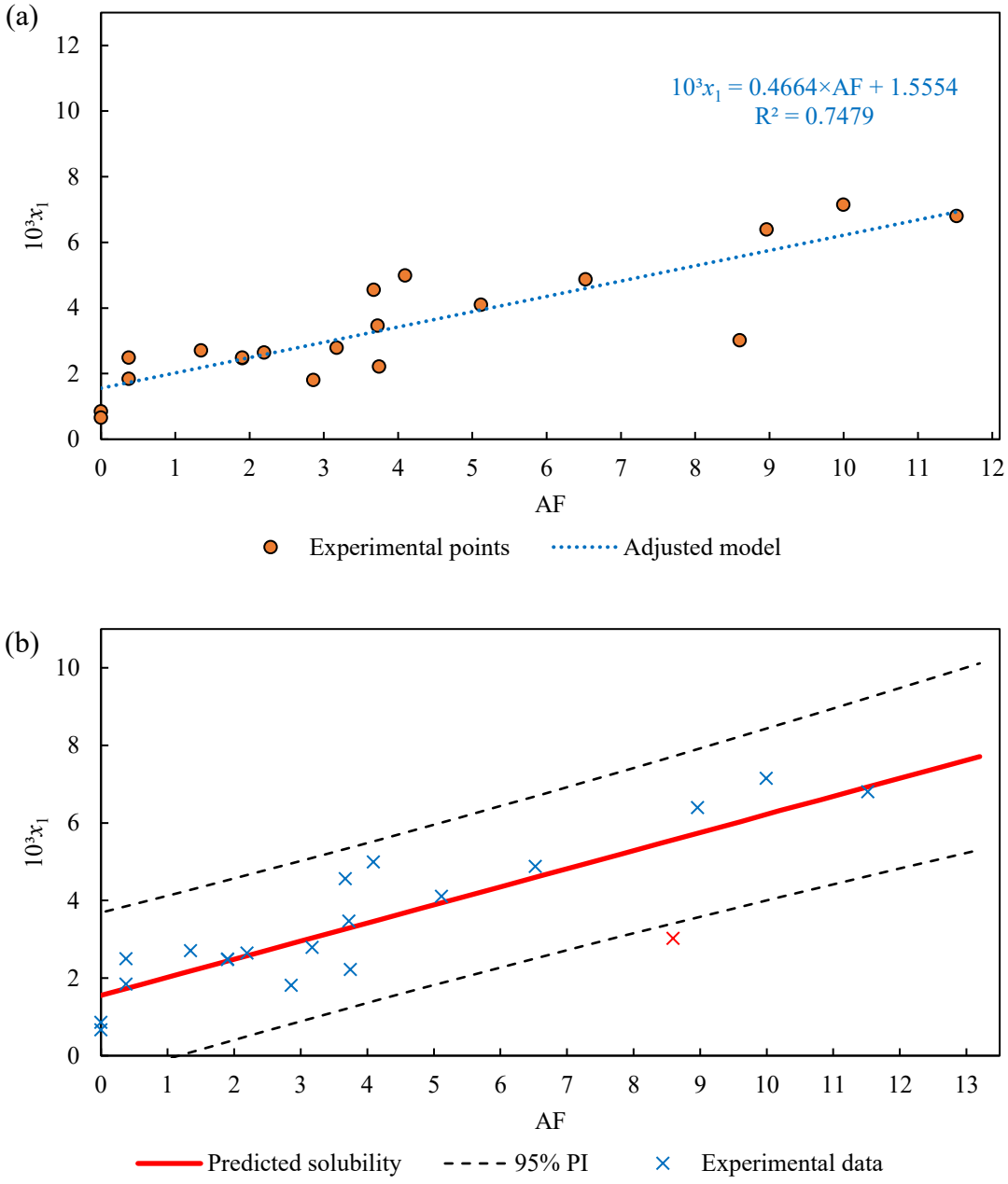


Figure 24. Correlation between apolar factor and acetaminophen's solubility at hydrotrope mass fraction of 0.1: (a) adjusted correlation, (b) comparison between experimental and predicted solubilities within a prediction interval of 95%. Red marker indicates the outlier [BMIm][Ac].

Furthermore, two distinct group of hydrotropes show strong correlations between the DF value and the solubility of acetaminophen, namely (i) organic solvents, and (ii) urea, choline-based salts and ILs (miscellaneous). It is important to highlight, that these groups

present very different values of DF, with ILs presenting (in general) higher values than ACP whereas organic solvents present DF values lower than ACP. Considering an $\alpha = 0.05$, p-values of 0.008 and 0.001 were obtained for urea, choline-based salts and ILs and organic solvents, respectively. Moreover, the miscellaneous group presented a R^2 of 71.44% regarding the correlation between DF and drug solubility, whereas organic solvents presented 95.70% for the same parameter. In both cases, the correlation is negative, with the solubility increasing when the DF decreases. Correlations are represented in **Figure 25**, as well as the prediction data using a prediction interval of 95%.

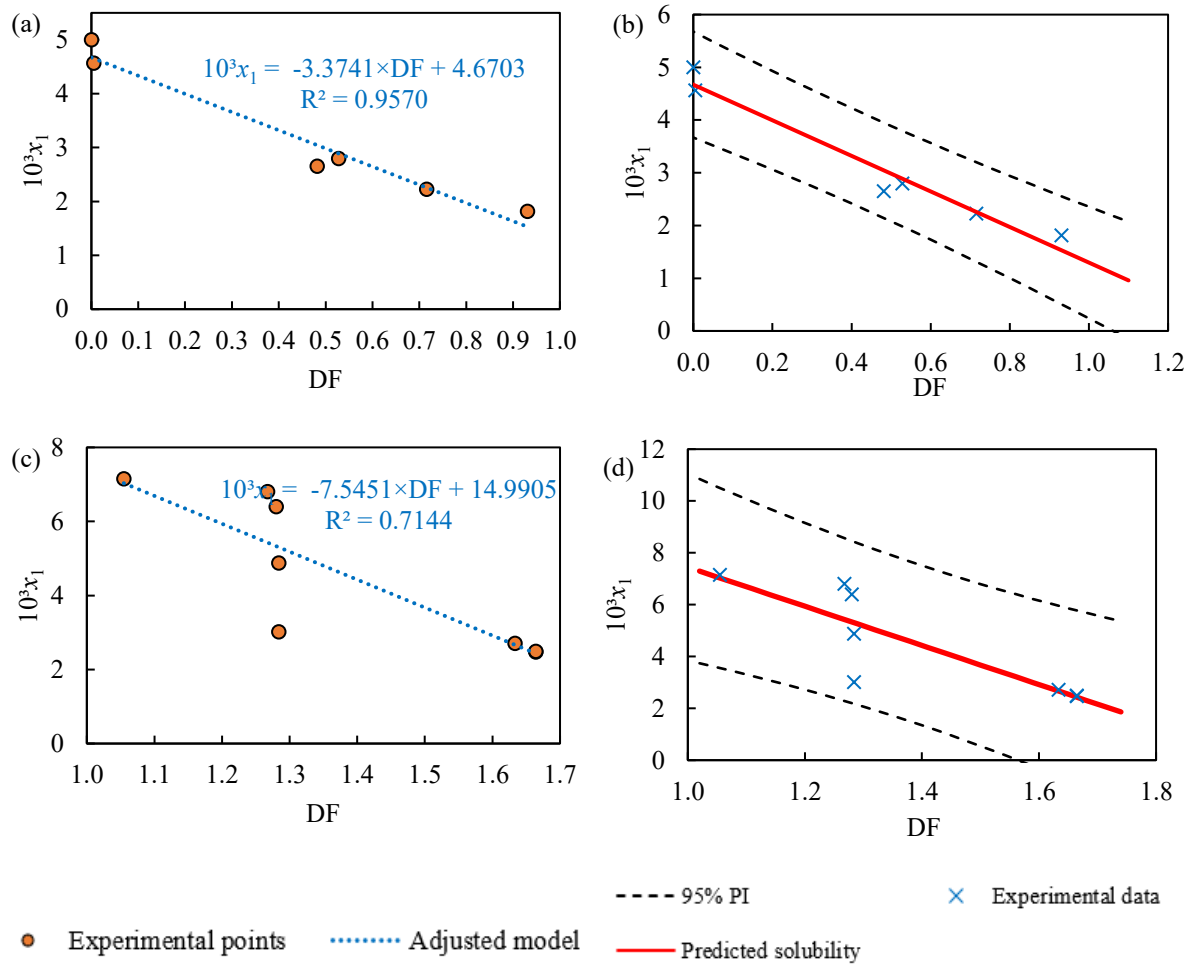


Figure 25. Linear regressions for ACP solubility at $w_{hydrotrope} = 0.1$ vs DF: (a) linear regression of ACP solubility in organic solvents vs DF; (b) comparison between the predicted solubility values and the experimental data obtained for organic solvents; (c) linear regression of ACP solubility in miscellaneous vs DF; (d) comparison between the predicted solubility values and the experimental data obtained for miscellaneous.

[BMIm][Ac] is a clear outlier to the above correlations, presenting elevate residuals. Therefore, its' data were excluded from the model of miscellaneous' regression and another model were generated, resulting in a better model, with p-value = 0.001 and R^2 indicating 91.60% of correlation, as shown in **Figure 26**.

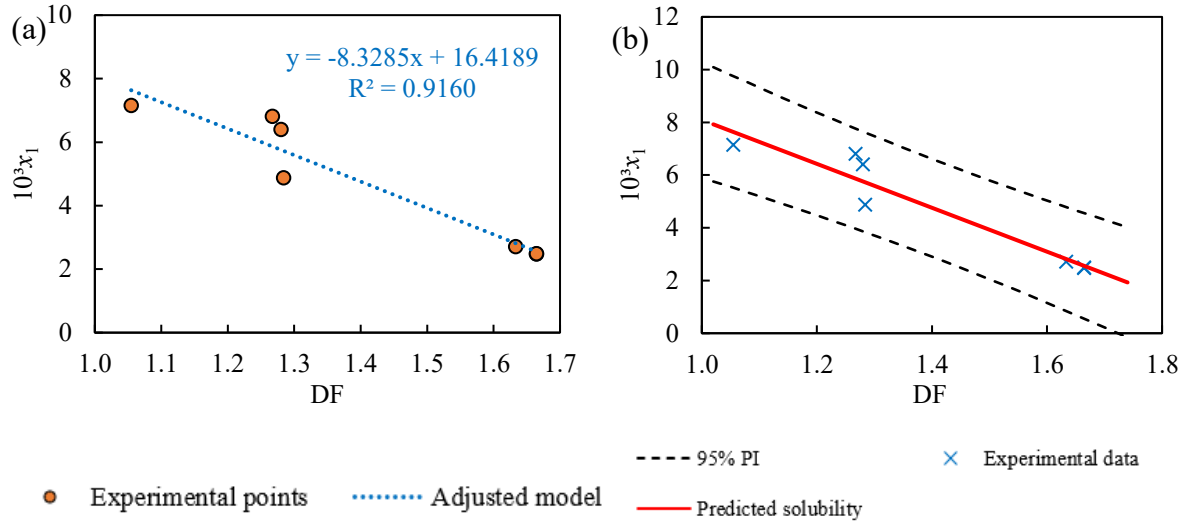


Figure 26. Adjusted model excluding [BMIm][Ac]: (a) ACP solubility at hydrotrope mass fraction of 0.1 vs DF with linear adjustment; (b) comparison between model predicted data and experimental points.

In future, the model should be adjusted using a larger dataset that includes compounds with DF value within both ranges (0 to 1.24 and 1.24 to 1.66) to test if the correlation remains valid. If the correlation proves to be consistent, it would facilitate the selection of hydrotropes based on target drug solubility and the desired application using a single easily calculable parameter.

5 CONCLUSIONS AND FUTURE WORK

Acetaminophen aqueous solubilities at 298.2 K were measured using shake-flask method coupled with UV-Vis or gravimetric techniques using different compounds that showed the ability to act as hydrotropes, enhancing drug's solubility, and thus they might be applied for drugs formulation.

After analysing the ACP solubility data, different behaviour was observed depending on the types of the hydrotropes. It must be highlighted for the clear non-linear correlation between drug's solubility and hydrotrope concentration (ethanol, NaCapry, NaBS and [BMIm][Ac]). Furthermore, comparing experimental data for salts with the same anion (SCN^- and SO_4^{-2}) but different cations ($Na^+$and NH_4^+), it was observed that salts containing Na^+ exhibited weaker interactions with ACP compared to salts containing NH_4^+. Salts with SO_4^{-2} induced a salting-out effect on ACP, making them suitable for promoting precipitation, and recovery of the drug from the solution. Conversely, salts with SCN^- caused a salting-in effect. Still, for alcohols it was observed that both alkyl chain and hydroxyl groups increase reduces the hydrotropic power. For ILs, merging this work data with available literature data, it was possible to notice that drug solubility enhancement increases with the cation apolarity.

Regarding the performance of hydrotropes at low hydrotropic concentrations, [BMIm][Ac], NaSal and NaTOS must be highlighted. In some cases, in particular for systems containing NaCapry or NaBen, solid phase studies should be carried out to understand the phenomena that caused solid precipitation under stirring (NaBen) and a peak formation in solubility diagram (NaCapry).

Regarding computational modelling and statistical analysis, using COSMO-RS, strong correlations between the hydrotrope apolarity, or the hydrogen bond factors, were observed at a fixed hydrotrope concentration. In general, the apolarity factor shows a positive correlation with drug solubility, whereas the hydrogen bond donor factor demonstrates a clear strong negative correlation for two distinct groups: organic solvents and choline-based salts, ionic liquids, and urea.

For future work it is suggested to include statistical and COSMO-RS studies involving different hydrotropes concentrations and temperature effects, attempting to establish a relevant correlation that allows the drug solubility prediction. It is also suggested to develop an experimental protocol based on HPLC as a method to determine ACP solubility in systems containing nicotinamide and define a set of chemical analysis to characterize the complexes formed between this hydrotrope and ACP.

6 REFERENCES

Abranches, D. O., Benfica, J., Soares, B. P., Leal-Duaso, A., Sintra, T. E., Pires, E., Pinho, S. P., Shimizu, S., & Coutinho, J. A. P. (2020). Unveiling the mechanism of hydrotropy: Evidence for water-mediated aggregation of hydrotropes around the solute. *Chemical Communications*, *56*(52), 7143–7146. https://doi.org/10.1039/d0cc03217d

Agrawal, S., & Kasturi, M. (2018). Hydrotropic solubilization: a promising technique to enhance solubility of poorly water soluble drug lumefantrine. *International journal of pharmaceutical sciences and research*, *9*(1), 175–181. https://doi.org/10.13040/IJPSR.0975-8232.9(1).175-81

Alsenz, J., & Kansy, M. (2007). High throughput solubility measurement in drug discovery and development. *Advanced Drug Delivery Reviews*, *59*(7), 546–567. https://doi.org/10.1016/j.addr.2007.05.007

Martins, M. A. R. (2012). *Densities and Speed of Sound in Aqueous Ammonium Sulfate Solutions Containing Glycine or Alanine Chemical Engineering*.

Augustijns, P., Wuyts, B., Hens, B., Annaert, P., Butler, J., & Brouwers, J. (2014). A review of drug solubility in human intestinal fluids: Implications for the prediction of oral absorption. *European Journal of Pharmaceutical Sciences*, *57*, 322–332. https://doi.org/10.1016/j.ejps.2013.08.027

Ayoub, S. S. (2021). Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action. *Temperature*, *8*(4), 351–371. https://doi.org/10.1080/23328940.2021.1886392

Azmi, R., Salamat-Ahangari, R., Soleymani, J., & Jouyban, A. (2016). Solubility of acetaminophen in Ethanol + Water + NaCl mixtures at various temperatures. *Chemical Engineering Communications*, *203*(4), 471–475. https://doi.org/10.1080/00986445.2015.1023301

Shekhawat, P. B., & Pokharkar, V. B. (2017). Understanding peroral absorption: regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles. *Acta Pharmaceutica Sinica B*, *7*(3), 260–280. https://doi.org/10.1016/j.apsb.2016.09.005

Bard, B., Martel, S., & Carrupt, P.-A. (2008). High throughput UV method for the estimation of thermodynamic solubility and the determination of the solubility in biorelevant media. *European Journal of Pharmaceutical Sciences*, *33*(3), 230–240. https://doi.org/10.1016/j.ejps.2007.12.002

Barrett, J. A., Yang, W., Skolnik, S. M., Belliveau, L. M., & Patros, K. M. (2022). Discovery solubility measurement and assessment of small molecules with drug development in mind. *Drug Discovery Today*, *27*(5), 1315–1325. https://doi.org/https://doi.org/10.1016/j.drudis.2022.01.017

Booth, J. J., Abbott, S., & Shimizu, S. (2012a). Mechanism of hydrophobic drug solubilization by small molecule hydrotropes. *Journal of Physical Chemistry B*, *116*(51), 14915–14921. https://doi.org/10.1021/jp309819r

Booth, J. J., Abbott, S., & Shimizu, S. (2012b). Mechanism of Hydrophobic Drug Solubilization by Small Molecule Hydrotropes. *The Journal of Physical Chemistry B*, *116*(51), 14915–14921. https://doi.org/10.1021/jp309819r

Booth, J. J., Omar, M., Abbott, S., & Shimizu, S. (2015). Hydrotrope accumulation around the drug: the driving force for solubilization and minimum hydrotrope concentration for nicotinamide and urea. *Physical Chemistry Chemical Physics*, *17*(12), 8028–8037. https://doi.org/10.1039/C4CP05414H

Bosch, M. E., Sánchez, A. J. R., Rojas, F. S., & Ojeda, C. B. (2006). Determination of paracetamol: Historical evolution. *Journal of Pharmaceutical and Biomedical Analysis*, *42*(3), 291–321. https://doi.org/10.1016/j.jpba.2006.04.007

Bustamante, P., Romero, S., Peña, A., Escalera, B., & Reillo, A. (1998). Enthalpy–entropy compensation for the solubility of drugs in solvent mixtures: Paracetamol, acetanilide, and nalidixic acid in dioxane–water. *Journal of Pharmaceutical Sciences*, *87*(12), 1590–1596. https://doi.org/10.1021/js980149x

Bustamante, P., Romero, S., & Reillo, A. (1995). Thermodynamics of Paracetamol in Amphiprotic and Amphiprotic—aprotic Solvent Mixtures. *Pharmacy and Pharmacology Communications*, *1*(11), 505–507. https://doi.org/10.1111/j.2042-7158.1995.tb00366.x

Chemicalize. (2023). Chemaxon.

Coffman, R. E., & Kildsig, D. O. (1996a). Effect of Nicotinamide and Urea on the Solubility of Riboflavin in Various Solvents. *Journal of Pharmaceutical Sciences*, *85*(9), 951–954. https://doi.org/10.1021/js960012b

Coffman, R. E., & Kildsig, D. O. (1996b). Self-Association of Nicotinamide in Aqueous Solution: Light-Scattering and Vapor Pressure Osmometry Studies. *Journal of Pharmaceutical Sciences*, *85*(8), 848–853. https://doi.org/10.1021/js9505197

Cohen-Adad, R., & Cohen-Adad, M.-T. (2004). Solubility of Solids in Liquids. In *The Experimental Determination of Solubilities* (pp. 257–314). John Wiley & Sons, Ltd. https://doi.org/10.1002/0470867833.ch8

Craig PN (1990) Drug compendium. In: Hansch C, Sammes PG, Taylor JB (eds) *Comprehensive medicinal chemistry. Pergamon, Oxford, p 245*

Das, S., & Paul, S. (2017). Hydrotropic Solubilization of Sparingly Soluble Riboflavin Drug Molecule in Aqueous Nicotinamide Solution. *The Journal of Physical Chemistry B*, *121*(37), 8774–8785. https://doi.org/10.1021/acs.jpcb.7b05774

Dhapte, V., & Mehta, P. (2015). Advances in hydrotropic solutions: An updated review. *St. Petersburg Polytechnical University Journal: Physics and Mathematics*, *1*(4), 424–435. https://doi.org/10.1016/j.spjpm.2015.12.006

Dhinakaran, M., Morais, A. B., & Gandhi, N. N. (2012). Separation of m/p-Aminoacetophenone Using Hydrotropy. *E-Journal of Chemistry*, *9*(4), 2006–2014. https://doi.org/10.1155/2012/504767

Di, L., & Kerns, E. H. (2003). Profiling drug-like properties in discovery research. *Current Opinion in Chemical Biology*, *7*(3), 402–408. https://doi.org/10.1016/S1367-5931(03)00055-3

Frank, H. S., & Franks, F. (1968). Structural Approach to the Solvent Power of Water for Hydrocarbons; Urea as a Structure Breaker. *The Journal of Chemical Physics*, *48*(10), 4746–4757. https://doi.org/10.1063/1.1668057

González, G., Nassar, E. J., & Zaniquelli, M. E. D. (2000). Examination of the Hydrotropic Effect of Sodium p -Toluenesulfonate on a Nonionic Surfactant (C 12 E 6) Solution. *Journal of Colloid and Interface Science*, *230*(2), 223–228. https://doi.org/10.1006/jcis.2000.7073

Graham, G. G., Davies, M. J., Day, R. O., Mohamudally, A., & Scott, K. F. (2013). The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*, *21*(3), 201–232. https://doi.org/10.1007/s10787-013-0172-x

Granberg, R. A., & Rasmuson, Å. C. (1999). Solubility of Paracetamol in Pure Solvents. *Journal of Chemical & Engineering Data*, *44*(6), 1391–1395. https://doi.org/10.1021/je990124v

Granberg, R. A., & Rasmuson, Å. C. (2000). Solubility of paracetamol in binary and ternary mixtures of water + acetone + toluene. *Journal of Chemical and Engineering Data*, *45*(3), 478–483. https://doi.org/10.1021/je9902721

Hajebrahimi, S., & Roosta, A. (2020). Solubility of acetaminophen in aqueous solutions of three natural deep eutectic solvents (NADESs) and individual components of the NADESs. *Journal of Molecular Liquids*, *316*. https://doi.org/10.1016/j.molliq.2020.113867

Hamza, E., & Paruta, A. N. (1985). ENHANCED SOLUBILITY OF PARACETAMOL BY VARIOUS HYDROTROPIC AGENTS. In *DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY* (Vol. 11, Issue 8).

Hojjati, H., & Rohani, S. (2006). Measurement and prediction of solubility of paracetamol in water-isopropanol solution. Part 1. Measurement and data analysis. *Organic Process Research and Development*, *10*(6), 1101–1109. https://doi.org/10.1021/op060073o

Hussain, M. A., Diluccio, R. C., & Maurin, M. B. (1993). Complexation of moricizine with nicotinamide and evaluation of the complexation constants by various methods. *Journal of Pharmaceutical Sciences*, *82*(1), 77–79. https://doi.org/10.1002/jps.2600820117

Hyde, A. M., Zultanski, S. L., Waldman, J. H., Zhong, Y.-L., Shevlin, M., & Peng, F. (2017). General Principles and Strategies for Salting-Out Informed by the Hofmeister Series. *Organic Process Research & Development*, *21*(9), 1355–1370. https://doi.org/10.1021/acs.oprd.7b00197

Ikeda, H., Chiba, K., Kanou, A., & Hirayama, N. (2005). Prediction of Solubility of Drugs by Conductor-Like Screening Model for Real Solvents. *Chemical and Pharmaceutical Bulletin*, *53*(2), 253–255. https://doi.org/10.1248/cpb.53.253

IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.

Jain, N. K., Patel, V. V, & Taneja, L. N. (1988). Hydrotropic solubilization of nifedipine. *Die Pharmazie*, *43*(3), 194—196. http://europepmc.org/abstract/MED/3380863

Jakubowska, E., & Lulek, J. (2021). The application of freeze-drying as a production method of drug nanocrystals and solid dispersions – A review. *Journal of Drug Delivery Science and Technology*, *62*, 102357. https://doi.org/10.1016/J.JDDST.2021.102357

Jiménez, J. A., & Martínez, F. (2006). Thermodynamic study of the solubility of acetaminophen in propylene glycol + water cosolvent mixtures. *Journal of the Brazilian Chemical Society*, *17*(1), 125–134. https://doi.org/10.1590/S0103-50532006000100018

Joncour, R., Duguet, N., Métay, E., Ferreira, A., & Lemaire, M. (2014). Amidation of phenol derivatives: a direct synthesis of paracetamol (acetaminophen) from hydroquinone. *Green Chemistry*, *16*(6), 2997. https://doi.org/10.1039/c4gc00166d

Joshi, S., Dubey, I., Bilaiya, A., Yadav, K., Dorwal, D., & Aditya Parashar, A. P. (2022). A Practical Approach for Solubility Enhancement of Albendazole. *Oriental Journal Of Chemistry*, *38*(1), 215–218. https://doi.org/10.13005/ojc/380129

Kale, S. S., Tamhankar, S. S., & Chaudhari, R. V. (1979). Solubility of cuprous chloride in aqueous hydrochloric acid solutions. *Journal of Chemical & Engineering Data*, *24*(2), 110–111. https://doi.org/10.1021/je60081a016

Kamble, S., Kumbhar, A., Jadhav, S., & Salunkhe, R. (2015). Aza-Micheal Reaction in Glycerol as a Sustainable Hydrotropic Medium. *Materials Today: Proceedings*, *2*(4–5), 1792–1798. https://doi.org/10.1016/j.matpr.2015.07.022

Kim, J. Y., Kim, S., Papp, M., Park, K., & Pinal, R. (2010). Hydrotropic solubilization of poorly water-soluble drugs. *Journal of Pharmaceutical Sciences*, *99*(9), 3953–3965. https://doi.org/10.1002/jps.22241

Klamt, A. (2018). The COSMO and COSMO-RS solvation models. *WIREs Computational Molecular Science*, *8*(1). https://doi.org/10.1002/wcms.1338

Klamt, A., & Schüürmann, G. (1993). COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. *J. Chem. Soc., Perkin Trans. 2*, *5*, 799–805. https://doi.org/10.1039/P29930000799

Lipper, R. A. (1999). How can we optimize selection of drug development candidates from many compounds at the discovery stage? *Mod. Drug Discov. 2, 55–60*.

Lindenberg, M., Kopp, S., & Dressman, J. B. (2004). Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *European Journal of Pharmaceutics and Biopharmaceutics*, *58*(2), 265–278. https://doi.org/10.1016/j.ejpb.2004.03.001

Mehrdad, A., & Miri, A. H. (2016a). Aqueous solubility of acetaminophen in the presence of 1-hexyl-3-methyl imidazolium bromide, ionic liquid as co-solvent. *Fluid Phase Equilibria*, *425*, 51–56. https://doi.org/10.1016/j.fluid.2016.05.012

Mehrdad, A., & Miri, A. H. (2016b). Influence of 1-butyl-3-methyl imidazolium bromide, ionic liquid as co-solvent on aqueous solubility of acetaminophen. *Journal of Molecular Liquids*, *221*, 1162–1167. https://doi.org/10.1016/j.molliq.2016.07.002

Mehrdad, A., Taeb, S., & Ehsani-Tabar, S. (2017). Solubility and thermodynamic properties of acetaminophen in 1-hexyl-4-methylpyridinium bromide and water mixtures. *Physics and Chemistry of Liquids*, *55*(5), 682–695. https://doi.org/10.1080/00319104.2016.1263631

Mehrdad, A., Taeb, S., Ehsani-Tabar, S., & Hossein Miri, A. (2020). Measurement and correlation on solubility of acetaminophen in aqueous solutions of 1-octyl-3-methyl imidazolium bromide, 1-butyl-4-methyl pyridinium bromide and 1-octyl-4-methyl pyridinium bromide. *Journal of Chemical Thermodynamics*, *144*. https://doi.org/10.1016/j.jct.2020.106072

Mehringer, J., & Kunz, W. (2021). Carl Neuberg's hydrotropic appearances (1916). *Advances in Colloid and Interface Science*, *294*, 102476. https://doi.org/10.1016/j.cis.2021.102476

831 KF Coulometer - Instructions for use, (April 2003).

Misra, S. K., & Pathak, K. (2020). Supercritical fluid technology for solubilization of poorly water soluble drugs via micro- and naonosized particle generation. *ADMET and DMPK*. https://doi.org/10.5599/admet.811

Morse HN. (1878) Ueber eine neue Darstellungsmethode der Acetylamidophenole. *Ber Deutscher Chem Ges. 11:232–233.*

Mullins, E., Oldland, R., Liu, Y. A., Wang, S., Sandler, S. I., Chen, C.-C., Zwolak, M., & Seavey, K. C. (2006). Sigma-Profile Database for Using COSMO-Based Thermodynamic Methods. *Industrial & Engineering Chemistry Research*, *45*(12), 4389–4415. https://doi.org/10.1021/ie060370h

Muñoz, M. M., Jouyban, A., & Martínez, F. (2016). Solubility and preferential solvation of acetaminophen in methanol + water mixtures at 298.15 K. *Physics and Chemistry of Liquids*, *54*(4), 515–528. https://doi.org/10.1080/00319104.2015.1121785

Namdev, B., Venkatachalam, S., Jawahar, N., & Chorsiya, A. (2022). A Brief Review on Solubility Enhancement Technique: Hydrotropy. *INDIAN JOURNAL OF PHARMACEUTICAL EDUCATION AND RESEARCH*, *56*(2), 347–355. https://doi.org/10.5530/ijper.56.2.54

Neuberg, C. (1916). Hydrotropische Erscheinungen I. Mitteilung. *Biochem. Z, 26, 107*

Padiyar, A., Agrawal, O. P., Rajpoot, K., & Tekade, R. K. (2020). Hydrotropy, mixed hydrotropy, and mixed solvency as trending concept for solubilization of lipophilic drugs. In *The Future of Pharmaceutical Product Development and Research* (pp. 145–178). Elsevier. https://doi.org/10.1016/B978-0-12-814455-8.00005-0

Patil, A. N., Shinkar, D. M., & Saudagar, R. B. (2017). REVIEW ARTICLE: SOLUBILITY ENHANCEMENT BY SOLID DISPERSION. *International Journal of Current Pharmaceutical Research*, *9*(3), 15. https://doi.org/10.22159/ijcpr.2017.v9i3.19583

Paul, R., Chattaraj, K. G., & Paul, S. (2021). Role of Hydrotropes in Sparingly Soluble Drug Solubilization: Insight from a Molecular Dynamics Simulation and Experimental Perspectives. *Langmuir*, *37*(16), 4745–4762. https://doi.org/10.1021/acs.langmuir.1c00169

Pourkarim, F., Mirheydari, S. N., Martinez, F., & Jouyban, A. (2020). Solubility of acetaminophen in 1-propanol + water mixtures at T = 293.2–313.2 K. *Physics and Chemistry of Liquids*, *58*(4), 456–472. https://doi.org/10.1080/00319104.2019.1611827

Prentis R.A. Lis Y. and Walker S.R (1988). Pharmaceutical innovation by the seven U.K.-owned pharmaceutical companies (1964–1984). *Br. J. Clin. Pharmacol. 25(3), 387–396*.

Prescott, L. F. (2000). Paracetamol: Past, Present and Future. *American Journal of Therapeutics*, *7*(2), 143–148. https://doi.org/10.1097/00045391-200007020-00011

Saleh, A. M., Badwan, A. A., & El-Khordagui, L. K. (1983). A study of hydrotropic salts, cyclohexanol and water systems. *International Journal of Pharmaceutics*, *17*(1), 115–119. https://doi.org/10.1016/0378-5173(83)90024-8

Sales, I., Abranches, Dinis. O., Sintra, T. E., Mattedi, S., Freire, M. G., Coutinho, J. A. P., & Pinho, S. P. (2022). Selection of hydrotropes for enhancing the solubility of artemisinin in aqueous solutions. *Fluid Phase Equilibria*, *562*, 113556. https://doi.org/10.1016/j.fluid.2022.113556

Sanghvi, R., Evans, D., & Yalkowsky, S. H. (2007). Stacking complexation by nicotinamide: A useful way of enhancing drug solubility. *International Journal of Pharmaceutics*, *336*(1), 35–41. https://doi.org/10.1016/j.ijpharm.2006.11.025

Saokham, P., Muankaew, C., Jansook, P., & Loftsson, T. (2018). Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes. *Molecules*, *23*(5), 1161. https://doi.org/10.3390/molecules23051161

Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug Solubility: Importance and Enhancement Techniques. *ISRN Pharmaceutics*, *2012*, 1–10. https://doi.org/10.5402/2012/195727

Sela, T., Lin, X., & Vigalok, A. (2017). Concentrated Aqueous Sodium Tosylate as Green Medium for Alkene Oxidation and Nucleophilic Substitution Reactions. *Journal of Organic Chemistry*, *82*(21), 11609–11612. https://doi.org/10.1021/ACS.JOC.7B01679/SUPPL_FILE/JO7B01679_SI_001.PDF

Shakeel, F., Alanazi, F. K., Alsarra, I. A., & Haq, N. (2013). Solubilization Behavior of Paracetamol in Transcutol–Water Mixtures at (298.15 to 333.15) K. *Journal of Chemical & Engineering Data*, *58*(12), 3551–3556. https://doi.org/10.1021/je4008525

Shekaari, H., Moattar, M. T. Z., & Ghaffari, F. (2015). Solvation properties of acetaminophen in aqueous ionic liquid, 1-hexyl-3-methylimidazolium bromide, solutions at different temperatures. *Journal of Molecular Liquids*, *202*, 86–94. https://doi.org/10.1016/j.molliq.2014.12.015

Shekaari, H., Zafarani-Moattar, M. T., & Ghaffari, F. (2017). Effect of Some Imidazolium-Based Ionic Liquids with Different Anions on the Thermodynamic Properties of Acetaminophen in Aqueous Media at T = 293.15 to 308.15 K. *Journal of Chemical and Engineering Data*, *62*(12), 4093–4107. https://doi.org/10.1021/acs.jced.7b00464

Shekaari, H., Zafarani-Moattar, M. T., & Mokhtarpour, M. (2018a). Experimental determination and correlation of acetaminophen solubility in aqueous solutions of choline chloride based deep eutectic solvents at various temperatures. *Fluid Phase Equilibria*, *462*, 100–110. https://doi.org/10.1016/j.fluid.2018.01.017

Shekaari, H., Zafarani-Moattar, M. T., & Mokhtarpour, M. (2018b). Experimental determination and correlation of acetaminophen solubility in aqueous solutions of choline chloride based deep eutectic solvents at various temperatures. *Fluid Phase Equilibria*, *462*, 100–110. https://doi.org/10.1016/j.fluid.2018.01.017

Silva, S. S., Abranches, D. O., Pinto, A. S., Soares, B. P., Passos, H., Ferreira, A. M., & Coutinho, J. A. P. (2023). Solubility Enhancement of Hydrophobic Compounds in Aqueous Solutions Using Biobased Solvents as Hydrotropes. *Industrial & Engineering Chemistry Research*, *62*(30), 12021–12028. https://doi.org/10.1021/acs.iecr.3c01469

Simamora, P., Alvarez, J. M., & Yalkowsky, S. H. (2001). Solubilization of rapamycin. *International Journal of Pharmaceutics*, *213*(1–2), 25–29. https://doi.org/10.1016/S0378-5173(00)00617-7

Singh, S., Talukdar, M., & Dash, U. N. (2017). Solute-solvent and solute-solute interactions of ibuprofen in aqueous and in aqueous solutions of urea, sodium salicylate and nicotinamide by volumetric and interferometric techniques. *Journal of Molecular Liquids*, *241*, 934–945. https://doi.org/10.1016/j.molliq.2017.06.112

Singh, S., Talukdar, M., & Dash, U. N. (2018a). Studies on molecular interactions in aqueous and aqueous urea systems of paracetamol (N-(4-hydroxyphenyl) ethanamide). *Journal of Molecular Liquids*, *265*, 679–686. https://doi.org/10.1016/j.molliq.2018.05.092

Singh, S., Talukdar, M., & Dash, U. N. (2018b). Ultrasonic studies on paracetamol in aqueous solutions of sodium salicylate and nicotinamide. *Journal of Molecular Liquids*, *249*, 815–824. https://doi.org/10.1016/j.molliq.2017.11.099

Soltanpour, S., & Jouyban, A. (2011). Solubility of acetaminophen and ibuprofen in polyethylene glycol 600, N-methyl pyrrolidone and water mixtures. *Journal of Solution Chemistry*, *40*(12), 2032–2045. https://doi.org/10.1007/s10953-011-9767-2

Somasundaran, P., Celik, M., Goyal, A., & Manev, E. (1984). The Role of Surfactant Precipitation and Redissolution in the Adsorption of Sulfonate on Minerals. *Society of Petroleum Engineers Journal*, *24*(02), 233–239. https://doi.org/10.2118/8263-PA

Soni, K., & Sharma, K. (2021). Eco-friendly Spectrophotometric analysis of Mefenamic acid (poorly water-soluble drug) using the mixed solvency concept. *Indian Journal of Science and Technology*, *14*(28), 2337–2341. https://doi.org/10.17485/IJST/v14i28.476

The United States Pharmacopeia (2007), USP 30-NF 25.

Thimmasetty, J., Ghosh, T., Nagar, S. N., Kamath, S., Seetharaman, S., & Mohamed, A. K. (2020). Enhanced Solubility of Modafinil via Solubilization Techniques. *Journal of Young Pharmacists*, *12*(2), 129–134. https://doi.org/10.5530/jyp.2020.12.26

Ts'o, P. O. P., & Chan, S. I. (1964). Interaction and Association of Bases and Nucleosides in Aqueous Solutions. II. Association of 6-Methylpurine and 5-Bromouridine and Treatment of Multiple Equilibria [2]. *Journal of the American Chemical Society*, *86*(19), 4176–4181. https://doi.org/10.1021/ja01073a054

U.S. Department of Health and Human Services Food and Drug Administration. (2021). *M9 Biopharmaceutics Classification System-Based Biowaivers Guidance for Industry*. https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

Varade, D., Sharma, R., Aswal, V. K., Goyal, P. S., & Bahadur, P. (2004). Effect of hydrotropes on the solution behavior of PEO/PPO/PEO block copolymer L62 in aqueous solutions.

European Polymer Journal, *40*(11), 2457–2464. https://doi.org/10.1016/j.eurpolymj.2004.06.022

Von Mering J. (1893) Beiräge zur Kenntniss der Antipyretica. *Therap. Monatsch*;7:558–577

Warmińska, D., Nowosielski, B., Szewczyk, A., Ruszkowski, J., & Prokopowicz, M. (2021). Effect of choline chloride based natural deep eutectic solvents on aqueous solubility and thermodynamic properties of acetaminophen. *Journal of Molecular Liquids*, *323*. https://doi.org/10.1016/j.molliq.2020.114834

Yalkowsky, S. H., He, Y., & Jain, P. (2016). *Handbook of Aqueous Solubility Data*. CRC Press. https://doi.org/10.1201/EBK1439802458

Yang, W., Gadgil, P., Krishnamurthy, V. R., Landis, M., Mallick, P., Patel, D., Patel, P. J., Reid, D. L., & Sanchez-Felix, M. (2020). The Evolving Druggability and Developability Space: Chemically Modified New Modalities and Emerging Small Molecules. *The AAPS Journal*, *22*(2), 21. https://doi.org/10.1208/s12248-019-0402-2

Appendix A. pH data

Table A. 1. Ternary solutions containing acetaminophen, hydrotrope and water measured pH at 298.2K and hydrotrope mass fraction of 0.2.

Compound	pH
Ethanol	6.3
1,2-propanediol	6.4
Glycerol	6.4
NaTos	4.3
NH4SCN	5.2
NaBenS	5.2
NaCapry	9.4
(NH4)2SO4	5.3
NaSCN	6.4
NaSO4	6.7
NaSal	6.8
ChCl	5.6
ChBr	5.6
[BMIm]Ac	7.0
Acetone	5.9
Urea	5.7

Table A. 2. Acetaminophen speciation data as function of solution pH

pH	Molecular	Ionic species 1	Ionic species 2
0	100%	0%	0%
0.1	100%	0%	0%
0.2	100%	0%	0%
0.3	100%	0%	0%
0.4	100%	0%	0%
0.5	100%	0%	0%
0.6	100%	0%	0%
0.7	100%	0%	0%
0.8	100%	0%	0%
0.9	100%	0%	0%
1	100%	0%	0%
1.1	100%	0%	0%
1.2	100%	0%	0%
1.3	100%	0%	0%
1.4	100%	0%	0%
1.5	100%	0%	0%
1.6	100%	0%	0%
1.7	100%	0%	0%
1.8	100%	0%	0%
1.9	100%	0%	0%
2	100%	0%	0%
2.1	100%	0%	0%
2.2	100%	0%	0%
2.3	100%	0%	0%
2.4	100%	0%	0%
2.5	100%	0%	0%
2.6	100%	0%	0%
2.7	100%	0%	0%
2.8	100%	0%	0%
2.9	100%	0%	0%
3	100%	0%	0%
3.1	100%	0%	0%
3.2	100%	0%	0%
3.3	100%	0%	0%
3.4	100%	0%	0%
3.5	100%	0%	0%
3.6	100%	0%	0%
3.7	100%	0%	0%
3.8	100%	0%	0%
3.9	100%	0%	0%
4	100%	0%	0%
4.1	100%	0%	0%
4.2	100%	0%	0%
4.3	100%	0%	0%
4.4	100%	0%	0%
4.5	100%	0%	0%
4.6	100%	0%	0%
4.7	100%	0%	0%
4.8	100%	0%	0%
4.9	100%	0%	0%
5	100%	0%	0%
5.1	100%	0%	0%
5.2	99.99%	0.01%	0%
5.3	99.99%	0.01%	0%
5.4	99.99%	0.01%	0%
5.5	99.99%	0.01%	0%

5.6	99.99%	0.01%	0%	9.9	26.83%	73.17%	0%
5.7	99.98%	0.02%	0%	10	22.56%	77.44%	0%
5.8	99.98%	0.02%	0%	10.1	18.79%	81.21%	0%
5.9	99.97%	0.03%	0%	10.2	15.53%	84.47%	0%
6	99.97%	0.03%	0%	10.3	12.74%	87.26%	0%
6.1	99.96%	0.04%	0%	10.4	10.39%	89.61%	0%
6.2	99.95%	0.05%	0%	10.5	8.44%	91.56%	0%
6.3	99.93%	0.07%	0%	10.6	6.82%	93.18%	0%
6.4	99.91%	0.09%	0%	10.7	5.49%	94.51%	0%
6.5	99.89%	0.11%	0%	10.8	4.41%	95.59%	0%
6.6	99.86%	0.14%	0%	10.9	3.54%	96.46%	0%
6.7	99.83%	0.17%	0%	11	2.83%	97.17%	0%
6.8	99.78%	0.22%	0%	11.1	2.26%	97.74%	0%
6.9	99.73%	0.27%	0%	11.2	1.80%	98.20%	0%
7	99.66%	0.34%	0%	11.3	1.44%	98.56%	0%
7.1	99.57%	0.43%	0%	11.4	1.15%	98.85%	0%
7.2	99.46%	0.54%	0%	11.5	0.09%	99.91%	0%
7.3	99.32%	0.68%	0%	11.6	0.07%	99.93%	0%
7.4	99.15%	0.85%	0%	11.7	0.06%	99.94%	0%
7.5	98.93%	1.07%	0%	11.8	0.05%	99.95%	0%
7.6	98.65%	1.35%	0%	11.9	0.37%	99.63%	0%
7.7	98.31%	1.69%	0%	12	0.29%	99.71%	0%
7.8	97.88%	2.12%	0%	12.1	0.23%	99.77%	0%
7.9	97.35%	2.65%	0%	12.2	0.18%	99.82%	0%
8	96.68%	3.32%	0%	12.3	0.15%	99.85%	0%
8.1	95.86%	4.14%	0%	12.4	0.12%	99.87%	0.010%
8.2	94.84%	5.16%	0%	12.5	0.09%	99.90%	0.010%
8.3	93.59%	6.41%	0%	12.6	0.07%	99.92%	0.010%
8.4	92.06%	7.94%	0%	12.7	0.06%	99.93%	0.010%
8.5	90.21%	9.79%	0%	12.8	0.05%	99.94%	0.010%
8.6	87.98%	12.02%	0%	12.9	0.04%	99.94%	0.020%
8.7	85.32%	14.68%	0%	13	0.03%	99.95%	0.020%
8.8	82.20%	17.80%	0%	13.1	0.02%	99.95%	0.030%
8.9	78.58%	21.42%	0%	13.2	0.02%	99.94%	0.040%
9	74.45%	25.55%	0%	13.3	0.01%	99.95%	0.040%
9.1	69.83%	30.17%	0%	13.4	0.01%	99.93%	0.060%
9.2	64.77%	35.23%	0%	13.5	0.01%	99.92%	0.070%
9.3	59.35%	40.65%	0%	13.6	0.01%	99.90%	0.090%
9.4	53.70%	46.30%	0%	13.7	0.01%	99.88%	0.110%
9.5	47.95%	52.05%	0%	13.8	0.00%	99.86%	0.140%
9.6	42.26%	57.74%	0%	13.9	0.00%	99.82%	0.180%
9.7	36.76%	63.24%	0%	14	0.00%	99.78%	0.220%
9.8	31.59%	68.41%	0%				

Appendix B. Solubility data.

Table B. 1. Acetaminophen measured solubility aqueous solubility at 298.2K in different hydrotropic systems.

Ethanol			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.47	0.15	1.41
0.1	2.80	0.47	1.60
0.2	6.00	0.39	3.43
0.5	33.99	2.10	19.45
0.7	62.27	2.78	35.63
0.8	73.57	3.03	42.09
0.85	72.27	2.10	41.35
0.9	71.08	1.40	40.67
1	49.18	0.83	28.14

1,2-propanediol			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	1.87	0.04	1.07
0.1	2.22	0.02	1.27
0.2	3.23	0.06	1.85

Glycerol			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	1.68	0.11	0.96
0.1	1.81	0.09	1.04
0.2	2.29	0.07	1.31

Acetone			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.86	0.05	1.64
0.1	4.56	0.04	2.61
0.2	9.65	0.05	5.52

Urea			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.1	2.71	0.19	1.55
0.2	3.59	0.13	2.05
0.4	6.15	0.85	3.52

ChCl			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	1.80	0.04	1.03
0.1	2.45	0.06	1.40
0.2	3.59	0.15	2.06

ChBr			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.00	0.01	1.14
0.1	2.49	0.04	1.43
0.2	3.68	0.09	2.10

$(NH_4)_2SO_4$			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.025	1.37	0.01	0.78
0.05	1.225965	0.026206	0.70
0.1	0.86	0.05	0.49
0.2	0.52	0.00	0.30

Na_2SO_4			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	1.06	0.12	0.60
0.1	0.67	0.05	0.38
0.2	0.28	0.02	0.16

NaSal			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.55	0.01	1.46
0.1	3.47	0.07	1.99
0.2	5.45	0.13	3.12

NaTOS			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	3.51	0.37	2.01
0.1	4.11	0.13	2.35
0.2	5.55	0.26	3.17

NH_4SCN			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.3589	0.064179	1.35
0.1	3.229889	0.10	1.85
0.2	4.7956	0.044773	2.74

NaBS			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	1.8966	0.042366	1.09
0.1	2.0958	0.079607	1.20
0.2	2.2305	0.047023	1.28

NaSCN			
w	**$10^3 x_1$**	**Std.**	***S*/*S*₀**
0.05	2.055769	0.16	1.18
0.1	2.72102	0.02	1.56

0.2	4.295794	0.28	2.46

NaCapry			
w	**$10^3 x_1$**	**Std.**	***S*/*S*$_0$**
0.05	2.72	0.10	1.56
0.1	4.37	0.05	2.50
0.2	3.33	0.26	1.91

[BMIm][Ac]			
w	**$10^3 x_1$**	**Std.**	***S*/*S*$_0$**
0.02	1.86	0.04	1.06
0.05	2.76	0.12	1.58
0.1	4.89	0.05	2.80

Appendix C. Sigma-profile data

Table C. 1. Computed sigma-profile for hydrotropes' molecules used in this work.

	Water	**Acetaminophen**	**Ethanol**	**1,2-propanediol**	**Glycerol**	**Acetone**	**Urea**	**ChCl**	**ChBr**	**$(NH_4)_2SO_4$**	**Na_2SO_4**	**NaSal**	**NaTOS**	**NH_4SCN**	**NaSCN**	**[BMIm][Ac]**
σ [e.Å^{-2}]	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$
-0.030	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
-0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
-0.028	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
-0.027	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	8.095	0.000	8.095	0.000	0.000	0.000
-0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	17.772	5.710	17.772	0.000	5.710	0.000
-0.025	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	11.257	15.889	11.257	0.000	15.889	0.000
-0.024	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.021	1.581	14.648	1.581	0.021	14.648	0.000
-0.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.329	0.000	4.469	0.000	0.329	4.469	0.000
-0.022	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	2.286	0.000	0.000	0.000	2.286	0.000	0.000
-0.021	0.000	0.165	0.000	0.000	0.000	0.000	0.000	0.000	0.000	10.282	0.000	0.000	0.000	10.282	0.000	0.000
-0.020	0.000	0.690	0.030	0.004	0.042	0.000	0.000	0.046	0.046	17.324	0.000	0.000	0.000	17.324	0.000	0.000
-0.019	0.049	1.179	0.239	0.190	0.323	0.000	0.003	0.367	0.367	11.767	0.000	0.000	0.000	11.767	0.000	0.000
-0.018	0.452	1.531	0.844	0.769	0.951	0.000	0.283	1.053	1.053	3.706	0.000	0.000	0.000	3.706	0.000	0.000
-0.017	1.723	2.279	1.202	1.196	1.368	0.000	1.522	1.413	1.413	2.115	0.000	0.000	0.000	2.115	0.000	0.046
-0.016	2.841	2.719	0.871	1.131	1.440	0.000	3.686	1.142	1.142	1.968	0.000	0.000	0.000	1.968	0.000	0.584
-0.015	2.570	2.040	0.840	1.331	1.890	0.000	4.885	0.982	0.982	1.118	0.000	0.000	0.000	1.118	0.000	1.746
-0.014	2.223	1.127	1.160	1.843	2.454	0.000	4.661	1.406	1.406	0.322	0.000	0.000	0.000	0.322	0.000	2.916
-0.013	2.446	0.815	1.067	1.957	2.288	0.000	4.633	2.092	2.092	0.019	0.000	0.000	0.000	0.019	0.000	3.962
-0.012	2.258	1.106	0.666	1.554	1.711	0.000	4.302	4.388	4.388	0.000	0.000	0.000	0.000	0.000	0.000	5.330
-0.011	1.486	1.727	0.391	1.021	1.469	0.000	3.002	10.241	10.241	0.000	0.000	0.000	0.000	0.000	0.000	6.872
-0.010	0.658	2.422	0.459	0.771	1.568	0.000	1.893	17.398	17.398	0.000	0.000	0.000	0.037	0.000	0.000	9.482
-0.009	0.466	3.931	0.650	0.906	1.859	0.473	1.940	20.611	20.611	0.000	0.000	0.100	0.713	0.000	0.000	12.858
-0.008	0.854	6.599	0.702	1.282	2.748	3.084	2.442	18.425	18.425	0.000	0.000	1.105	2.917	0.000	0.000	13.143
-0.007	0.935	8.916	1.686	2.303	5.792	7.612	1.970	14.454	14.454	0.000	0.000	3.497	5.860	0.000	0.000	12.392
-0.006	0.648	9.512	5.594	5.461	10.388	10.909	1.230	12.612	12.612	0.000	0.000	5.803	8.186	0.000	0.000	15.244
-0.005	0.575	8.464	9.959	10.056	11.883	10.645	1.159	13.168	13.168	0.000	0.000	6.004	9.524	0.000	0.000	21.070
-0.004	0.464	7.481	10.162	12.079	8.931	8.034	1.158	10.899	10.899	0.000	0.000	4.702	8.990	0.000	0.000	25.055
-0.003	0.151	7.551	7.674	9.950	5.761	6.441	1.266	5.223	5.223	0.000	0.000	4.005	7.165	0.000	0.000	22.975
-0.002	0.284	7.888	6.073	6.894	4.823	6.535	1.518	1.553	1.553	0.000	0.000	3.909	6.241	0.000	0.000	18.486

-0.001	0.693	8.934	5.374	5.772	4.604	8.061	1.755	0.739	0.739	0.000	0.000	3.702	6.315	0.000	0.000	14.388
0.000	0.568	9.376	5.270	5.738	3.732	9.279	2.403	0.768	0.768	0.000	0.000	3.779	7.605	0.067	0.067	11.706
0.001	0.259	8.028	5.377	5.944	2.785	6.587	3.022	0.742	0.742	0.000	0.000	4.628	9.066	0.216	0.216	11.239
0.002	0.323	8.727	3.923	5.353	2.604	2.576	3.024	0.668	0.668	0.000	0.000	6.096	8.269	0.811	0.812	11.255
0.003	0.623	11.212	1.826	3.204	2.558	1.050	2.672	0.753	0.753	0.000	0.000	8.228	7.740	1.489	1.490	10.190
0.004	0.924	11.803	0.857	1.622	2.121	0.500	2.440	0.902	0.902	0.000	0.000	10.409	10.214	1.073	1.071	6.230
0.005	0.919	11.070	0.808	1.421	1.929	0.296	2.347	0.747	0.747	0.000	0.000	11.351	11.657	0.878	0.886	2.405
0.006	0.836	8.112	1.092	1.636	1.952	0.580	1.989	0.450	0.450	0.000	0.000	12.021	7.857	3.962	3.989	1.366
0.007	0.832	3.438	0.930	1.620	1.945	0.567	1.628	0.673	0.673	0.000	0.000	11.035	2.934	8.102	8.072	1.175
0.008	0.662	1.746	0.628	1.629	2.416	0.760	1.318	1.001	1.001	0.000	0.000	6.495	1.290	7.061	7.019	0.883
0.009	0.787	2.210	0.613	1.766	2.791	1.286	0.952	1.032	1.032	0.000	0.000	2.637	1.241	3.613	3.580	0.658
0.010	0.957	2.127	0.575	1.521	2.500	1.473	1.619	1.002	1.002	0.044	0.044	1.686	1.012	4.662	4.671	0.781
0.011	0.620	2.668	0.665	1.460	2.479	1.874	3.031	0.740	0.740	0.266	0.266	2.071	0.850	7.322	7.507	1.170
0.012	0.632	3.490	1.085	1.834	2.745	3.242	2.926	0.617	0.617	0.549	0.549	3.049	1.273	9.121	9.102	1.079
0.013	1.229	3.751	1.587	2.227	3.093	3.796	1.777	0.732	0.732	0.768	0.768	3.542	3.486	10.410	10.198	0.504
0.014	1.527	4.142	1.622	2.556	3.544	2.544	1.723	0.738	0.738	1.379	1.379	3.276	6.526	8.352	8.378	0.409
0.015	1.484	3.605	1.462	2.716	3.783	1.719	2.692	0.729	0.729	2.313	2.313	3.733	8.546	5.532	5.609	0.807
0.016	1.504	1.977	1.592	2.760	3.833	1.594	3.674	0.616	14.449	2.470	2.470	5.350	11.198	4.393	4.390	1.179
0.017	1.689	1.081	1.516	2.616	3.089	0.909	3.868	1.152	28.795	3.301	3.301	6.233	13.892	3.571	3.571	1.789
0.018	2.070	0.715	0.919	1.728	1.524	0.215	2.993	14.106	15.536	4.501	4.501	5.480	11.392	3.175	3.174	3.674
0.019	1.846	0.261	0.257	0.561	0.349	0.010	1.539	25.557	0.824	6.036	6.036	4.021	4.293	2.175	2.176	6.691
0.020	0.851	0.038	0.002	0.051	0.011	0.000	0.403	12.354	0.000	8.898	8.898	2.700	0.271	0.670	0.671	7.778
0.021	0.152	0.000	0.000	0.000	0.000	0.000	0.022	0.000	0.000	12.505	12.505	2.318	0.000	0.039	0.039	6.232
0.022	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	20.217	20.217	2.208	0.000	0.000	0.000	4.790
0.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	21.361	21.361	1.185	0.000	0.000	0.000	3.460
0.024	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	9.600	9.600	0.261	0.000	0.000	0.000	2.046
0.025	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.108	1.108	0.039	0.000	0.000	0.000	1.602
0.026	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.386
0.027	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.083
0.028	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.804
0.029	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.291
0.030	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table C. 2. Computed sigma-profile for hydrotropes used to enhance ACP solubility at literature and used for comparison purposes.

	Methanol	**[HMIm]Br**	**[BMIm]Br**	**[OMIm]Br**	**[HMPyr]Br**	**[OMPyr]Br**
σ [e.Å^{-2}]	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$	$p(\sigma)$
-0.030	0.000	0.000	0.000	0.000	0.000	0.000
-0.029	0.000	0.000	0.000	0.000	0.000	0.000
-0.028	0.000	0.000	0.000	0.000	0.000	0.000
-0.027	0.000	0.000	0.000	0.000	0.000	0.000
-0.026	0.000	0.000	0.000	0.000	0.000	0.000
-0.025	0.000	0.000	0.000	0.000	0.000	0.000
-0.024	0.000	0.000	0.000	0.000	0.000	0.000
-0.023	0.000	0.000	0.000	0.000	0.000	0.000
-0.022	0.000	0.000	0.000	0.000	0.000	0.000
-0.021	0.000	0.000	0.000	0.000	0.000	0.000
-0.020	0.000	0.000	0.000	0.000	0.000	0.000
-0.019	0.034	0.000	0.000	0.000	0.000	0.000
-0.018	0.306	0.000	0.000	0.000	0.000	0.000
-0.017	0.997	0.050	0.046	0.046	0.000	0.000
-0.016	1.354	0.572	0.584	0.562	0.000	0.000
-0.015	1.016	1.672	1.746	1.695	0.132	0.175
-0.014	0.892	2.893	2.916	2.860	1.338	1.435
-0.013	1.081	4.065	3.962	3.984	3.912	3.922
-0.012	1.021	5.374	5.330	5.446	6.138	6.082
-0.011	0.610	6.806	6.872	6.780	7.911	7.818
-0.010	0.322	9.426	9.482	9.059	9.400	9.283
-0.009	0.503	12.817	12.858	12.636	9.866	9.967
-0.008	0.761	13.253	13.143	13.466	11.849	12.044
-0.007	0.988	12.579	12.392	12.764	15.204	15.152
-0.006	2.515	14.595	14.903	14.736	15.955	15.733
-0.005	5.581	18.536	19.403	18.553	17.717	17.404
-0.004	7.146	22.304	21.877	23.248	24.035	24.821
-0.003	5.975	23.231	18.997	27.096	29.036	32.632
-0.002	4.774	22.248	14.448	29.052	29.396	35.924
-0.001	4.338	19.503	11.341	27.409	24.738	32.725
0.000	3.655	15.170	9.333	21.920	16.455	23.263
0.001	2.883	12.080	8.338	16.962	10.275	15.060
0.002	1.995	10.128	6.942	13.652	8.526	12.056
0.003	1.419	7.807	4.494	10.691	7.387	10.274
0.004	1.276	3.866	1.508	6.223	3.698	5.915
0.005	1.040	0.685	0.015	1.609	0.613	1.426
0.006	0.831	0.000	0.000	0.000	0.000	0.000
0.007	0.720	0.000	0.000	0.000	0.000	0.000
0.008	0.654	0.000	0.000	0.000	0.000	0.000
0.009	0.681	0.000	0.000	0.000	0.000	0.000
0.010	0.615	0.000	0.000	0.000	0.000	0.000
0.011	0.595	0.000	0.000	0.000	0.000	0.000
0.012	1.028	0.000	0.000	0.000	0.000	0.000
0.013	1.284	0.000	0.000	0.000	0.000	0.000
0.014	1.181	0.000	0.000	0.000	0.000	0.000
0.015	1.337	0.000	0.000	0.000	0.000	0.000
0.016	1.676	13.833	13.833	13.833	13.833	13.833

0.017	1.876	28.491	28.491	28.491	28.491	28.491
0.018	1.601	15.481	15.481	15.481	15.481	15.481
0.019	0.869	0.824	0.824	0.824	0.824	0.824
0.020	0.224	0.000	0.000	0.000	0.000	0.000
0.021	0.000	0.000	0.000	0.000	0.000	0.000
0.022	0.000	0.000	0.000	0.000	0.000	0.000
0.023	0.000	0.000	0.000	0.000	0.000	0.000
0.024	0.000	0.000	0.000	0.000	0.000	0.000
0.025	0.000	0.000	0.000	0.000	0.000	0.000
0.026	0.000	0.000	0.000	0.000	0.000	0.000
0.027	0.000	0.000	0.000	0.000	0.000	0.000
0.028	0.000	0.000	0.000	0.000	0.000	0.000
0.029	0.000	0.000	0.000	0.000	0.000	0.000
0.030	0.000	0.000	0.000	0.000	0.000	0.000