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Understanding the Solubility behaviour of Ibuprofen and Xylitol in Natural Deep Eutectic Systems through Hansen Solubility Parameters and Physicochemical Properties

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ABSTRACT

Most of the recent studies have been praising the peculiar ability of deep eutectic systems (DES), especially the natural-based ones (designated by NADES), in dissolving a wide variety of compounds. Despite their remarkable physicochemical properties, it is still true that little is known about the factors that would help to comprehend their interesting behaviour when they are used as solvents. Hence, it is important to gather as many tools as possible that can be useful for understanding it. First, the affinity degrees between the two selected compounds (Ibuprofen and Xylitol) and the various NADES, were analysed using Hansen Solubility Parameters (HSPs), which confirmed to be a good tool for screening good and bad NADES for solubilising Ibuprofen and Xylitol. Although, in general, the empirical models (EM) such as the one proposed by Hoftyzer-Van Krevelen and Fedors (HKF) and Yamamoto (Ymt) performed better than the semi-empirical models (SEM), when it came to assessing affinity, it was found that this actually depends on the type of assessment carried out, i.e., if it is in 1- or 2-dimension. Furthermore, it was also found that, except for the dispersive parameter (δ_d), all the others play a significant role in the interaction between the two compounds and NADES, especially the total solubility parameter (δ_t). Finally, the correlations between a set of physiochemical properties of NADES and the solubility data were evaluated in this work where it was possible to conclude that surface tension, density and molar volume are those that present the highest contribution for the variations in the solubility.

1. Introduction

When two or more organic compounds extracted directly from natural resources are combined in a specific molar ratio and heated, form a liquid with very special characteristics named Natural Deep Eutectic Systems (NADES) [1,2]. Although this recipe seems so simple, there are actually, a lot of factors, that can affect this process, such as the stirring time and temperature; the right choice of the components and the affinity between them; the hydrogen bond available; or the presence of highly hygroscopic components [3–5]. These may not only influence their stability but also the way these systems will interact with solutes. In fact, focusing on the hydrogen bonds, they are widely described as one of the most important intermolecular forces involved in the formation of NADES; however, it is still very difficult to predict, based solely on the molecular structure of the starting materials, which components and molar ration can form a specific NADES or even how these systems interact with external compounds. Most of the NADES currently formulated have been found through trial and error, which can represent a huge cost for companies or research groups due to the waste of reagents [6]. Furthermore, given that NADES are classified as design solvents with up to 10^6 possible combinations [7], a lot of this waste could be actually avoided if it were possible to predict which components were most likely to form a eutectic system.

A good understanding of the mechanisms underlying the formation of eutectic systems may be the key to better understanding not only their special physicochemical characteristics but also their behaviour as a solvent [5,6,8]. In fact, the way in which NADES act as a solvent, i.e. their good solubilisation capacity, has attracted more and more researchers to this field [4,9–11]. However, regarding this topic, there are unanswered questions, such as: what are the physiochemical properties of NADES that the most contribute to such behaviour? A very recent study has demonstrated that the interaction forces present in eutectic mixtures, such as hydrogen bonding and π–π stacking, can contribute to enhance the solubilization capacity by promoting effectively the

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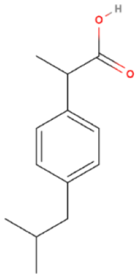
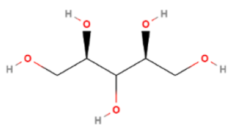
Table 1
Molecular structure and physicochemical properties of Ibuprofen and Xylitol.

Compound	Structure	Mw (g/mol)	ρ (g/cm^3)	V_m (cm^3/mol)	n_D	ε′	μo	σ • (mN/m)	Ref
Ibuprofen		206.28	1.119^c	184.34	1.5220^c	2.99*	0.95*	35.76$^\Psi$	[30]^c
Xylitol		152.12	1.500^d	110.93	1.5710^d	3.96*	1.03*	79.85$^\Psi$	[31]^d

* Calculated using the procedures explained in section 2.2.
Ψ Estimated using values, using the molar Parachor method [28] (**The group`s contribution used can be seen in Tables S.13 and S.14**).

dissolution of complex components in essential oils, facilitating, consequently, the formation of stable nano-formations in aqueous conditions [12]. Additionally, besides the hydrogen bonding ability, other physicochemical properties of eutectic systems such as viscosity and polarity have also been pointed out as some of the most important parameters allow to understand the enhance of the solubilisation capacity of bioactive compounds in these mixtures [13]. In fact, both these relationships between this peculiar characteristic of NADES and other related physicochemical properties as well as the prediction on the solubility of different compounds in these systems have been more and more explored, mostly for eventual applications in the pharmaceutical field. For example, the most recent work of M. A. Nica *et al.* [14] studied and discussed the influence of different physicochemical properties (e.g., density, rheology, surface tension, etc) on the ability of various eutectic systems to work as drug delivery and concluded that the enhancing on the solubility of compounds such as Ibuprofen and Mefenamic acid in NADES can be affected by the systems viscosity and surface tension. On the other hand, the current lack of information on some specific NADES properties has led some researchers to use computational tools such as Hansen Solubility Parameters (HSPs), COnductor like Screening MOdel for Real Solvents (COSMO-RS) and machine learning to predict and understand solubility behaviour [15–17].

Our latest works [18,19], have not only provided a very comprehensive study on the physicochemical properties of NADES but also their application in the set of semi-empirical models in order to estimate the HSPs. However, these studies alone are not sufficient to understand the role of the physicochemical properties of NADES in the solubilisation of compounds, nor to determine which of the current HSPs models are most suitable for use in NADES. Therefore, this work aimed two main objectives: first, determine the solubility of two chosen model compounds, a polar (Xylitol) and a non-polar (Ibuprofen), in various different NADES combinations; and second, correlate these data with the results of the various HSPs and some NADES' physicochemical properties (density, molar volume, dielectric constant, viscosity, refractive index, surface tension, dielectric constant, polarity and Kamlet-Taft parameters (KTPs)), obtained in this previous work. The idea here was to understand, through statistical correlations, which solubility parameters, affinity degree models or physicochemical properties explain better the acquired solubility data of these two distinct compounds in NADES.

2. Materials and methods

2.1. Chemicals

The chemical compounds used in this work, namely, Ibuprofen (CAS: 15687-27-1; Mass fraction (purity): 0.99) and Xylitol (CAS: 87-99-0; Mass fraction (purity): ≥0.99), were acquired from Alfa Aesar and Merk, respectively. These were chosen as solutes in this study after considering the following factors:

- The researching Interest: Although both compounds are commonly used as eutectic systems components [20–23], the first factor of choice was in fact explore the solubility of compounds that were not components of any of the studied NADES, in order to make this study less complex and be easier to understand the solubility behaviour.
- Analytical methods: As is well known, not all the equipment or methodologies used to analyse normal solvents work effectively in eutectic mixtures. However, the solubility of Ibuprofen in NADES has been widely studied and so there are currently several protocols that could be used or adapted for this specific study. On the other hand, since the vast majority of hydrophilic eutectic systems have sugars in their composition, Xylitol was suggested here because of its easy identification by the HPLC method.
- Polar and non-polar nature: By studying the solubility of both compound with a polar (Xylitol) and non-polar (Ibuprofen) character, it is possible to have a more comprehensive study about the real efficiency of HSPs in the eutectic mixtures.
- Structural complexity: As discussed in the previous work [19], the structural complexity of molecules can be one of greatest limitations for an eventual use of the studied empirical models, based on the group contribution (e.g., Hoftyzer and Van Krevelen), in the eutectic systems field. Therefore, by varying the type and degree of complexity, it may be enabled evaluate this limitation and its extension.
- Theoretical models validation: By using these distinct compounds, it is also possible to evaluate and validate the applicability of the theoretical models in NADES field and understand their limitations.

Some of their physicochemical properties can be seen in Table 1. On the other hand, an extensive list of NADES and physicochemical parameters described in the previous work [19] was used in this study, and this can be seen in the supplementary information (SI), in Table S.1.

Table 2
List of Empirical and Semi-Empirical Models used to estimate the HSPs of Ibuprofen and Xylitol.

Solubility Parameter		Theoretical Model	Abb.	Ref.
Dispersive (δ_d)	**SEM**	Koenhen and Smolders	KoS	[32]
		Yamamoto-Abbott-Hansen	YAH	[33]
	EM	Stefanis and Panayiotou	StP	[34,35]
		Hoftyzer and Van Krevelen	HK	[36,37]
		Hoftyzer-Van Krevelen and Fedors	HKF	[36,37]
		Yamamoto	Ymt	[33,38]
Polar (δ_p)	**SEM**	Böttcher	Böt	[39,40]
		Hansen and Beerbower	HB	[40,41]
		Beerbower	Bb	[32]
		Koenhen and Smolders	KoS′	[32]
	EM	Stefanis and Panayiotou	StP	[34,35]
		Hoftyzer and Van Krevelen	HK	[36,37]
		Hoftyzer-Van Krevelen and Fedors	HKF	[36,37]
		Yamamoto	Ymt	[33,38]
Hydrogen Bond (δ_h)	**SEM** *	"Hansen-This Work" (Hans-TW)	Hans *	[19,42]
		(D1.1.3)	(D1)	[19]
		(D2.1.3)	(D2)	
		(D3.1.3)	(D3)	
		(D4.1.3)	(D4)	
		(D5.1.3)	(D5)	
		(D6.1.3)	(D6)	
		(D7.1.3)	(D7)	
	EM	Stefanis and Panayiotou	StP	[34,35]
		Hoftyzer and Van Krevelen	HK	[36,37]
		Hoftyzer-Van Krevelen and Fedors	HKF	[36,37]
		Yamamoto	Ymt	[33,38]
Total (δ_t)	**SEM**	Reid, Prausnitz and Poling	RPP	[43]
		Kabo's	Kab	[44]
		Beerbower	Bb′	[32]
		Hildebrand and Scott and Lee	HSL	[28]
		Sheldon	She	[45]
		Jarray	Jar	[46]
		Gordon	Gor	[47]
	EM	Stefanis and Panayiotou	StP	[34,35]
		Hoftyzer and Van Krevelen	HK	[36,37]
		Hoftyzer-Van Krevelen and Fedors	HKF	[36,37]
		Yamamoto	Ymt	[33,38]
		Hoy	Hoy	[48]

* $\delta_{h\ (\mathbf{D1.1.3})} = \delta_{t\ (\mathbf{RPP})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D2.1.3})} = \delta_{t\ (\mathbf{Kab})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D3.1.3})} = \delta_{t\ (\mathbf{Bb'})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D4.1.3})} = \delta_{t\ (\mathbf{HSL})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D5.1.3})} = \delta_{t\ (\mathbf{Bb'})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D6.1.3})} = \delta_{t\ (\mathbf{Jar})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$; $\delta_{h\ (\mathbf{D7.1.3})} = \delta_{t\ (\mathbf{Gor})} - (\delta_{d\ (KoS)} + \delta_{h\ (Bb)})$.

2.2. Dielectric constant and dipole moment

The dielectric constants and dipole moments of Ibuprofen and Xylitol were determined using the same methodology described in the previous work [18], that is, using the Dielectric Relaxation Spectroscopy (DRS) to assess the dielectric constants of each compound and then using it, along with their respective refractive index, to estimate dipole moment (using Onsager method [24,25], μ_O). However, in this case, for each of them, thin tablets (thickness of 0.343 ± 0.006 mm and 0.352 ± 0.012 mm, respectively) were prepared from their powder and then put between the two Au electrodes of 10 mm diameters, without using silicon spacers. The analysis was then performed at room temperature (299.15 K ± 0.5 K and 298.15 K ± 0.5 K, respectively), and the data was obtained in the frequency range from 10^{-1} Hz to 10^{-6} Hz (**see** Table S.2**, in SI**).

2.3. Fourier Transform Infrared (FTIR) spectroscopy

The FTIR spectrums of the studied solutes (Ibuprofen and Xylitol) were obtained using a PerkinElmer Spectrum Two equipment (Waltham, MA, USA) with an attenuated total reflection (ATR) in the Transmittance mode and resolution of 4 cm^{-1}. The spectrums, analysed in a wavenumber range of 400–4000 cm^{-1}, can be seen in the supplementary information (Fig. S.1), along with the wavenumber values used in the prediction of the δ_h parameter (Table S.3).

2.4. Solubility measurement

The solubility of Ibuprofen and Xylitol in NADES was quantified by high-pressure liquid chromatography (HPLC), following the protocols described by P. Joana *et al.* [26], and L. Ascar *et al.* [27], with some adaptations. In the case of ibuprofen, each system was initially saturated with an excess of ibuprofen and allowed to stir at 298.15 K for 24 h. For the hydrophobic systems, the supernatant was collected with hydrophobic syringe filters PTFE (pore size: 0.45 μ m and diameter: 4 mm), non-sterile, from Laborspirit, and the filtrated transferred to thread HPLC vials with Label (2 mL, clear glass, 12 × 32 mm). In the case of hydrophilic systems, due to their high viscosity, before filtration, the samples were diluted in water at a 1:1 (w/w) ratio, while hydrophobic systems were diluted 1000 × with acetonitrile. For the chromatographic separation, a Dionex (Summit model) equipped with a column Agilent Eclipse XDB – C18 (250 mm × 4.6 mm, and particle size of 5 μm) was used. The analysis was carried out at room temperature, using a mixture of buffer K_2HPO_4 pH 6.8 (H_3PO_4): acetonitrile (65:35). 10 μL of each sample were injected at a flow rate of 0.7 mL/min. The quantification proceeded using the absorbances of solutions detected at 222 nm. The calibration curves were made using each NADES as standard. In case of xylitol, the first stage (saturation and stirring) was similar to ibuprofen. However, here, the hydrophilic NADES saturated with xylitol were left still for another 24 still, while the hydrophobic ones for 24 days, without heating and stirring. Following, the supernatants were filtered with a hydrophilic PTFE syringe filter (pore size: 0.22 μm and diameter: 13 mm) and the samples were then analysed at room temperature (293.15 K) using an HLPC Dionex (model ICS3000) equipped with a Thermo Carbopac MA1 column (240 × 4 mm); 480 mM NaOH was used as eluent and the volume of sample injected for the quantification was 10 μL, at a rate flow of 0.4 mL/min; finally, the signals were detected with the electrochemical detection method.

Table 3
Theoretical models used to evaluate the affinity/miscibility degree.

Equations*		**Rule/Condition**	**Ref.**
$\Delta\delta_t = \lvert \delta_t^{S1} - \delta_t^{S2} \rvert$	eqn. 1	– **Miscible:** $\Delta\delta_t < 7$ $MPa^{1/2}$ – **Immiscible:** $\Delta\delta_t > 10$ $MPa^{1/2}$	Greenhalgh *et al.* [49]
		– **Miscible:** $\Delta\delta_t < 3.7$ $MPa^{1/2}$	Hansen [40]
$\Delta\bar{\delta} = \sqrt{(\delta_d^M - \delta_d^{S1})^2 + (\delta_p^M - \delta_p^{S1})^2 + (\delta_h^M - \delta_h^{S1})^2}$	eqn. 2	– **Miscible:** $\Delta\bar{\delta} \leq 5.0$ $MPa^{1/2}$	Hoftyzer and Van Krevelen [36]
$Ra_{(V)} = \sqrt{4(\delta_V^M - \delta_V^{S1})^2 + (\delta_h^M - \delta_h^{S1})^2}$ Where: $\delta_V = \sqrt{\delta_d^2 + \delta_p^2}$	eqn. 3 eqn. 4	– **Miscible:** $Ra_{(V)} \leq 5.6$ $MPa^{1/2}$	Bagley [50]

* $\mathbf{Ra_{(v)}}$ – relative distance of Bagley.

Table 4
Solubility of Ibuprofen and Xylitol in water, some organic solvents and in the studied NADES, at 293.15 K.

Solvent	Ibuprofen		Ref.	Xylitol		Ref.
	Solubility (mg/mL)	Class. [a]		Solubility (mg/mL)	Class. [a]	
Water	0.059 ± 0.001	(★)	This work	786.488 ± 2.181	(★★★★★★)	This work
	0.056 ± 0.003	(★)	[14]	625	(★★★★★★)	[31]
	0.055 ± 0.004	(★)	[16]	1690	(★★★★★★★)	[52]
	0.070 ± 0.000	(★)	[53]	1631.13	(★★★★★★★)	[54]
				–	–	–
Methanol	129.04	(★★★★★★)	[55]	23.04	(★★★★)	[56]
Ethanol	707.90	(★★★★★★)	[57]	4.51	(★★★)	[54]
	585.84	(★★★★★★)	[55]	4.46	(★★★)	[56]
1-propanol	595.00	(★★★★★★)	[57]	N/A	N/A	N/A
2-propanol	622.70	(★★★★★★)	[57]	2.25	(★★★)	[54]
Ethylene glycol	71.60	(★★★★★)	[55]	N/A	–	–
Glycerol	7.81	(★★★)	[55]	N/A	–	–
Cyclohexane	342.45	(★★★★★★)	[55]	N/A	–	–
Hexane	N/A	–	–	N/A	–	–
Bet:Glc:W (5:2:10)	0.921 ± 0.001	(★★)	This work	119.343 ± 0.318	(★★★★★★)	This work
Bet:Gly:Suc:W (2:3:1:5)	0.449 ± 0.000	(★★)		60.627 ± 0.489	(★★★★★)	
Bet:Suc:Pro:W (5:2:2:21)	0.734 ± 0.000	(★★)		129.356 ± 0.728	(★★★★★★)	
Fru:Glc:Suc:W (1:1:1:10)	0.088 ± 0.001	(★)		155.811 ± 0.029	(★★★★★★)	
Glc:Pro:Gly:W (3:5:3:20)	N/D[c]	–		144.685 ± 0.194	(★★★★★★)	
Gly:Fru (4:1)	0.236 ± 0.000	(★★)		74.261 ± 0.387	(★★★★★)	
Gly:Fru:Sorb:W (1:1:1:3)	0.047 ± 0.000	(★)		73.116 ± 0.419	(★★★★★)	
Gly:Glc (4:1)	0.251 ± 0.001	(★★)		47.202 ± 0.281	(★★★★★★)	
Gly:Glc:Sorb:W (1:1:1:3)	0.115 ± 0.002	(★★)		N/D[c]	–	
Gly:Suc:Sorb:W (2:1:2:10)	0.063 ± 0.000	(★)		88.737 ± 1.144	(★★★★★)	
Gly:Tre:Sorb:W (2:1:2:10)	0.105 ± 0.001	(★★)		146.949 ± 1.067	(★★★★★★)	
Pro:Gly:Sorb:W (1:1:1:13)	0.352 ± 0.001	(★★)		152.039 ± 0.238	(★★★★★★)	
Tre:Fru:W (1:2:13)	0.112 ± 0.001	(★★)		204.284 ± 0.945	(★★★★★★)	
Tre:Glc:W (1:2:13)	0.461 ± 0.075	(★★)		N/D[c]		
Men:AcetA (1:1)	298.053 ± 59.369	(★★★★★★)	This work	7.654 ± 0.07	(★★★)	This work
Men:Bor (7:2)	170.851 ± 22.87	(★★★★★★)		0.230 ± 0.012	(★★)	
Men:DecA (1:1)	159.463 ± 11.111	(★★★★★★)	This work	0.370 ± 0.02	(★★)	
	294.80 ± 22.976	(★★★★★★)	[14]	N/D[c]	–	
Men:DecA (2:1)	210.908 ± 3.989	(★★★★★★)	This work	0.401 ± 0.009	(★★)	
	268.33 ± 11.584	(★★★★★★)	[14]	N/D[c]	–	
Men:DecA (4:1)	211.169 ± 1.031	(★★★★★★)		0.314 ± 0.023	(★★)	
Men:DecA (7:2)	147.425 ± 2.110	(★★★★★★)		N/D[c]	–	
Men:LauA (2.7:1)	222.924 ± 9.987	(★★★★★★)		0.290 ± 0.014	(★★)	
Men:LauA (2:1)	162.045 ± 1.647	(★★★★★★)		3.401 ± 0.099	(★★)	
Men:LauA (4.5:1)	224.197 ± 2.633	(★★★★★★)		0.287 ± 0.026	(★★)	
Men:LauA (4:1)	204.668 ± 11.742	(★★★★★★)		0.244 ± 0.086	(★★)	
Men:LauA (5.3:1)	138.970 ± 0.386	(★★★★★★)		0.307 ± 0.008	(★★)	
Men:LauA (8:1)	131.410 ± 0.984	(★★★★★★)		0.311 ± 0.008	(★★)	
Men:LauA:DecA (2:1:1)	152.310 ± 41.953	(★★★★★★)		0.358 ± 0.016	(★★)	
Men:LauA:DecA (4:1:1)	161.872 ± 4.955	(★★★★★★)		0.322 ± 0.021	(★★)	
Men:LevA (1:1)	198.055 ± 10.866	(★★★★★★)		3.082 ± 0.007	(★★★)	
Men:MyrA (4:1)	204.218 ± 5.756	(★★★★★★)		0.308 ± 0.002	(★★)	
Men:MyrA (8:1)	207.860 ± 4.667	(★★★★★★)		0.400 ± 0.012	(★★)	
Men:Thy (1:1)	128.949 ± 24.092	(★★★★★★)		0.328 ± 0.011	(★★)	
Men:Thy (2:1)	181.355 ± 0.330	(★★★★★★)		0.131 ± 0.004	(★★)	
Men:Thy (4:1)	170.731 ± 5.094	(★★★★★★)		0.282 ± 0.013	(★★)	
Men:Thy (8:1)	171.261 ± 11.312	(★★★★★★)		0.216 ± 0.024	(★★)	
ChCl:Xyl:W (2:1:4)	0.442 ± 0.015	(★★)	[23]	N/A	–	–
ChCl:Xyl:W (2:1:10)	0.107 ± 0.00196	(★★)		N/A	–	–
ChCl:Gly (1:2)	3.820 ± 0.03	(★★★)	[53]	N/A	–	–
ChCl:EG (1:2)	24.209 ± 0.18	(★★★★)		N/A	–	–
ChCl:P (1:2)	183.300 ± 2.61	(★★★★★★)		N/A	–	–
ChCl:OA (1:2)	31.510 ± 0.20	(★★★★)		N/A	–	–
ChCl:LevA (1:2)	78.690 ± 0.93	(★★★★★)		N/A	–	–
ChCl:U (1:2)	4.500 ± 0.01	(★★★)		N/A	–	–
Men:Camp (1:1)	282.11 ± 6.67	(★★★★★★)	[58]	N/A	–	–

N/A – Not available.
[b] **ChCl** = Choline chloride; **P** = 1,2-propandediol; **OA** = Oxalic acid; **U** = Urea; **Camp** = Camphor.
[a] Classification according to BCS: (★) – Practically insoluble; (★★) – Very slightly soluble; (★★★) – Slightly Soluble; (★★★★) – Sparingly Soluble; (★★★★★) – Soluble; (★★★★★★)- Easily soluble; (★★★★★★★)- Very soluble (see more details in SI, Table S.6).
[c] **N/D** – Not determined.

Table 5
HSPs values of Ibuprofen and Xylitol estimated through the theoretical models.

Solubility Parameter	Theoretical Model*		Ibuprofen	Xylitol
Dispersive (δ_d)	**SEM**	KoS	18.37	19.33
		YAH	18.68	19.92
	EM	StP	17.55	17.72
		HK	18.93	18.28
		HKF	17.85	23.11
		Ymt	16.64	18.25
Polar (δ_p)	**SEM**	Böt	1.17	2.34
		HB	2.47	3.64
		Bb	1.28	1.89
		KoS″	1.79	3.08
	EM	StP	3.52	14.09
		HK	2.36	11.17
		HKF	2.22	14.12
		Ymt	2.36	8.34
Hydrogen Bond (δ_h)	**SEM**	Hans*	9.30	29.21
		(D1)	10.90	39.35
		(D2)	15.61	32.43
		(D3)	3.87	22.33
		(D4)	–	18.52
		(D5)	20.09	36.06
		(D6)	14.86	35.39
		(D7)	8.11	24.98
	EM	StP	6.77	43.11
		HK	7.37	31.61
		HKF	7.15	35.53
		Ymt	4.94	17.47
Total (δ_t)	**SEM**	RPP	21.41	43.88
		Kab	24.15	37.80
		Bb′	18.83	29.59
		HSL	18.19	26.84
		She	27.26	40.96
		Jar	23.67	40.37
		Gor	20.13	31.64
	EM	StP	19.14	48.70
		HK	20.45	38.18
		HKF	19.36	44.67
		Ymt	17.52	26.60
		Hoy	19.71	36.60

* **SEM** = Semi-empirical models; **EM** = Empirical models; **KoS** = Koenhen and Smolders; **YAH** – Yamamoto-Hansen-Abbott model; **Böt** = Böttcher; **HB** = Hansen and Beerbower; **Bb** = Beerbower; **KoS′** = Koenhen and Smolders; **Hans*** = Model of Hansen using FTIR values; **RPP** = Reid, Prausnitz and Poling; **Kab** = Kabo; **Bb′** = Beerbower; **HSL** = Hildebrand-Scott-Lee; **She** = Sheldon; **Jar** = Jarray; **Gor** = Gordon; From (D1) to (D7) = Combination of SEM (**see** Table 2); **StP** = Stefanis-Panayiotou model; **HK** = Hoftyzer and Van Krevelen; **HKF** = Hoftyzer-Van Krevelen and Fedors; **Ymt** – Yamamoto.

2.5. Theory

2.5.1. Prediction of physicochemical properties

The surface tension values of Ibuprofen and Xylitol presented in Table 1 were estimated using the molar Parachor method [28] (Sugden's approach). On the other hand, the thermodynamic properties (critical points and acentric factor), used to estimate the enthalpy of vaporization were calculated using the group contribution method of J. Valderrama et al. [29] (more details can be seen in Tables S.3 **and S.4 or from** Tables S.11 **to S.14**).

2.5.2. Evaluation of the correlation by statistical analysis

The statistical analysis was computed using the software GraphPad prism 8, assuming two-tailed and a confidence interval of 95 %. The procedure was similar to what was described in the previous work [18], and the analysis here presented was carried out using mainly the Pearson correlation coefficient (r).

2.5.3. Hansen solubility parameters (HSPs)

The theoretical semi-empirical (SEM) and empirical models (EM) used to estimate the HSPs of the two solutes are listed in Table 2.

2.5.4. Assessment of the affinity/miscibility

The affinity or miscibility degree between the two solutes and NADES was estimated using the HSPs, through the following approaches shown in Table 3.

3. Results and discussion

3.1. Solubility of Ibuprofen and Xylitol

The experimental data on the solubility of Ibuprofen and Xylitol in NADES is shown in Table 4, along with some values reported in the literature of their solubility in a few conventional solvents. Additionally, the solubility values were classified following the Biopharmaceutical Classification System (BCS) [51] (in mg/mL): practically insoluble (less than 0.1), very slightly soluble (from 0.1 to 1.0), sparingly soluble (from 10 to 33), soluble (from 33 to 100) and easily soluble (from 100 to 1000).

Although the solubility values of these solutes, Ibuprofen and Xylitol, in the same listed NADES, could not be found in the literature, a recent work reports the solubility of ibuprofen in two of the combinations evaluated in this study (Men:DecA (1:1) and Men:DecA (2:1)). These are also presented in Table 4, and as can be noted there is some discrepancy between the two set of values. There are in fact various factors that may had contributed for this, such as variations in the experimental conditions of NADES preparation (temperature, pH, stirring and heating mixing time, purity of the components, etc), equilibration time (the saturation time is different between the two methods, moreover, the authors used 15 min of vortex in this step which may have allowed a more complete equilibrium) and HPLC methodology (the calibration, mobile phase composition and column type are different). On the hand, it is also possible to draw some conclusions with the data collected in this study. First, regarding Ibuprofen, as can be noted, the experimental values are within the range of those reported in the literature, not only for water but also for hydrophilic (e.g., B2 ≈ C1) and hydrophobic systems. Another interesting observation is the significant improvement in the solubility of ibuprofen in hydrophilic systems in comparison to water, in both cases (this work and literature data). This information is very important, given the fact that non-steroid drugs such as ibuprofen have poor aqueous solubility, which consequently decreases their absorption rate and bioavailability [59–61]. On the other hand, concerning xylitol, it can also be seen that the experimental water solubility results are within the range of values found in the literature. In contrast to Ibuprofen, it was not possible to find the solubility of pure Xylitol in any eutectic mixtures, except for its wide use as a NADES component [11,23,62–64].

In general, it can be said that the solubility results are within the expected behaviour, i.e. the solubility of a polar solute is much higher in equally polar systems than in nonpolar ones, and vice-versa.

3.2. Correlation: solubility vs affinity

In a previous study [19], several semi-empirical (SEM) and empirical models (EM) were evaluated to determine the HSPs of NADES. However, a key question remained unanswered: which of them is the most suitable one to be employed? The best way to assess the effectiveness of these models is certainly by applying them in a practical case study, where experimental data is available to support the results. But, before this evaluation, it is important to know the HSP values of Ibuprofen and Xylitol (Table 5), estimated using the same theoretical models previously tested on NADES (Table 2) [19], as these will allow the calculation of the degree of affinity that exists between the two solutes and NADES.

According to Hansen data [65], the HSPs of Ibuprofen (in $MPa^{1/2}$)

Table 6
Values of Pearson correlation coefficient (r) resulted from the correlation between experimental solubility data of Ibuprofen ($S_{(Ibu)}$) and Xylitol ($S_{(Xyl)}$) in NADES* and their respective affinity degree (in $\Delta\delta_t$ and $\Delta\bar{\delta}$ scales), using the listed models. Here, "General" – Correlations made using the general list of the studied NADES (hydrophilic and hydrophobic); "Hydrophilic" – Correlations using solely hydrophilic systems list; and Hydrophobic – Correlations made using solely exclusively the hydrophobic list (see more in Table S.1, in supplementary information).

Affinity Scale	Theoretical model	List	$S_{(Ibu)}$ General	$S_{(Ibu)}$ Hydrophilic	$S_{(Ibu)}$ Hydrophobic	$S_{(Xyl)}$ General	$S_{(Xyl)}$ Hydrophilic	$S_{(Xyl)}$ Hydrophobic
$\Delta\delta_t$	**EM**	**StP**	−0.8816	−0.6597	−0.2748	−0.8462	0.2232	−0.0752
		HK	−0.9024	−0.7719	−0.0855	−0.8828	−0.2033	−0.4588
		HKF	−0.9062	**−0.8716**	0.0892	−0.8687	−0.0939	−0.4000
		Ymt	−0.8746	−0.6318	−0.3513	−0.7768	0.6800	−0.7025
		Hoy	−0.9100	−0.8193	0.2584	−0.8689	0.1124	−0.5721
	SEM	**RPP**	−0.8657	−0.2892	0.4960	**−0.9217**	**−0.5230**	**−0.7509**
		Kab	−0.9116	0.0959	0.3131	−0.6999	0.8324	−0.7090
		Bb″	−0.9124	0.0949	0.3058	−0.7226	0.8263	−0.7006
		HSL	**−0.9134**	0.0954	0.3050	−0.7346	0.8239	−0.6977
		She	−0.9131	0.0949	0.3061	−0.7312	0.8251	−0.6992
		Jar	−0.9110	0.0946	0.3082	−0.7053	0.8290	−0.7001
		Gor	−0.9124	0.0952	0.3077	−0.7225	0.8264	−0.7003
$\Delta\bar{\delta}$	**EM**	**StP**	−0.8921	−0.6731	0.2952	−0.7272	0.3610	−0.2240
		HK	**−0.9126**	−0.7885	0.1847	−0.7580	0.1428	−0.4018
		HKF	−0.9102	**−0.8604**	0.1860	−0.7482	0.1609	−0.4085
		Ymt	−0.8982	−0.5848	0.0390	−0.7069	0.3338	**−0.8224**
	SEM	**(D1)**	−0.8749	−0.2180	0.4883	−0.7151	−0.0167	−0.8041
		(D2)	−0.9076	0.1653	0.3969	−0.3087	0.3899	−0.7821
		(D3)	−0.9043	0.0789	0.3816	−0.2910	0.3497	−0.7723
		(D4)	–	–	–	−0.0722	0.3208	−0.7558
		(D5)	−0.9096	0.2020	0.3872	−0.2938	0.3719	−0.7680
		(D6)	−0.9072	0.1167	0.3813	−0.4875	0.4130	−0.7660
		(D7)	−0.9066	0.1294	0.3904	−0.2748	0.3571	−0.7796

are $\delta_d = 17.62$, $\delta_p = 2.47$, $\delta_h = 7.64$, and $\delta_t = 19.36$. Therefore, when comparing these data with the estimated ones presented in Table 5, it is possible to confirm that most of the calculated results are within the range of expected values, mainly for empirical models. On the other hand, there is no reported data regarding the HSPs of Xylitol, so it is not possible to confirm how comparable they are. Additionally, the results also show that in the case of Ibuprofen, the larger differences between EM and SEM are found in the estimation of the δ_h parameter, while for Xylitol, it is in the δ_p parameter. These deviations between EM and SEM may be justified by the methods and models used in the estimation of these two parameters (δ_p and δ_h). For example, as mentioned in **section 2.2**, the technique used to obtain the dielectric constant used to calculate the dipole moments and consequently the δ_p parameter of the solid solutes is different than the one used in the determination of liquids such as NADES. Furthermore, unlike NADES, the surface tension values used to calculate δ_t and then the parameter δ_h for the two solids are estimates and not rely on experimental data. Therefore, such discrepancy is somehow expected.

With the solubility data known, it was then possible to identify the most suitable theoretical models for eutectic mixtures. To do such an evaluation, the individual HSPs were used to calculate the affinity/miscibility degrees between NADES and the two solutes, using the methods proposed by Greenhalgh ($\Delta\delta_t$, **eqn. 1**) and Hoftyzer and Van Krevelen ($\Delta\bar{\delta}$, **eqn. 2**) (see Table 3). Following, these values (in SI, from Tables S.7 **to S.10**) were then correlated with the solubility data and the results (in terms of Pearson r parameter) can be seen in Table 6, knowing that according to the statistical assumption, a negative value of ***r*** (values in green) indicates an inversely proportional relationship between the two parameters (solubility versus $\Delta\delta_t/\Delta\bar{\delta}$). Therefore, the higher the value (in module), the better the correlation.

Since, theoretically, compounds with high affinities have small values of $\Delta\delta_t/\Delta\bar{\delta}$ (due to the small differences in their solubility parameters), it is expected that the closer the correlation is to −1, the better the model (highlighted with darker green). On the other hand, a positive value (highlighted in red) means that solubility increases with the decreasing of affinity (higher values of $\Delta\delta_t/\Delta\bar{\delta}$), which is not a realistic scenario. Thus, taking these assumptions into account, it is then possible to draw some conclusions from Table 6:

While in $S_{(Ibu)}$, if considering the **general list**, it is possible to note that all the models used to calculate the affinity degrees exhibit a good correlation with the solubility data, in the case of $S_{(Xyl)}$ not all models can be applied, in particular, the ones that use the combined method (from (D2) to (D7)). In addition, evaluating the theoretical models (SEM Vs EM), it can also be seen that while the semi-empirical models (RPP, Kab, Bb″, HSL, She, Jar, Gor and the combinations from (D1) to (D7)) show a better correlation with $S_{(Ibu)}$, the empirical models (StP, HK, HKF, Ymt and Hoy), in turn, show better correlations with $S_{(Xyl)}$ solubility.

When analysing the correlations made using only the list of **hydrophilic** NADES, it can be concluded that only empirical models, such as the HKF, are suitable for this purpose, and these are mainly useful for studies that involve nonpolar solutes in polar solvents, in this case, Ibuprofen in NADES. In the case of the solubility of a polar solute in polar solvents (Xylitol in NADES), the results do not show a good correlation between affinity and solubility, except for a very slight correlation when using the RPP model.

On the other hand, if considering only the solubility of the two solutes in the **hydrophobic** NADES, it is possible to observe that none of the studied models are useful for understanding the solubility of Ibuprofen in NADES. However, most of the semi-empirical models present a reasonable correlation with the data on the solubility of Xylitol in NADES. The limitations seem to occur mainly in empirical models such as StP, HK and HKF. Factors such as the structural complexity of Ibuprofen versus Xylitol, models with contribution groups that are not so obvious (e.g., StP) or those that have limited groups (e.g., HK), can be pointed out as some of the reasons behind the ineffective of these models, as this can often lead to the wrong choice of contribution groups, which consequently leads to the wrong prediction of solubility parameters.

Lastly, taking into account the two affinity scales used ($\Delta\delta_t$ and $\Delta\bar{\delta}$), it can be presumed that, in general, the correlations made using the $\Delta\delta_t$ approach show values slightly higher than those using $\Delta\bar{\delta}$. This is

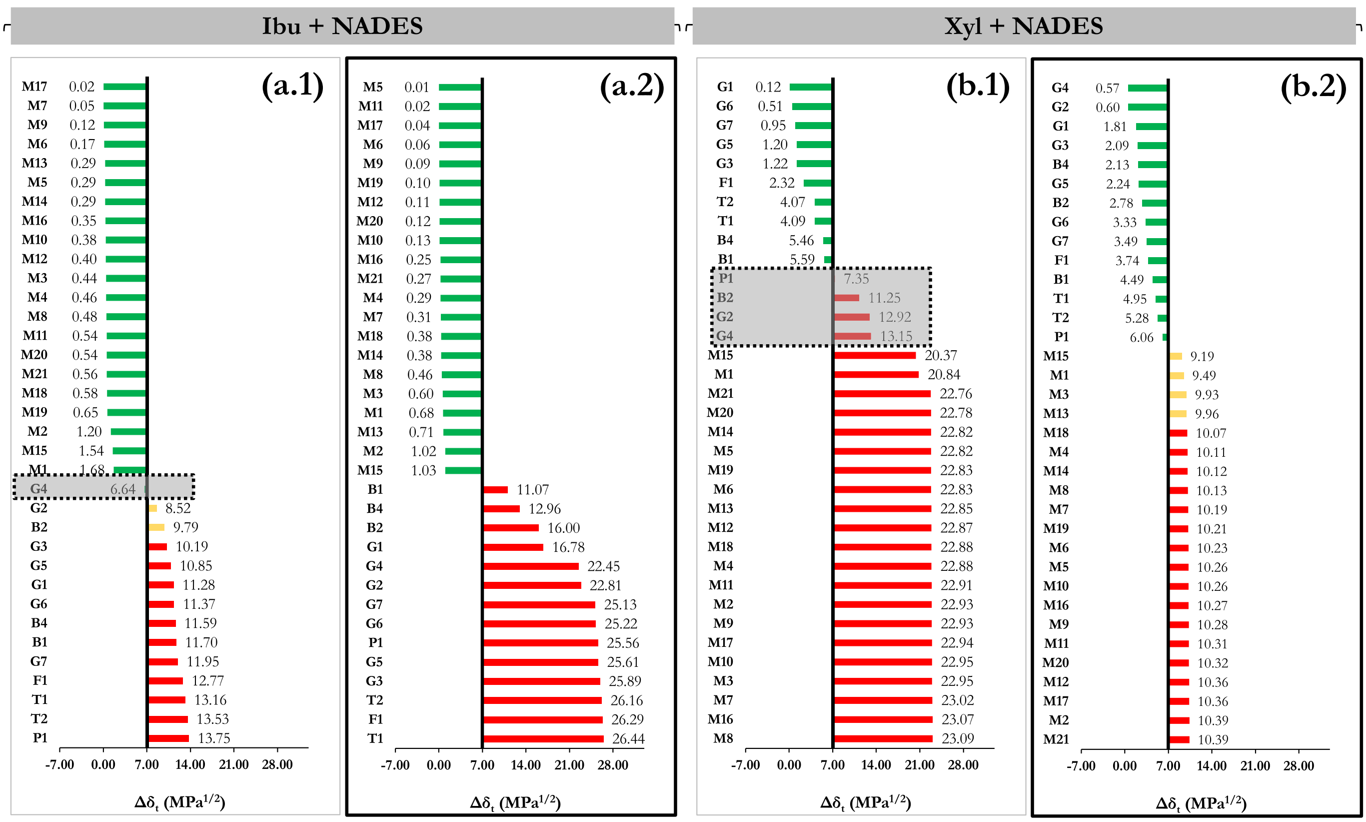


Fig. 1. 1-Dimensional evaluation of the affinity between Ibuprofen (Ibu + NADES) and Xylitol (Xyl + NADES) and the studied NADES, using the semi and empirical models HSL (**a.1**), HKF (**a.2**), RPP (**b.1**) and Ymt (**b.2**). For the screening and according to Greenhalgh (**eqn. 1**): $\Delta\delta_t \le 7.0$ MPa$^{1/2}$ = miscible (green bars); $7.0 \le \Delta\delta_t \le 10.0$ MPa$^{1/2}$ = miscibility borderland (yellow bars); $\Delta\delta_t > 10.0$ MPa$^{1/2}$ = not miscible. Here the hydrophilic NADES are identified as **B1** – Bet:Glc:W (5:2:10); **B2** – Bet:Gly:Suc:W (2:3:1:5); **B4** – Bet:Suc:Pro:W (5:2:2:21); **F1** – Fru:Glc:Suc:W (1:1:1:10); **G1** – Glc:Pro:Gly:W (3:5:3:20); **G2** – Gly:Fru (4:1); **G3** – Gly:Fru:Sorb:W (1:1:1:3); **G4** – Gly:Glc (4:1); **G5** – Gly:Glc:Sorb:W (1:1:1:3); **G6** – Gly:Suc:Sorb:W (2:1:2:10); **G7** – Gly:Tre:Sorb:W (2:1:2:10); **P1** – Pro:Gly:Sorb:W (1:1:1:13), **T1** –Tre:Fru:W (1:2:13) and **T2** – Tre:Glc:W (1:2:13); while, **M1** – Men:AcetA (1:1); **M2** – Men:Bor (7:2); **M3** – Men:DecA (1:1); **M4** – Men:DecA (2:1); **M5** – Men:DecA (4:1); **M6** – Men:DecA (7:2); **M7** – Men:LauA (2.7:1; **M8** – Men:LauA (2:1); **M9** – Men:LauA (4.5:1); **M10** – Men:LauA (4:1); **M11** – Men:LauA (5.3:1); **M12** – Men:LauA (8:1); **M13** –Men:LauA:DecA (2:1:1); **M14** – Men:LauA:DecA (4:1:1); **M15** – Men:LevA (1:1); **M16** – Men:MyrA (4:1); **M17** – Men:MyrA (8:1); **M18** – Men:Thy (1:1); **M19** – Men:Thy (2:1); **M20** – Men:Thy (4:1) and **M21** – Men:Thy (8:1), represent hydrophobic ones.

somehow unexpected because contrary to $\Delta\bar{\delta}$ that use three solubility parameters (δ_d, δ_p and δ_h) for the affinity evaluation, $\Delta\delta_t$ uses only the total solubility parameter (δ_t). Although the idea of using one or three solubility parameters to explain the miscibility between materials is not so well accepted by the scientific community [66], it is also true that such discussions are mainly made for regular solvents. NADES, in turn, are and behave fundamentally differently from these solvents, so these limitations may not apply to them. In fact, when combining the "subtractive approach" proposed by Hansen with the theories behind the formation of the eutectic system [67,68], it is possible to hypothesize a possible reason for $\Delta\delta_t$ showing a better performance than $\Delta\bar{\delta}$. This is because if assuming that the constituents of a eutectic mixture interact with each other by their main intermolecular forces (e.g., hydrogen bonding, polar and Van der Waals), then, otherwise these forces are broken when introducing a new compound (solute), and consequently the eutectic's components will be only able to use the remaining forces to interact with the solute, which according to Hansen are in δ_t parameter. In other words, while the affinity between the NADES components can be studied using $\Delta\bar{\delta}$, the affinity between NADES and a solute can be understood better if using the $\Delta\delta_t$ scale.

The results of the correlations allowed to us identify the models/combinations which better describe the solubility through affinity degree. In practice, these miscibility/affinity degrees between substances are commonly evaluated using 1-, 2- or 3-dimensional graphs.

3.2.1. *Affinity: 1-Dimensional evaluation*

One-dimensional graphs are very helpful tools for quickly evaluating which solvents are good and bad for a certain solute. These can be done using either Greenhalgh ($\Delta\delta_t$, **eqn. 1**) or Hoftyzer and Van Krevelen ($\Delta\bar{\delta}$, **eqn. 2**) affinity scale, however since $\Delta\delta_t$ showed a relatively better performance than $\Delta\bar{\delta}$, Hoftyzer and Van Krevelen's model was then used to create the graphics shown in Fig. 1.

As can be confirmed, even though the correlation results in Table 6 indicate that the semi-empirical models HSL and RPP are statistically the ones that best describe solubility, when assuming the general list, these models are actually not very representative of the expected screening. This is because in both cases, HSL and RPP (Fig. 1**(a.1)** and **(b.1)**, respectively), some affinities are not consistent with the solubility data. For example, according to the HSL 1D graph, Ibuprofen has a slight affinity for the system **G4** (Gly:Glc (4:1)) (in the grey box), however, the solubility data in Table 4 indicate that ibuprofen has very low solubility in this system. In fact, taking the found solubility values into account, **B1** (Bet:Glc:W (5:2:10)) would be the hydrophilic system whereas Ibuprofen would have the highest affinity. Additionally, the semi-empirical model RPP also shows some irregularities in the separation of good/bad NADES for Xylitol. Using this model, systems where xylitol is significantly soluble, namely, **P1** (Pro:Gly:Sorb:W (1:1:1:13)), **B2** (Bet:Gly:Suc:W (2:3:1:5)), **G2** (Gly:Fru (4:1)) and **G4** (Gly:Glc (4:1)) (in the grey box), appear as those that Xylitol would have little or no affinity. Therefore, due to the errors presented by these two models, the models that showed the best correlations when evaluating the list containing

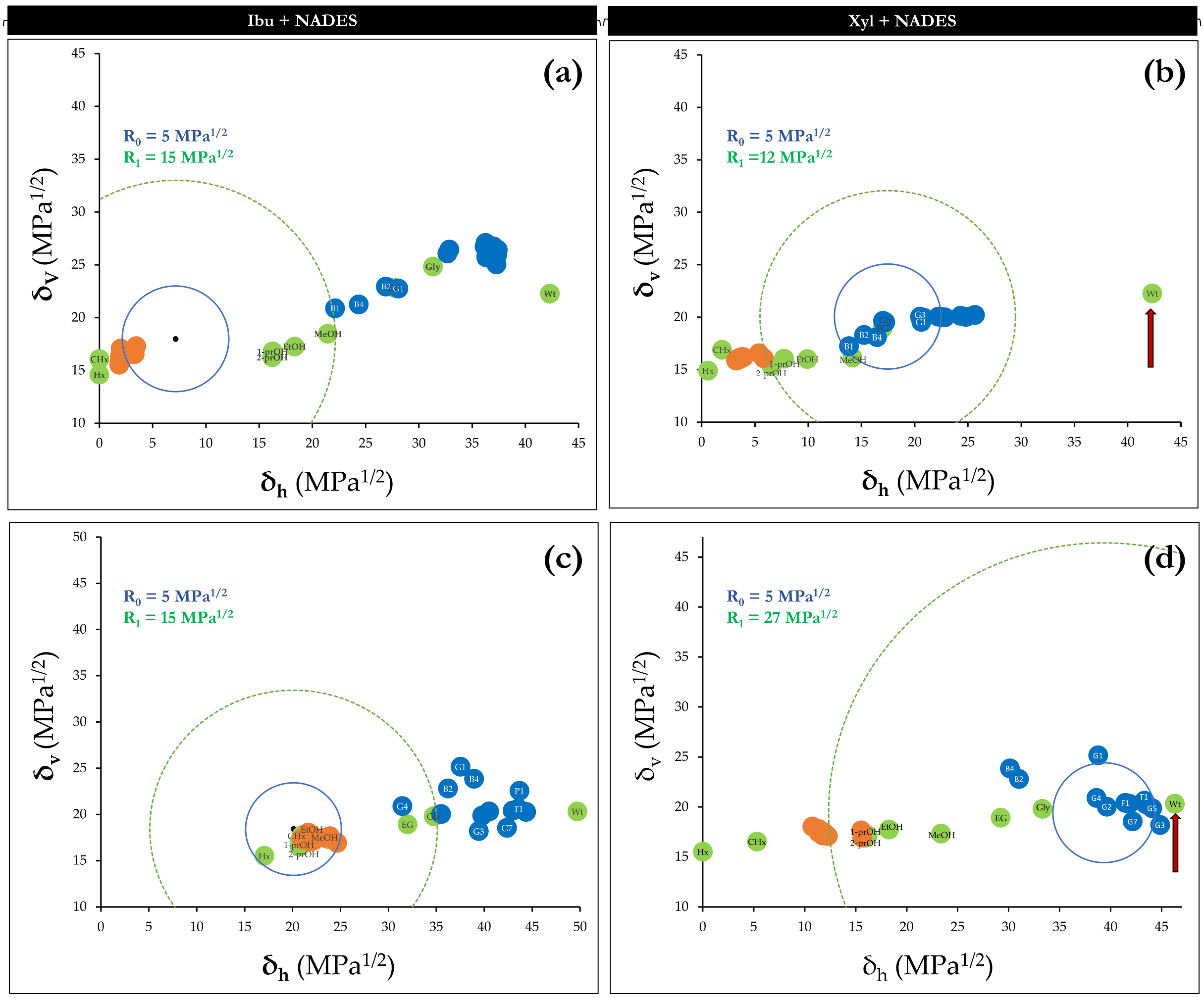


Fig. 2. Bagley plots used to evaluate 2-dimensionally the affinity between the solutes, Ibuprofen and Xylitol, and the studied NADES (hydrophilic (blue spheres) and hydrophobic (orange spheres)) and organic solvents (green spheres). Graphs (a) and (b) were generated using the δ_h and δ_v values of the empirical models HKF and Ymt, respectively, while (c) and (d), using, in turn, the semi-empirical combinations (D5) and (D1). For these graphics, the circle's centre of each solute (Ibuprofen and Xylitol) was obtained by crossing the estimated values of the two axes (δ_v and δ_h).

solely the hydrophilic and hydrophobic systems (HKF (Fig. 1**(a.2)**) and Ymt (Fig. 1**(b.2)**), respectively). As can be confirmed, these two empirical models can correctly represent the screening process. The evaluation with the Ymt approach even shows some systems with which xylitol has an affinity in the zone considered to be the limit of miscibility (bars in yellow), and this is in line with the experimental solubility results.

In conclusion, it can be said that empirical models are better than semi-empirical ones in screening good and bad NADES for a given solute, that is, when using the 1D evaluation. The HKF is particularly useful for studies that involve understanding the solubility of a non-polar solute, such as ibuprofen, in NADES (mainly hydrophilic). On the other hand, for polar compounds in NADES (mostly hydrophobic ones), Ymt can be a good choice for assessing their affinities degrees and inferring their possible solubility.

3.2.2. *Affinity: 2-Dimensional evaluation*

2D plots can also be used to evaluate the affinity/miscibility between materials and these are commonly performed using the Bagley method [50], which states that contrarily to δ_h, the parameters δ_d and δ_p have similar thermodynamic properties, and therefore these two last can be combined in one solubility parameter, δ_v (**eqn. 4**). Bagley's approach is based on correlating δ_v as a function of δ_h; once Bagley's relative distance, $Ra_{(v)}$ (calculated by the **eqn. 3**) is known, it is then possible to build the 2D plot, assuming that the solute's interaction radius (R_0) is 5.0 $MPa^{1/2}$. Thus, considering the empirical models used (HKF and Ymt) in the 1D evaluation, a 2D study of the affinity between Ibuprofen or Xylitol and NADES, was also carried out and it is illustrated in Fig. 2.

From this analysis, it is noticeable that by using the value of solubility radius proposed by Bagley (R_0 = 5.0 $MPa^{1/2}$) (solid blue circle), there is an incorrect separation on what are good and bad solvents for Ibuprofen or Xylitol. This is due to the fact that according to Bagley's theory, many hydrophobic systems (outside the sphere) would not be theoretically considered a good solvent for Ibuprofen Fig. 2**(a)**, as well as some hydrophilic NADES for Xylitol, which is contrary to the experimental data of solubility Fig. 2**(b)**. Therefore, an extension of Bagley's solubility radius was proposed here (dashed green circle) (R_1), taking into account the experimental data on the solubility of these two solutes (in water and the NADES studied) that were determined in this work. This allowed us to fit and enlarge their solubility radius and by including the organic solvents in this evaluation it was then possible to do a more comprehensive study. From this, it was found that the best solubility radius for Ibuprofen and Xylitol would be approximately 15.0 $MPa^{1/2}$ and 12.0 $MPa^{1/2}$, respectively. Nevertheless, as well as in 1D evaluations, 2D also fails to explain the solubility order. For example, the results shown in Fig. 2**(a)** infer that ibuprofen's affinity for alcoholic solvents (e.g., methanol) is very similar to that of some hydrophilic systems such as B1 and B4 despite them having very different solubility

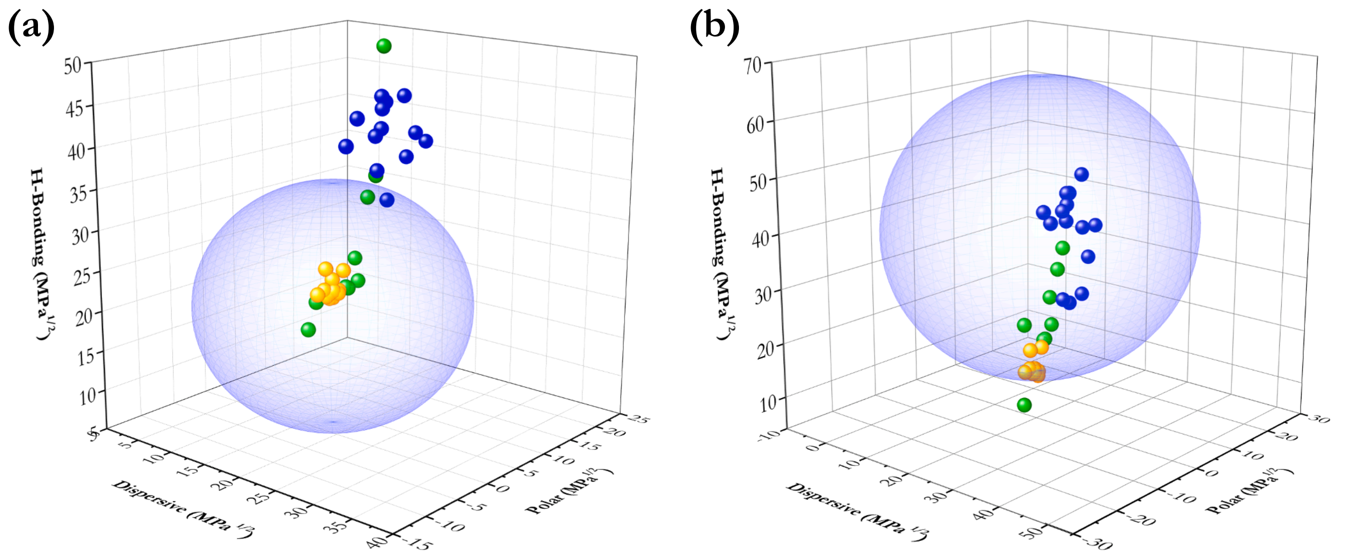


Fig. 3. 3D plots used to evaluate the interaction between Ibuprofen/NADES and Xylitol/NADES, created using the HSPs obtained through the theoretical models (D5) (a) and (D1) (b), respectively. For the solubility spheres of Ibuprofen and Xylitol, it was used the interaction radius proposed in this work (15 MPa$^{1/2}$ and 27 MPa$^{1/2}$, respectively). Here the green, blue and orange small spheres represent, in turn, the organic solvents (including water), the hydrophilic and hydrophobic NADES. The graphs were created using the OriginPro 9.0 software. The centres of the spheres were obtained by crossing the values of the three axes (x, y and z) that correspond to the solubility parameters δ_d (dispersive), δ_p (polar) and δ_h (H-bonding), respectively.

values, as shown in Table 4. Concerning Xylitol, the position of water in Fig. 2**(b)** is quite contradictory to the high solubility of Xylitol in water. However, it also is important to mention that the HSPs values of water used in this evaluation are those described by Hansen [40] this means that it would not be possible to guarantee that the position of the water shown in Fig. 2**(b)** would be the same if its HSPs were estimated using the Ymt model. Because of this, the 2D evaluation was also tested with other models, in particular using the semi-empirical combinations ((D1) to (D7)), since for these models the water's HSPs are known. Interestingly, the two combinations that exhibit the best performance are those that, according to Table 6, presented the highest correlations with the solubility data, when $\Delta\bar{\delta}$ is used, namely, (D5) (for Ibu + NADES) (Fig. 2**(c)**) and (D1) (in the case of Xyl + NADES) (Fig. 2**(d)**). As can be seen, the position of water in these SEM combinations is very similar to the EM ones, however, contrarily to what is observed in Fig. 2**(b)**, there is a closer approach between water and the solubility zone of Xylitol in Fig. 2**(d)**, which is mostly in line with what would be expected. On the other hand, while the R_1 (15 MPa$^{1/2}$) proposed for the HK model (graph **(a)**) is also applicable for (D5) (graph **(c)**), in the case of Ymt and (D1) (graphs **(b)** and **(d)**, respectively) this does not apply (12 MPa$^{1/2}$ versus 27 MPa$^{1/2}$). For model (D1) it is necessary to more than double R_1 to include all the solvents that have been classified as soluble. However, in reality, according to another of Hansen's theories [40], there is an inverse relationship between the interaction radius and the molar volume, i.e., the higher the molar volume of the compound, the lower its R_0; thus, taking into account that the molar volume of Ibuprofen is higher than Xylitol (206.28 cm^3.mol^{-1} versus 152.12 cm^3.mol^{-1}), it would be expected that $R_{1(Ibuprofen)} < R_{1(Xylitol)}$. Therefore, it can be said that the SEM combinations, in particular, (D5) and (D1) are relatively better than the EM HKF and Ymt in representing the 2D screening.

In conclusion, the results suggest that the type of evaluation, whether in 1D or 2D, depends mainly on the model, i.e. a model that performs well in 1D screening may not be efficient for 2D evaluation and vice versa. Therefore, while EM are good for 1D studies, SEM are more suitable for 2D affinity studies.

3.2.3. Affinity: 3-Dimensional evaluation

When it comes to studies involving HSPs, 3D plots are certainly the most used ones by researchers to study solubility behaviour. In terms of analysis, 3D graphs give us a better perspective on the results found in 2D. Therefore, such evaluation was also performed in this study, using the results obtained from the semi-empirical combinations that showed the greatest screening potential in the 2D evaluation ((D5) and (D1)) and the 3D graphs are illustrated in Fig. 3.

From the two 3D plots, it is then possible to re-state the efficiency of the HSPs as a good tool for screening solvents. However, even after such an extensive study with all the presented theoretical models, the most important piece of information that can be taken from this study is the fact that, although most of the investigated approaches showed a reasonable performance in distinguishing the best/bad NADES for solubilising Ibuprofen and Xylitol, neither empirical nor semi-empirical models were able to correctly explain the order of solubility/selectivity found. For example, the solubility results in Table 4 showed that Men:AcetA (1:1), is not only the greatest solvent for Ibuprofen but also the hydrophobic system where Xylitol presents the highest solubility. However, as can be seen in Fig. 1, none of the affinity scales used to create the 1D graphs points to this fact. In other words, according to the affinity scales used, Men:AcetA (1:1) does not have the most ideal HSPs that would infer a great affinity with Ibuprofen and consequently a good solubility.

3.3. Correlation: Solubility vs HSPs

The solubility scales ($\Delta\delta_t$ and $\Delta\bar{\delta}$) confirmed the importance of using HSPs in solubilisation studies, specifically as a screening tool. But which solubility parameters contribute the most to solubilization? In order to answer this question, the experimental solubility of the two solutes in NADES ($S_{(Ibu)}$ and $S_{(Xyl)}$) was correlated with all the individual solubility parameters of NADES, estimated using the EM (Fig. 4) and SEM (Fig. 5). Apart from the fact that the correlation values of the EM are slightly higher than those of the SEM models, other conclusions can be drawn when analysing these results.

Regarding the empirical models (Fig. 4), the total solubility parameter estimated using the Hoy model (Hoy (δ_t)) is the one that displays the highest correlation with the solubility data of both Ibuprofen and Xylitol in NADES ($S_{(Ibu)}$ and $S_{(Xyl)}$, respectively), however, in general terms, it

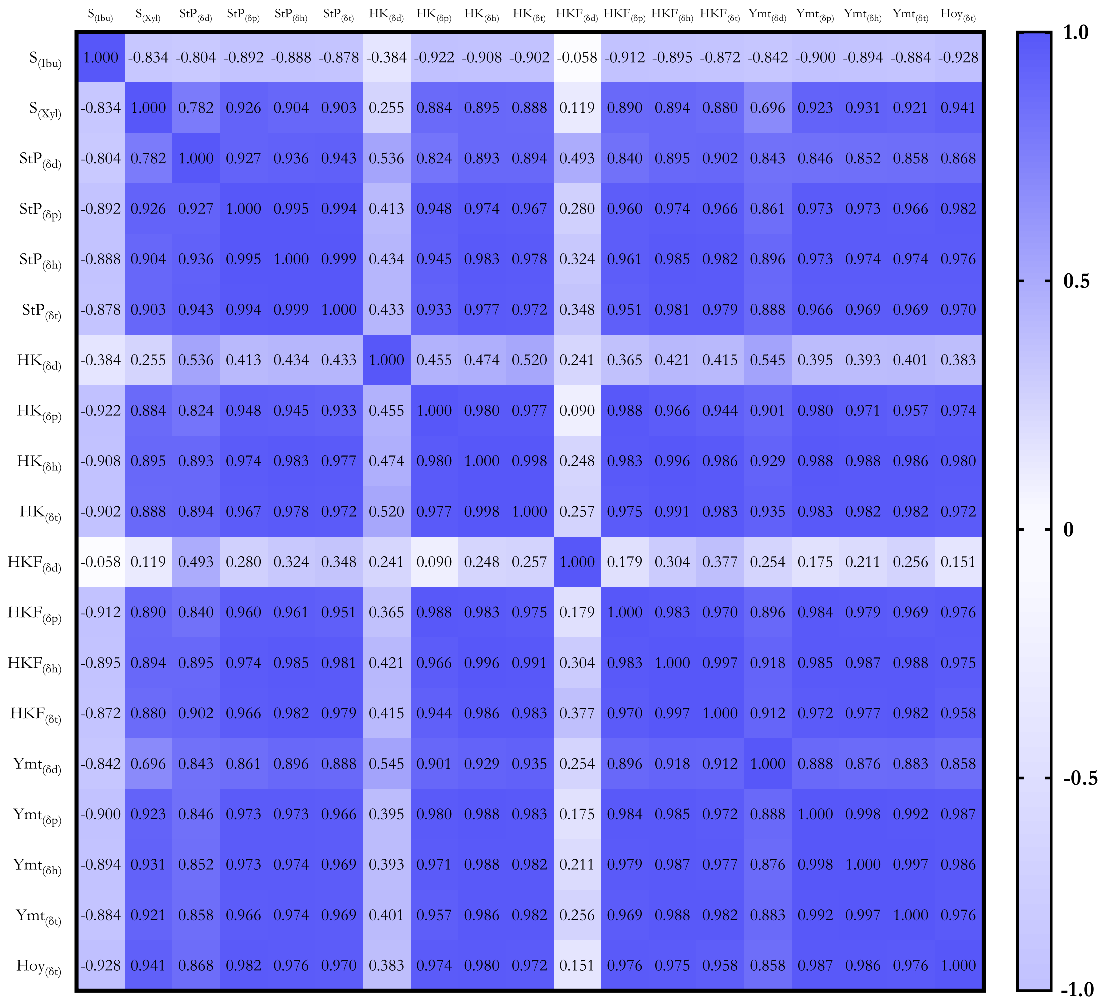


Fig. 4. Heat map of the correlation between the solubility of Ibuprofen ($S_{(Ibu)}$) and Xylitol ($S_{(Xyl)}$) in NADES and the individual HSPs (δ_d, δ_p, δ_h and δ_t) of these solvents, calculated using the empirical models of Stefanis and Panayiotou (StP), Hoftyzer and Van Krevelen (HK), Hoftyzer-Van Krevelen and Fedors (HKF), Yamamoto (Ymt) and Hoy. For this correlation, it was used the **general list** of NADES (Table S.1, in SI).

can be said that δ_p and δ_h are those that show a better correlation with $S_{(Ibu)}$, while for $S_{(Xyl)}$ are the δ_t and δ_p parameter. While $S_{(Ibu)}$ is inversely proportional to the Hoy (δ_t) of NADES, $S_{(Xyl)}$, in turn, increases with increasing of the Hoy (δ_t). This can be explained by the simple fact that NADES have several polar groups in their composition, which increases the contribution of the polar intermolecular forces and, consequently, the total forces, so that hydrophobic molecules, such as ibuprofen, have little affinity and solubility in NADES. On the other hand, in the case of xylitol, increasing the contribution of these parameters, especially hydrogen bonds, further favours its interaction with NADES. Additionally, when looking at the correlation values of the $S_{(Ibu)}$, it can be seen that for most of the empirical models, the two most important solubility parameters of NADES required in the interaction Ibuprofen/NADES are δ_p and δ_t. On the other hand, $S_{(Xyl)}$ seems to be affected predominantly by the δ_h parameter of NADES.

According to correlations values listed in Fig. 5, δ_t and δ_h are the solubility parameters that show the highest correlations with $S_{(Ibu)}$, while δ_h and δ_t parameters for $S_{(Xyl)}$.

The correlations made using the semi-empirical models (Fig. 5), confirm that among all the solubility parameters, δ_t and δ_h are those that show that greatest linearity with $S_{(Ibu)}$ and $S_{(Xyl)}$, respectively. As it was also observed in Fig. 4, all the models show an inverse relationship between $S_{(Ibu)}$-SEM and $S_{(Xyl)}$-SEM. Surprisingly, the highest correlation found was between $S_{(Xyl)}$ and the δ_h estimated using the Hans* approach. Although this model is widely rejected and has all the limitations previously discussed [19], it seems that it can still be somehow useful in the NADES field.

On the other hand, the correlations using individually the list of hydrophilic and hydrophobic NADES were also carried out and the results found are very similar to what was here discussed (see Figs. S.2 to S.5, in SI). What was common between all the evaluations is the fact that the dispersive parameter (δ_d) has the lowest correlation values with the solubility data, which means that it does not play as important a role as the other parameters in the interaction between the NADES and a given solute.

It is a fact that for this type of study, the most desired model would be certainly the one that allows not only the screening of good/bad solvents for the selected solutes but also the predicting the order of solubility (highest/lowest solubility). Furthermore, an approach that can be applied to different scenarios (e.g., polar solute in a non-polar solvent and vice-versa) could be a great achievement. However, the results found here strongly suggest that the models currently used are mainly useful for a screening process. Therefore, HSPs by itself may not be enough to explain the solubility behaviour of solutes in NADES.

3.4. Correlation: Solubility vs physicochemical properties

One of the greatest difficulties when working with NADES (e.g., fundamental studies, scale-up, database, etc) is the lack of data on its physicochemical properties. But once they are known, it is easy to

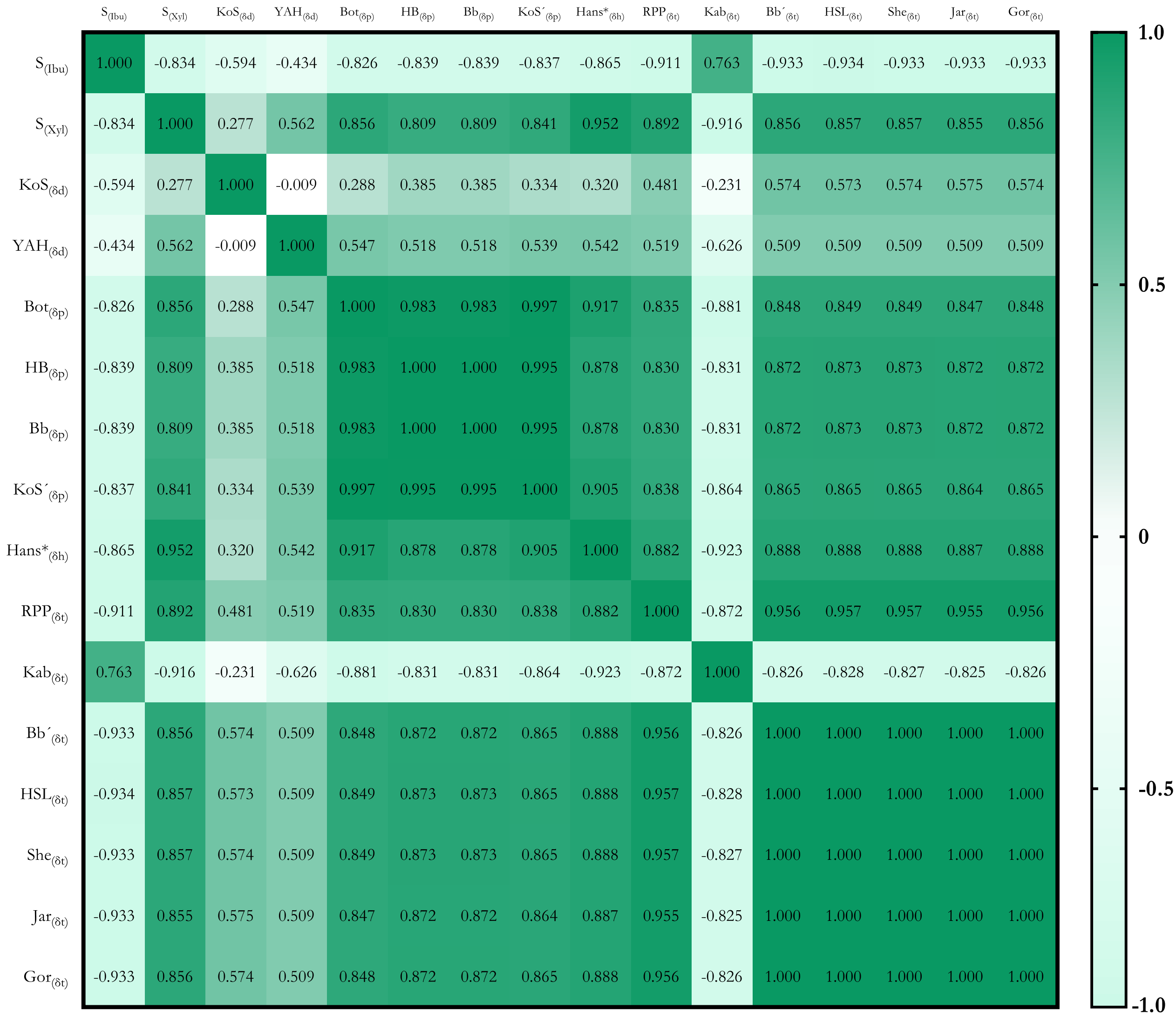


Fig. 5. Heat map of the correlation between the solubility of Ibuprofen ($S_{(Ibu)}$) and Xylitol ($S_{(Xyl)}$) in NADES and the individual HSPs (δ_d, δ_p, δ_h and δ_t) of these solvents, calculated using the Semi-empirical models of Koenhen-Smolders (KoS and KoS′), Yamamoto-Abbott-Hansen (YAH), Böttcher (Bot), Hansen and Beerbower (HB), Beerbower (Bb and Bb′), Hansen using FTIR data (Hans*), Reid, Prausnitz and Poling (RPP), Kabo (Kab), Hildebrand-Scott-Lee (HSL), Sheldon (She), Jarray (Jar) and Gordon (Gor). For this correlation, it was used the **general list** of NADES (Table S.1, in SI).

understand processes such as the solubilisation of compounds. Hence, an additional study was also carried out. This consisted of correlating the solubility of Ibuprofen and Xylitol in NADES with the properties of NADES (Fig. 6), investigated in our last work [18].

As can be seen, according to the values of the correlation, the solubility of Ibuprofen in NADES increases principally with the decrease of the density (ρ), surface tension (σ) and polarizability (π*) of the systems, as well as the increase of their acidic character (α). In the case of surface tension, such effect had been in fact recently proven by M. A. Nica *et al.* [14], which suggest that the low surface tension of hydrophobic NADES contribute for improve the wettability of poorly soluble drugs (in this case, Ibuprofen) and enhance their solubility/bioavailability, because less energy is need to expand to the surface area of these fluids. On the other hand, an increase in the solubility of Xylitol in NADES may be due to the increase in the surface tension and a decrease in the molar volume (V_m) of the NADES. Actually, low densities and surface tensions are properties very characteristic of hydrophobic NADES, while small molar volumes and high surface tensions point out to hydrophilic NADES. Overall and among all the parameters tested, surface tension is apparently the one that is mostly related to the solubility of both Ibuprofen and Xylitol in NADES. This is quite curious because, in fact, practically all the SEM found in the literature and presented here use surface tension in their models, which suggest that it can be one of the crucial variables for comprehending the organic compounds' solubility in NADES.

4. Conclusions

In the search for a tool that could explain the solubility behaviour of hydrophobic (Ibuprofen) and hydrophilic (Xylitol) compounds in different types of Natural Deep Eutectic Systems (NADES), Hansen Solubility Parameters (HSPs) were studied. This evaluation was carried out using a set of theoretical models (semi- and empirical models), which, allowed us to find out the affinity/miscibility degree between each of the two solutes and NADES, and consequently, correlated these values with the experimental data of solubility. From the correlation's results, it was concluded that for evaluating the affinity of Ibuprofen or Xylitol and NADES, the affinity scale proposed by Greenhalgh ($\Delta\delta_t$) is slightly better than the one suggested by Hoftyzer and Van Krevelen ($\Delta\bar{\delta}$). The hypothesis raised here was that the bond between the components of NADES is so strong that these may only interact with the solutes through other, weaker interactions that are normally described

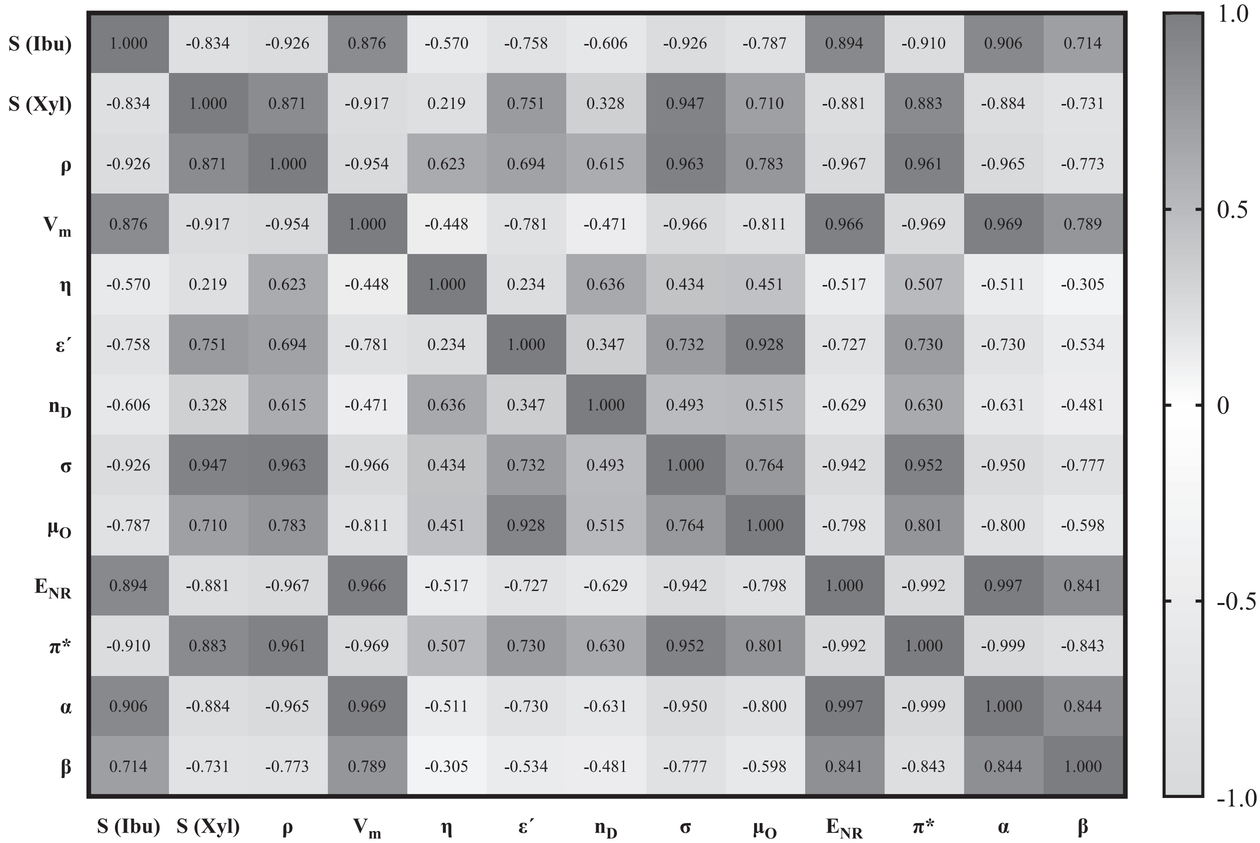


Fig. 6. Heat map representing the correlation (in terms of Pearson correlation coefficient, r) between the solubility of Ibuprofen and Xylitol (S(Ibu) and S(Xyl), respectively) in NADES and the physicochemical properties of these studied NADES, namely, density (ρ, in g/cm^3), molar volume (V_m, in cm^3/mol), viscosity (η, in mPa.s), dielectric constant (ε′), refractive index (n_D), surface tension (σ, in mN/m), dipole moment (μ_O), polarity (E_{NR}, Kcal/mol), polarizability (π*), acidity (α) and basicity (β). For this correlation, it was used the **general list** of NADES (Table S.1, in SI).

by the δ_t parameter. Furthermore, it was also concluded that despite the empirical models, in particular HKF and Ymt, are better than semi-empirical ones in representing one-dimensionally the screening process, i.e., which NADES could be good and bad for solubilizing Ibuprofen and Xylitol, respectively, in a 2D or 3D studies the semi-empirical combinations designated as D5.1.3 and D1.1.3 seem to be more appropriate for this kind of screening. This approach of using a different model for each type of screening was carried out taking into account mainly the experimental values, i.e. selecting the models that best represented the expected behaviour of the solubility.

Additionally, to find out which individual Hansen solubility parameter(s) would be more relevant to the solute solubility in NADES, a correlation between the two was conducted and the results prove that, except δ_d, all the other solubility parameters show a good correlation with solubility, especially the δ_t parameters. On the other hand, when these same solubility data were correlated with the physicochemical properties of NADES, and it was found that the solubility behaviour of the two solutes in the studied NADES can be mostly explained by the properties of these systems such as their surface tension, density and molar volume.

With this, it is then possible to conclude that HSPs, despite the limitations that have been presented here can still be useful in the field of NADES as a tool for screening which solute + NADES are most likely to be compatible or soluble.

CRediT authorship contribution statement

Cláudio C. Fernandes: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexandre Paiva:** Writing – review & editing, Resources, Funding acquisition, Formal analysis. **Reza Haghbakhsh:** Writing – review & editing, Validation, Supervision, Formal analysis, Conceptualization. **Ana Rita C. Duarte:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2025.127544.

Data availability

Data will be made available on request.

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