

Comparative Screening of Organic Solvents, Ionic Liquids, and Their Binary Mixtures for Vitamin E Extraction from Deodorizer Distillate

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Abstract

Although it is well known that the solvent is one of the most important decision variables in liquid-liquid extraction processes, many previous studies focused on a specific class of solvents while neglecting alternatives. This work presents a comparative screening of two types of most extensively studied solvents, i.e., organic solvents (OS) and ionic liquids (ILs), as well as their binary systems for the extraction of vitamin E from methylated oil deodorizer distillates (modelled as a mixture of α -tocopherol and methylinoleate). For this practically relevant task, the ternary liquid-liquid equilibria (LLE) of {OS or IL + α -tocopherol + methylinoleate} are first calculated by use of the CONductor-like Screening Model for Real Solvents (COSMO-RS), after which the physical and environmental, health, and safety (EHS) properties of solvents are assessed to identify the top-ranked OS and ILs. To intensify the separation performance, binary solvent systems are also explored, where one of the pre-selected ILs is taken as the first solvent for α -tocopherol and

an OS is screened as the second solvent for methylinoleate. Then, the IL-OS combinations are investigated regarding their binary immiscibility and ranked with respect the LLE performance in the quaternary system {IL + α -tocopherol + methylinoleate + OS}. By comparing the extraction distribution coefficient and the selectivity of the top-ranked OS, ILs and IL-OS systems, the notable intensified performance of binary solvent system is proven.

Keywords: solvent screening, organic solvent, ionic liquids, binary solvent mixtures, separation, process intensification

1. Introduction

Solvents are of central importance for the design of efficient separation processes such as extractive distillation [1], reactive extraction [2], gas absorption [3] and liquid-liquid extraction [4]. Conventional organic solvents (OS) have been well known by scientists owing to their generally low cost, eminent solubility property and numerous application options. However, following the “green chemistry” principles, many OS are being subjected to regulatory constraints because of the hazards of flammability, volatility, toxicity, and etc. There is burgeoning awareness and demand to minimize or fully eliminate the use of noxious OS [5], [6], [7], [8], [9]. In this context, different neoteric solvents, especially ionic liquids (ILs), have received significant attention from both, academia and industry.

ILs, also known as molten salts and generally comprised of asymmetric organic cation (e.g. imidazolium, pyridinium, etc.) and anion, feature unique physicochemical properties including low vapor pressure, non-flammability, wide liquid range, and flexible structure tenability, see [10], [11], [12], [13], [14], [15]. These attractive properties make ILs highly promising alternatives to

OS and triggered extensive studies thereon. So far, many relevant applications such as liquid-liquid extraction [16], gas absorption [17], material preparation [18], and organic synthesis [19] have been extensively investigated. However, one could note that most of these studies have empirically postulated the superiority of ILs to many OS, which is questionable from the following two aspects. First, it is gradually realized that some ILs also suffer from underlying hazards, depending on the substructural elements of alkyl side chain, head group, and anion type [20-22]. As an example, the toxicity of ILs is found to increase with the length of cation side chain and the addition of non-polar fragments on cation. Second, the big family of OS also contains a considerable number of members with benign environmental, health, and safety (EHS) properties, which may also provide high application potential. For instance, Bennett *et al.* employed the biomass-derived ethyl lactate as the solvent for synthesizing aryl aldimines, which achieves excellent yield within minutes at ambient temperature and does not require recrystallization or other solvent-intensive isolation or purification process [23]. Zhang *et al.* screened the effective and environmental-friendly solvent of dodecane for automatic separation of aldehyde and ketone in aldol reaction, exhibiting a high yield of 63% along with 92% conversion after 2 h residence time [24].

Moving beyond a single OS or IL, binary systems combining OS and IL represent another huge space of solvent options and provides great benefit in some special cases, see e.g. [25], [26], [27], [28]. One example is the isolation of difficult-to-separate mixtures, for which a single solvent is not be able to achieve satisfactory performance, but binary solvent systems could greatly enhance the separation efficiency. For instance, for the extraction of vitamin E (VE) from methylated oil deodorizer distillates (MODD, an abundant by-product in vegetable refining [29], Cheng *et al.* established a biphasic system consisting of n-hexane and $[N_{4,4,4,4}]Cl$. The introduction

of a n-hexane phase to constitute a binary solvent system notably enhances the selectivity towards VE in comparison to the single solvent of [N_{4,4,4,4}]Cl [30].

By considering the above aspects, OS, ILs, and their combinations as binary solvent systems all hold the potential to serve as suitable solvent option for different applications. In this sense, a systematic evaluation of different solvent options is highly desirable when facing a specific task. However, until now, there is a dearth of studies for the comparative selection of different types of solvents or solvent combinations. In this contribution, taking the VE separation as a case study, we demonstrate the comparative screening of OS, IL, and their binary mixtures. Practical MODD mainly consists of fatty acid methyl ester (FAME) and VE, wherein VE exists mostly as α -tocopherol due to the highest biological activity among different tocopherol isomers [30, 31]. Therefore, α -tocopherol and methylinoleate are used as the representatives for VE and FAME, respectively, to constitute the model oil.

For the screening of top OS or ILs as single solvents, the ternary liquid-liquid equilibria (LLE) of {OS or IL + α -tocopherol + methylinoleate} are calculated by use of the CONductor-like Screening Model for Real Solvents (COSMO-RS), followed by the evaluation of important physical and EHS properties of them. As for the binary solvent system, the pre-selected ILs are directly fixed as *Solvent 1*, aiming to extract α -tocopherol from methylinoleate; OS are screened and the fixed as *Solvent 2*, targeting to preferentially attract methylinoleate against α -tocopherol, which also undergoes the assessment of thermodynamic, physical, and EHS properties. Afterwards, the combinations of *Solvent 1* and *Solvent 2* are checked by binary immiscibility and quaternary LLE of {IL (*Solvent 1*) + α -tocopherol + methylinoleate + OS (*Solvent 2*)} to figure out the top-ranked binary solvent systems. The optimal solvent option for the case study is identified by

comparison of the thermodynamic performance of the top-ranked OS, ILs and binary OS-IL systems.

2. Methods applied

The comparative screening of different solvent options for the VE extraction task mainly consists of two steps namely the thermodynamic evaluation and the assessment of some physical and EHS properties. In the following, a brief summary of these solvent selection steps is given.

2.1 Thermodynamic evaluation

The evaluation of key thermodynamic properties is indispensable for selecting solvents for any separation task. To this end, experimental measurements are time-consuming, costly, and thus can only practically cover a tip of the iceberg in comparison to the enormous database of solvents or solvent combinations. Therefore, it is highly advisable to introduce a reliable and efficient theoretical screening method. Classical thermodynamic models, including G^E models (e.g., NRTL, UNIQUAC) and equations of state (e.g., SAFT and its derivatives) are widely used to describe phase equilibrium behaviors, see e.g. [32], [33], [34], [35], [36]. However, the applicability of these methods is often limited by the availability of reliable model parameters. *Ab initio* methods such as molecular dynamic and quantum chemical calculations have also been employed to determine thermodynamic properties from the molecular perspective [37], [38], [39], but they are computationally expensive and thus infeasible for extensive solvent screening in large structure spaces. UNIFAC models are also promising for solvent screening and design [40], [41], whereas the group interaction parameters that are regressed from experimental data are still insufficient to cover the large diversity of IL and OS as well as diverse separation systems.

In comparison, COSMO-RS is a fully predictive model that applies the statistical thermodynamic approaches to quantum chemical calculation results. It has been proven to be a reliable fast solvent screening tool for the prediction of thermodynamic properties of liquid and liquid mixtures, including IL-containing mixtures [42], [43], [44], [45], [46], [47]. Based on the COSMO-RS prediction, ionic liquid and organic solvent screening have been widely conducted in the literatures [48], [49], [50], [51]. However, most researchers only empirically focused on a specific type of solvent while neglecting the others, and the solvent EHS-related properties are always not taken into account. Since the comparative studies are very scarce, this work presents a systematic solvent screening considering different solvent options (i.e. OS, IL, and IL-OS binary solvent systems), which combines COSMO-RS model for thermodynamic prediction with a series of QSAR models for physical and EHS-related solvent properties assessment.

In this section, the thermodynamic properties prediction by use of COSMO-RS will be introduced. A detailed introduction of the COSMO-RS theory can be found in [52, 53]. Briefly speaking, the screening charge density distributions (also known as σ -profiles) of molecules is obtained through standard quantum chemical calculations (once for a specific compound, without the need of repetitive calculation for already covered ones). On the basis of the σ -profiles, the chemical potential of a specific compound in a system (pure compound or mixture) is quantified from the statistical thermodynamics treatment of molecular interactions. A wide variety of thermodynamic properties can be derived from the chemical potential. In particular, it is a key quantity for solvent selection in liquid-liquid extraction. For instance, the activity coefficients and the LLE distribution coefficients can be calculated as follows:

$$\gamma_s^i = \exp \left\{ \frac{\mu_i^S - \mu_i^0}{RT} \right\} \quad (1)$$

$$K_i = \left(\frac{\mu_i^I - \mu_i^{II}}{RT} \right) \quad (2)$$

where μ_i^S is the chemical potential of component i in the solvent S , μ_i^0 is the chemical potential of pure compound i , K_i represents the partition coefficient of component i , μ_i^I and μ_i^{II} denote the chemical potentials of compound i in phase I and phase II, respectively. It is feasible to calculate the activity coefficient at a specific finite concentration by correspondingly setting the mixture composition, wherein the activity coefficient at infinite dilution can be computed by assigning the mole fraction of the solute to zero. Referring to the LLE calculation, all chemical potentials depend on the phase composition and consequently the final equilibrium distribution has to be solved iteratively. With the given composition at the beginning, a set of new concentrations is computed that is further adopted to calculate updated chemical potentials and thus another updated set of concentrations. This iteration procedure is repeated until the compositions in the two phases do no longer change.

The good qualitative and, in many cases, acceptable quantitative prediction capability of COSMO-RS has been elucidated for activity coefficients and LLE calculations in many previous studies [54], [55], [56], [57], [58]. In the present work, the COSMO-RS calculations are performed with the BP_TZVP_C30_1901 parametrization in COSMOthermX (Version 19.0.5). The COSMO files of all involved anions and cations of IL, as well as OS are directly taken from the COSMObase (Version 1301 for OS and 1701 for ILs). Ternary LLE of a large number of {IL or OS + α -tocopherol + methylinoate} systems and infinite dilution activity coefficient of α -tocopherol and methylinoate (i.e., γ_α^∞ and γ_{Me}^∞) in OS are automatically implemented via the auxiliary batch-processing program in COSMOthermX. Quaternary LLE of {IL + α -tocopherol + methylinoate + OS} are performed using the *LIQUID EXTRACTION* option in the PROPERTIES tab. In the

following descriptions, the binary solvent system of IL and OS is abbreviated as IL-OS, e.g. IL970-OS1523 represents the binary system of IL970 and OS1523. The number following IL and OS represents the ID of a candidate within the specific group of solvents, which is tabulated in detail in Table S1 and S2 (Supporting Information).

To evaluate the extraction performances of different possible solvents, the mass-based distribution coefficient (β) and selectivity (S) are calculated from the LLE compositions:

$$\beta = w_{\alpha}^E / w_{\alpha}^R \quad (3)$$

$$S = \frac{w_{\alpha}^E / w_{\alpha}^R}{w_{Me}^E / w_{Me}^R} \quad (4)$$

where w_{α} and w_{Me} are the mass fractions of solute (α -tocopherol) and dilute (methylinoleate), respectively; superscripts E and R indicate the extract phase and the raffinate phase, respectively. For the selection of *Solvent 2* when forming IL-OS mixtures, the extractive capacity C_{Me}^{∞} and selectivity S_{Me}^{∞} of OS towards methylinoleate at infinite dilution are quantified as follows:

$$C_{Me}^{\infty} = (1/\gamma_{Me}^{\infty})^{OS} \quad (5)$$

$$S_{Me}^{\infty} = (\gamma_{\alpha}^{\infty}/\gamma_{Me}^{\infty})^{OS} \quad (6)$$

where γ_{α}^{∞} and γ_{Me}^{∞} refer to the infinite dilution activity coefficients of α -tocopherol and methylinoleate in the OS, respectively. It is worth mentioning that β and S directly allude to the extraction performance at practical conditions, whereas C_{Me}^{∞} and S_{Me}^{∞} indicate the extraction potential from the ideal molecular interaction point of view; both sets of parameters are commonly used as thermodynamic performance measures in solvent screening [59, 60].

2.2 Physical and EHS property assessment

In the second step, the retained IL and OS after the thermodynamic evaluation are further examined considering their important physical and EHS properties, which aims at identifying practically applicable and potentially sustainable candidates.

The melting point of ILs directly determines their applicability as extraction solvents. Herein, the group contribution (GC) model developed by Lazzus *et al.* [61] is used for predicting the melting point T_m of ILs, which can be expressed as:

$$T_m(K) = 288.7 + \sum_{i=1}^{31} n_i \Delta t_{ci} + \sum_{j=1}^{36} n_j \Delta t_{aj} \quad (7)$$

where n_i and n_j are the numbers of the cation group i and anion group j in IL; Δt_{ci} and Δt_{aj} are the contributions of the cation and anion groups to the melting point, respectively. The parameters of this model are regressed from the experimental melting points of 200 ILs incorporating 31 cation groups and 36 anion groups with an average deviation of 7%.

The toxicity of ILs is an important property related to the environmental and health concerns on them, which is widely studied in literature. In this work, the toxicity of ILs towards the leukemia rat cell line (IPC-81) is evaluated based on the quantitative structure-activity relationship (QSAR) proposed by Peng *et al.* [22]. This is a nonlinear model built from a multilayer perceptron (MLP) technique, which uses the group contribution COSMO (GC-COSMO) method, calculated from σ -profiles of ILs as the input. A satisfactory toxicity-structure relationship for 127 ILs is established with $R^2 = 0.975$, $MSE = 0.019$ for the training set and $R^2 = 0.938$, $MSE = 0.037$ for the test set. The reliability and robustness of this model were confirmed by cross and external validations. The cytotoxicity of ILs towards IPC-81 can be divided into four categories, that is, very high ($EC50 < 1.0$), high ($1.0 < EC50 < 100$), moderate ($100 < EC50 < 5000$), and low ($EC50 > 5000$). Only ILs

with low toxicity are selected in order to minimize their potential impact on human health and environment.

Regarding OS, the EHS impact with regard to solvent's persistence, bioconcentration factor (BCF), mutagenicity, carcinogenicity, and toxicity are estimated by use of VEGA - a free software package comprising a series of QSAR models [62]. From the SMILES codes of molecules, the EHS-related properties can be predicted through the QSAR models, supplemented by the prediction reliability that is classified into four levels (experimental, good, moderate, low). VEGA offers more than one QSAR model for each of the EHS relevant properties, which are all integrated in this work in order to achieve a comprehensive assessment. As introduced in our previous work [63], each EHS-related property is categorized into five grades:

Grade 1 (green): consistent predictions obtained by different models with good reliability or experimental data available for negative result;

Grade 2 (purple): consistent predictions obtained by different models with only moderate or low reliability for negative result;

Grade 3 (blue): inconsistent predictions obtained by different models while negative result obtained with good reliability by at least one model;

Grade 4 (yellow): inconsistent predictions obtained by different models while no negative result obtained with good reliability by any model;

Grade 5 (red): consistent predictions obtained by different models or experimental data available for positive result.

Here, the negative result indicates nonpersistent, nonbioaccumulative, nonmutagenic, noncarcinogenic, and nontoxic, respectively, while the positive result denotes the opposite. The

break-even values of the EHS criteria and the details of each QSAR model can be found in the Model's guide incorporated in the VEGA platform. The compound is nontoxic if the predicted LC50 value is more than 100 mg/L; the compound is nonbioaccumulative if the predicted logBCF value is less than 2.7; the compound is nonpersistent if the predicted half-life (HL) is below 40 days. As for the EHS-related properties of mutagenicity and carcinogenicity, the predicted negative results are NON-Mutagenic, and NON-Carcinogen, respectively. Only the molecules with all five EHS-related properties ranking in the first three grades are retained. Then, all the kept molecules are searched in the PubChem database to eliminate the ones with other detrimental concerns such as flammability, corrosivity, air or moisture sensitivity. The melting point lower than 298.15 K and a boiling point range of 323.15 - 473.15 K are also imposed as constraints in order to ensure safe handling and facile operation.

3. Results and discussion

Considering that the practical VE content in MODD varies from 2 wt% to 20 wt%, an exemplary mass ratio of 0.1:0.9 (α -tocopherol to methylinoleate) is taken for the LLE calculations in the thermodynamic evaluation step, where the OS and/or IL masses are set equal to that of the model oil. The extraction temperature is set to 298.15 K. A representative composition and temperature are fixed for better comparison among different solvent options and a huge variety of candidates. This manner is also commonly adopted in most solvent screening studies. The solvent screening results for OS, IL, and binary IL-OS combinations based on such conditions are discussed and compared in the following.

3.1 Screening results of organic solvents

The ternary LLE of {OS + α -tocopherol + methylinoleate} under the same fixed global composition are calculated to evaluate the extraction ability of different OS as a single solvent. In

total, 7626 OS are first taken from the COSMObase, as tabulated in Table S1a (Supporting Information). Among these 7626 OS, only 1516 of them are found to be able to achieve phase splitting, which is the prerequisite for extraction process (Table S1b, Supporting Information); the rests of them are correspondingly discarded. The mass-based β and S of the 1516 remaining OS based on the LLE compositions are compared in Figure 1. The generally low β and S of the 1516 OS well indicate the difficulty of extracting α -tocopherol from methylinoleate. A large proportion of these 1516 OS locate closely to the origin, and when moving to the right upper corner (toward higher β and S), the number of retained OS becomes much smaller. As a result, ten OS are used to roughly construct a pseudo Pareto front in this case (as marked in Figure 1), which represents the best thermodynamic performances that these 1516 OS exhibit. In other words, these ten OS are superior to all the other organic solvents from thermodynamic point of view, which could be rationalized from the σ -profiles point of view. The σ -profiles of α -tocopherol, methylinoleate, and the selected ten OS are depicted in Figure S1 (Supporting Information). In the hydrogen bond donor (HBD) region ($\sigma < -0.0082 \text{ e}/\text{\AA}^2$), a small peak for α -tocopherol reflects its weak HBD ability while methylinoleate has no HBD ability since no peak is found, which is the most straightforward difference between α -tocopherol and methylinoleate and could be utilized to selectively separate them. The top-ranked ten OS all have obvious peaks in the hydrogen bond acceptor (HBA) region ($\sigma > -0.0082 \text{ e}/\text{\AA}^2$), and thus they could selectively interact with α -tocopherol through hydrogen bond.

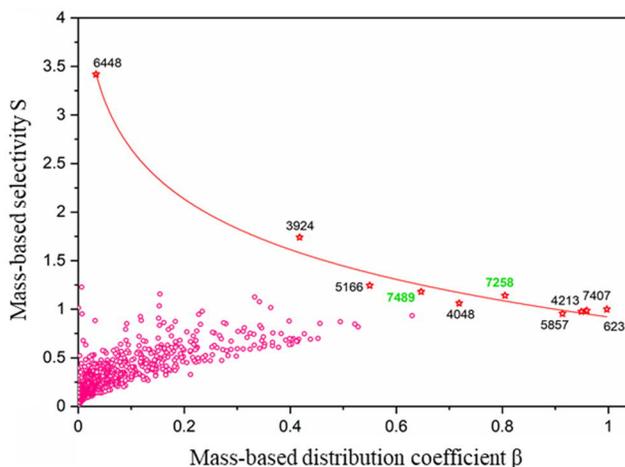


Figure 1. Mass-based β and S of OS for α -tocopherol extraction from methylinoate. The pseudo Pareto front is determined from regression of the data points obtained for the ten top-ranked OS.

More specifically from Figure 1, it is of high interest to note that OS6448 possesses high S but relatively low β , while the other nine OS around the pseudo Pareto front present close S but different β . For better illustration of the dissimilar solvent performance, the σ -profiles of α -tocopherol, methylinoate, and three representative OS (OS6448, OS5166, and OS4213) are depicted in Figure 2. As seen from the nonpolar region ($-0.0082 \text{ e}/\text{\AA}^2 < \sigma < 0.0082 \text{ e}/\text{\AA}^2$), the wider σ -profile distributions from OS4213 to OS5166 to OS6446 reflects the stronger vdW forces with α -tocopherol, which is responsible for the increasing β . Nevertheless, in the HBA region, a reverse trend is observed, that is, the HBA ability follows the order OS6446 > OS5166 > OS4213. Since α -tocopherol has weak HBD ability while methylinoate has no HBD ability, the increasing HBA ability of OS could account for the improved S . The superiority of these ten OS over other 1506 OS could also be similarly explained based on the COSMO-RS theory from the σ -profile point of view.

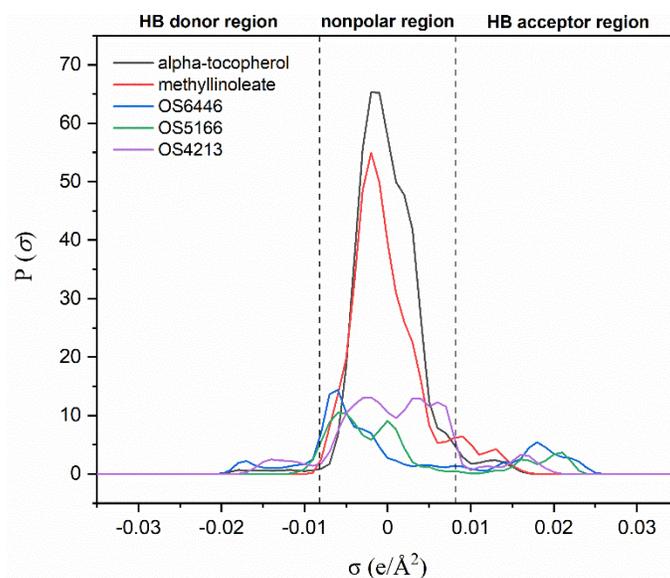


Figure 2. The sigma-profiles of α -tocopherol, methylinoate, and three representative OS (OS6448, OS7489 and OS7258)

	Persistence	BCF	Mutagenicity	Carcinogenicity	Toxicity	
6448	Green	Green	Green	Yellow	Blue	3-(methylamino)propanoic acid
3924	Green	Purple	Purple	Yellow	Red	55-dibenzo-30-crown-10-ether
5166	Purple	Purple	Purple	Yellow	Purple	dimethylselenoxide
7489	Green	Purple	Purple	Blue	Blue	triethyleneglycol n-propylether
4048	Green	Purple	Green	Blue	Red	6-amino-1-hexanol
7258	Purple	Purple	Green	Blue	Blue	tetraethyleneglycol monobutylether
5857	Green	Purple	Red	Yellow	Blue	meparfynolcarbamate
623	Yellow	Purple	Yellow	Yellow	Yellow	1,3,6-trimethyluracil
7407	Green	Purple	Blue	Blue	Red	trans-3-hexene-2,5-dione
4213	Purple	Purple	Green	Blue	Red	α -ethylbenzeneacetamide

Figure 3. Grade table of the five EHS-related properties for the ten OS considered for α -tocopherol extraction from pre-screening by use of the LLE (numbers on the left denote the ID number of the specific OS named on the right).

Afterwards, the five EHS properties of the top-ranked ten OS are further estimated and summarized as a grade table in Figure 3, and the detailed predicted results are available in Table

S2 (Supporting Information). As a result, two out of ten OS are found to be suitable regarding the five EHS criteria. These two OS are two long chain ethers namely tetraethyleneglycol monobutylether (TEGBE) and triethyleneglycol n-propylether (TEGPE). After further going through them in the PubChem database, they have no other reported EHS concerns and also satisfy the constraints on the melting point and boiling point range. Therefore, they are finally selected as the two top-ranked OS candidates among the 7626 initial candidates and their structures are depicted in Figure 4. It is worth mentioning that the extraction performance of these two OS (TEGBE: $\beta = 0.6467$, $S = 1.1811$; TEGPE: $\beta = 0.8051$, $S = 1.1403$) are not sufficient for an effective extraction process, which indicates that the consideration of other solvent options is of high practical relevance.

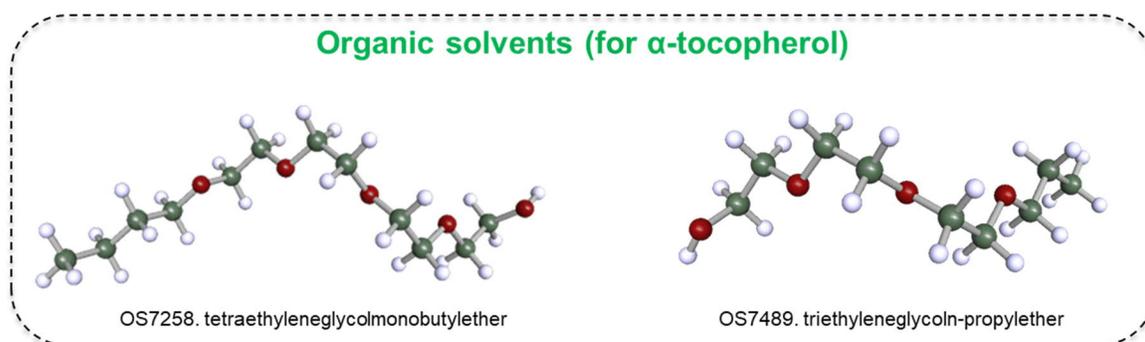


Figure 4. Structures of the two top-ranked OS, suitable for α -tocopherol extraction.

3.2 Screening results of ILs

Similar to the OS screening, the ternary LLE of {IL + α -tocopherol + methylinoate} are first calculated to evaluate the extraction capability of ILs. To be specific, 45360 ILs from the combinations of 420 cations and 108 anions in the COSMObase are initially included for the LLE evaluation. The detailed information about the cations and anions is recorded in Table S3a (Supporting Information).

According to the COSMO-RS predicted LLE, there are 33374 ILs that satisfy the prerequisite of phase splitting. The mass-based β and S of the 33374 ILs are given in Table S3b (Supporting Information) and depicted in Figure 5a. As seen, in comparison with OS (Figure 1), a wider distribution of ILs towards the right upper corner is observed, manifesting an improved extraction performance that ILs can achieve. To ascertain more promising ILs than OS, the pseudo Pareto front regressed from the top ten OS is used as the boundary to further filtrate ILs. As shown in Figure 5b, 2865 ILs are retained by this boundary (Table S4, Supporting Information).

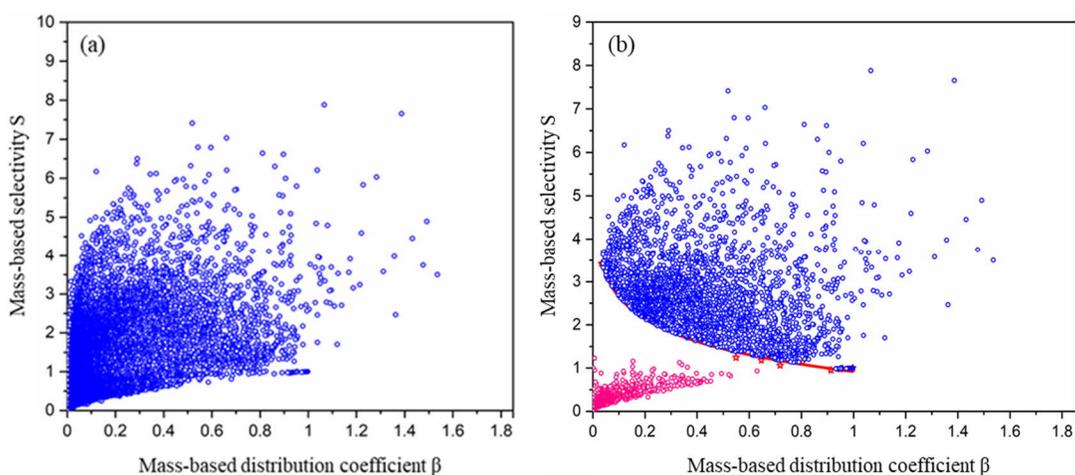


Figure 5. Mass-based LLE performance of IL (blue circles) for α -tocopherol extraction: (a) all 33374 phase splitting cases and (b) 2865 ILs with better LLE performance than OS (red circles).

After the LLE evaluation, the melting points of the retained 2865 ILs is estimated by the GC model (Table S5a, Supporting Information). The upper threshold of T_m is set to 298.15 K to ensure that the screened ILs can be used as extraction solvent under room temperature. By this threshold, 549 of the 2865 ILs survive, as listed in Table S5b (Supporting Information). Subsequently, the toxicity of ILs is estimated by the GC-COSMO based nonlinear QSPR method, from which 25 ILs (Table S6a and S6b, Supporting Information) satisfy the low toxicity constraint of $\log(\text{EC}_{50}) > 3.6990$. It is worth noting that the adopted models for the T_m and toxicity estimation have not

included all the groups for the involved cations and anions of the 2865 ILs. Therefore, only the results for the ILs predictable by the models are recorded in Table S4 and S5 (Supporting Information), but the ones that cannot be covered are discarded. However, once experimental properties of the discarded ILs or other more general applicable models are available in the future, such ILs could be further assessed.

From the 25 ILs remaining after the T_m and toxicity estimation, five ILs are finally selected featuring notably higher S while having a competitive β (> 0.5) in comparison to the top two OS. The detailed information of the five ILs is given in Table 1 with their structures depicted in Figure 6. As one can see, three of them are simple combinations of alkylated pyrrolidinium or piperidinium cations and the acetate anion; the other two are based on the acetate or formate anion with an ether group functionalized piperidinium cation. Such structures of the involved cations and anions are commonly reported in literature. Thus, the identified ILs are of practical relevance.

Table 1. Top five ILs for α -tocopherol extraction.

ID	Cation	Anion	log(EC50)	β	S	T_m/K
IL330	1-butyl-1-methyl-pyrrolidinium	acetate	4.0767	0.7678	5.0337	281.82
IL339	1-butyl-1-methylpiperidinium	acetate	4.2378	0.7610	4.8031	252.14
IL496	1-(3-methoxypropyl)-1-methylpiperidinium	acetate	4.5894	0.6929	5.2037	241.67
IL683	1-pentyl-1-methylpiperidinium	acetate	4.1551	0.6223	4.2232	248.38
IL970	1-(3-methoxypropyl)-1-methylpiperidinium	formate	4.6223	0.5437	4.1619	297.37

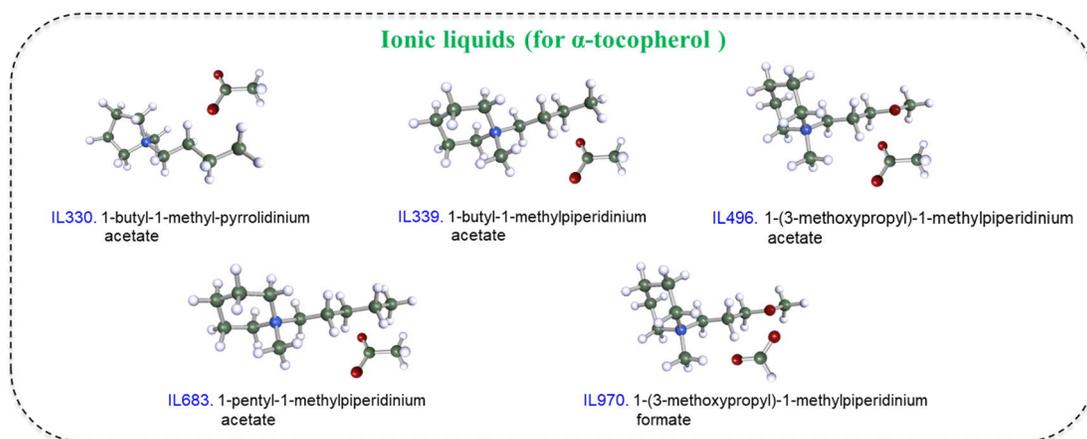


Figure 6. Structures of the five top-ranked ILs, identified for α -tocopherol extraction.

3.3 Screening results of IL-OS binary systems

Apart from a single solvent (OS or IL), binary systems combining OS and IL are another option for separating α -tocopherol from methyl linoleate by liquid-liquid extraction. To screen such binary solvent systems, an IL is assigned as *Solvent 1* to preferentially extract α -tocopherol while an OS is assigned as *Solvent 2* to selectively attract methyl linoleate, which follows the same strategy as proposed experimentally by Cheng *et al.* [30]. In this manner, α -tocopherol and methyl linoleate are expected to enrich in different phases, realizing an intensified extraction process. Considering the IL screening for the selective extraction of α -tocopherol from methyl linoleate is already performed in Section 3.2, the five ILs obtained in that case are directly taken here as the top candidates for *Solvent 1*. As for *Solvent 2*, we again attempt to screen suitable OS from the overall 7626 candidates stored in the COSMObase.

Thermodynamically, the C_{Me}^{∞} and S_{Me}^{∞} of the 7626 OS for methyl linoleate are evaluated by COSMO-RS. As shown in Figure 7, OS that are located in the upper right section with both higher $\log C_{Me}^{\infty}$ and $\log S_{Me}^{\infty}$ are more favorable to preferentially attract methyl linoleate against α -tocopherol. As n-hexane is experimentally proved to be a suitable *Solvent 2* [30], it is chosen as

the reference for the OS screening in this step. Correspondingly, 594 of 7626 OS are superior to this reference solvent. To further find out potential EHS-compatible candidates among these 594 OS, their EHS profiles are assessed in the same approach as introduced above. It turns out that 24 of the 594 potential OS are retained with benign EHS properties (see detailed results in Table S7 and Table S8, Supporting Information). Going through these 24 OS in the PubChem database, consequently three of them are kept, that are free of other EHS concerns and meet the constraints on the melting point and boiling point range. The structures of these three OS namely 3-ethyl-2,4-dimethyl-1h-pyrrole (OS3086), 3,4,4-trimethyl-3-pentanol (OS2851), and 2,2-dimethyl-3-pentanone (OS1523) are depicted in Figure 8, and their detailed information is listed in comparison to n-hexane in Table 2. Moreover, the EHS properties of OS3086, OS2851, OS1523 and hexane are shown in Figure 9. It is noted that the reference solvent n-hexane is potentially hazardous since its properties of persistence and toxicity rank in the fourth and fifth grade, respectively. Therefore, finding alternative OS to n-hexane in this screening is favorable from both thermodynamic and EHS point of view.

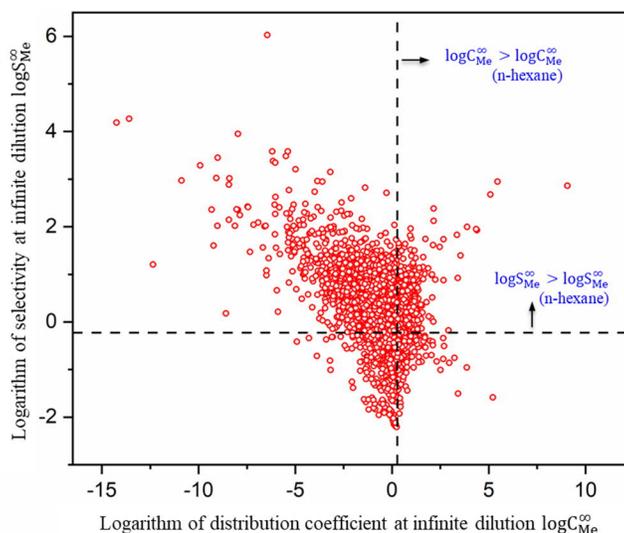


Figure 7. Capacity and selectivity at infinite dilution of the 7626 OS investigated for methylinoleate extraction at infinite dilution.

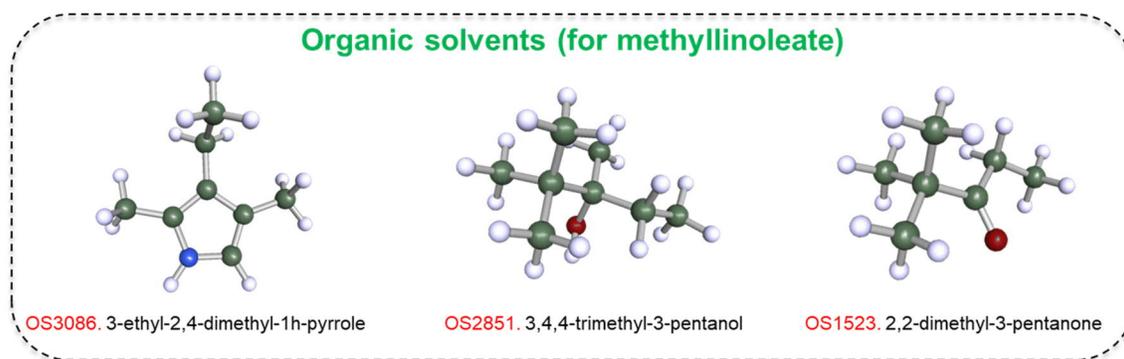


Figure 8. Structures of the three top-ranked OS for the extraction of methylloleate.

	Persistence	BCF	Mutagenicity	Carcinogenicity	Toxicity	
5625	Yellow	Blue	Green	Green	Red	hexane
3086	Purple	Green	Blue	Blue	Blue	3-ethyl-2,4-dimethyl-1h-pyrrole
2851	Green	Purple	Green	Blue	Blue	3,4,4-trimethyl-3-pentanol
1523	Green	Purple	Green	Blue	Blue	2,2-dimethyl-3-pentanone

Figure 9. Grade table of the five EHS-related properties for the three top-ranked OS and hexane as reference solvent for the extraction of methylloleate.

Table 2. Detailed information of three top-ranked OS considered for methylloleate extraction and comparison to n-hexane (MP and BP represent the melting point and boiling point, respectively).

ID	OS	$\log C_{Me}^{\infty}$	$\log S_{Me}^{\infty}$	MP/K	BP/K
OS3086	3-ethyl-2,4-dimethyl-1h-pyrrole	0.5601	0.0858	273.15	470.15
OS2851	3,4,4-trimethyl-3-pentanol	0.3060	-0.0512	267.15	425.15
OS1523	2,2-dimethyl-3-pentanone	0.3416	-0.2258	228.15	398.75
OS5625	n-hexane	0.2652	-0.2263	177.85	341.85

Table 3. Phase splitting check between the selected IL (for α -tocopherol) and OS (for methylinoleate).

	OS3086	OS2851	OS1523
IL330	No	No	Yes
IL339	No	No	Yes
IL496	No	No	Yes
IL683	No	No	Yes
IL970	No	No	Yes

To check whether the selected five ILs and three OS can form binary solvent systems as expected, the immiscibility of the IL-OS combinations is analyzed by means of COSMO-RS. As recorded in Table 3, when OS3086 and OS2851 are involved, the IL-OS combinations are completely miscible; in contrast, phase splitting can occur between OS1523 and the five ILs. That is to say, only OS1523-containing IL-OS combinations can meet the design target of the binary solvent system. Quaternary LLE of {IL + α -tocopherol + methylinoleate + OS1523} are then calculated to evaluate the extraction performance of these binary IL-OS systems. The β and S values of them are illustrated in a bar diagram (Figure 10), and also compared to the corresponding results of the top-ranked two OS and top-ranked five ILs as single solvents (as already introduced in Section 3.1 and Section 3.2). As can be seen, the S -values of the five binary IL-OS systems is notably higher than that in the corresponding single IL cases (i.e., without the addition of OS1523), which confirms the original design idea of binary solvent systems. Regarding β , two of the binary IL-OS systems namely IL339-OS1523 and IL683-OS1523 achieve a higher β -value in comparison to the corresponding single IL; by contrast, the β -values of the other three binary IL-OS systems show a decrease to a certain extent. The different changes of the β -values of the five binary solvent systems could be attributed to the difference in the mutual solubility of OS1523 and the ILs. When comparing the binary IL-OS systems to the two single OS cases, the much higher S -value also

holds and a sufficient high β -value is obtained with an exception of IL970-OS1523. Under consideration of both β and S , the top-ranked binary solvent systems IL330-OS1523 ($\beta = 0.7275$, $S = 7.2018$) and IL339-OS1523 ($\beta = 0.7789$, $S = 6.8475$) are selected.

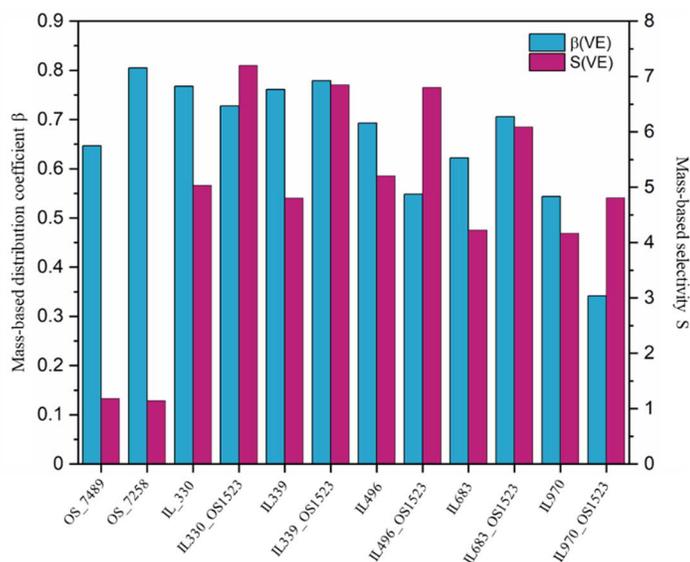


Figure 10. Comparison of mass-based distribution coefficient β and selectivities S of the top-ranked OS, IL, and their binary IL-OS solvent systems for the extraction of α -tocopherol from methylinoleate.

As summarized in Table 4, IL330-OS1523 and IL339-OS1523 are superior to the top-ranked single solvents (OS and ILs) for separating α -tocopherol from methylinoleate from the thermodynamic performance point of view. However, it should be mentioned that the solvent recovery and product purification are of central importance in a practical production process. The introduction of OS to form biphasic solvent system with IL may complicate the solvent recovery and product purification due to the certain mutual miscibility of two phases. Therefore, the rigorous evaluation of the binary solvent system should be based on the process performance, where multi-stage counter current-extraction are preferred to maximize the extraction potential of the selected extraction solvents [64], [65].

Table 4. Summarization of the extraction performance for the top-ranked OS, IL and binary IL-OS solvent systems for the extraction of α -tocopherol from methylinoleate.

Extraction solvent	Solvent name	β	S
IL330-OS1523	1-butyl-1-methyl-pyrrolidinium acetate	0.7275	7.2018
	2,2-dimethyl-3-pentanone		
IL339-OS1523	1-butyl-1-methylpiperidinium acetate	0.7789	6.8475
	2,2-dimethyl-3-pentanone		
IL330	1-butyl-1-methyl-pyrrolidinium acetate	0.7678	5.0337
IL339	1-butyl-1-methylpiperidinium acetate	0.7610	4.8031
OS7489	tetraethyleneglycol monobutylether	0.6467	1.1811
OS7258	triethyleneglycol n-propylether	0.8051	1.1403

4. Conclusion

In this work, a comparative solvent screening of OS, ILs and their binary pairs is performed, exemplified by the case of VE extraction from MODD. To screen single solvents (OS or IL), the ternary LLEs of {OS or IL + α -tocopherol + methylinoleate} are calculated with the help of COSMO-RS, following which the physical and EHS properties of OS or IL are then investigated. The top two OS and five ILs via screening are filtered out from a large number of candidates. For screening binary IL-OS systems, the five ILs selected in the single solvent case are taken directly as *Solvent 1* to extract α -tocopherol; similarly, OS are selected as *Solvent 2* for methylinoleate through the thermodynamic evaluation as well as physical and EHS properties estimation. Correspondingly, three top-ranked OS are chosen and their combinations with the five ILs are examined in terms of binary miscibility and quaternary LLE of {IL + α -tocopherol + methylinoleate + OS}. The comparison of the extraction performance of the top-ranked OS, IL and binary IL-OS systems demonstrates a distinct enhancement of the selectivity from single OS

to single IL and to binary IL-OS systems. Two top-ranked IL-OS binary systems are consequently identified as the best option for the case study due to the highest selectivity, S , and a very competitive mass-based distribution coefficient, β .

As proven in the present study, the rational screening of different solvent options is of great interest for the intensification of extraction processes. Thus, it is anticipated that this work could provide a practical guidance for solvent selection for many other applications. Moving beyond the OS, ILs, and IL-OS binary systems considered here, more types of solvents and their mixtures will be included in our future work.

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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