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Ionic Liquid Screening for Solvent Design of Herbal Phytochemical Extraction

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Ionic liquids (ILs) have been used in many applications and currently have been a favourable solvent in separation technology due to their solvation power compared to organic solvent. A development of IL solvent design approach is necessary in order to apply the most optimal solvents in herbal phytochemical extraction. In this study, solvent design utilised a systematic approach combined with property predictive model rather than trial-and-error experimental approach to reduce the amount of solvent waste and extraction time. This work focus on the screening of ILs as phytochemical extraction solvents of phenolic acids (e.g. gallic acid and caffeic acid) where we used property models of solubility and toxicity as part of solvent design. The methodology consisted of several stages. Stage 1 specifies the user needs of an extraction solvent, problems and constraints of new solvent design. Stage 2 involved in the development of a comprehensive Excel-based database of ionic liquid properties (e.g. solubility, heat capacity etc.) and factors that affect phytochemical extraction (e.g. extraction time, particle size etc.). In Stage 3, property library was assembled by collecting property models relevance for ILs from other studies to identify the most suitable models and estimate property values for solvent design. In Stage 4, ILs available in the database were first screened based on four factors: toxicity, heat capacity, density and viscosity (properties which represent characteristics of solvent and which affect the extraction). Only those ILs which have acceptable value range of each properties were selected. Finally, the ILs candidates were further screened down based on their solvation performance by using a solubility parameter-solid-liquid equilibrium approach involving UNIFAC-IL models to select most optimal solvent that can extract highest amount of phytochemicals. From the screening process, 16 best IL solvent candidates for the phenolic acid extraction were obtained from a database of 880 imidazolium-based IL.

1. Introduction

Ionic liquid (IL) also called room-temperature ionic liquids (RTILs), are composed only of anions and cations and have melting point below 100◦C (Ngo et al., 2000). Ionic liquid differ from salts as they remain in liquid in room temperature. IL can be divided into two groups of aprotic and protic ILs. The aprotic ILs or conventional ILs mainly constructed by bulky organic cations such as imidazolium or pyridinium and large variety of anions such as Cl−, Br−, BF4− and PF6− while protic ILs prepared by neutralisation reaction of an organic base and an acid (Chen et al., 2014).

Ionic liquid first introduced as a battery electrolyte and evolved into many other applications such as lubricants, solvents for catalysis and extraction; and used for analysis in gas chromatography and protein crystallisation (Chávez-Islas et al., 2011). Many ILs are readily available or simply prepared by reacting appropriate cation and anion. There are two basic methods to prepare IL, which are metathesis of a halide salt with the group of desired anion or by acid–base neutralisation (Tang et al., 2012). They are an interesting potential solvent due to the following reasons; (1) ionic liquid have a wide range of both inorganic and organic materials, and unusual combinations of reagents brought into one phase, (2) composed of poorly organised ions, so they have the potential to be highly polar yet noncoordinating solvents, (3) they can be hydrophilic or

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hydrophobic depending on the structures of the ions and (4) Ionic liquids are nonvolatile thus eliminate many containment problems (Welton et al., 2011).
Although ionic liquid is considered an expensive chemical, however many academics and industries are still interested in this area of chemistry. Recently there are more than ten thousand of research papers on ionic liquid and the trend keep increasing making it the fastest growth area in chemistry. Due to their unique properties, ILs are favoured in many applications especially as solvents. The existence of clusters in ionic liquid is one of the main characters that provide unique environment for reactions and processes (Chen et al., 2014). Another major purpose for the interest in ILs is their negligible vapour pressure, therefore decreases the risk of technological exposure and loss of solvent into atmosphere (Domańska, 2005). Other than the ability to dissolve organic, inorganic and organometallic materials, ionic liquid is thermally stable that makes them suitable for extraction of thermal sensitive products. IL is considered an attractive alternative to conventional solvents which have strong volatility and toxicity that can cause pollution (Chen et al., 2014).
Many researchers attempt to design and synthesis various ILs for many applications recently. To design this product and process, one requires knowledge of the thermophysical and transport properties of ILs. The experimental value and data of ionic liquid is lacking (Coutinho et al., 2012) although many potential candidates can be design. Owing to the lack of ionic liquid property data, many researchers step forward in identifying and develop the database of ionic liquid either through experimental verification or by developing a model using applicable data. Some of the growing databases of ionic liquid such as IUPAC and NIST which makes the task easier and ionic liquid models more reliable.
The name designer solvent for ionic liquid comes from the fact that IL can be design according to the specific application we intended by combining different type of cation and anion. The skeletons of anion and cation are treated as one (Yang et al., 2012) can be hydrophobic or hydrophilic depending on the structures (Zhao et al., 2005). Many ionic liquid designs involve in modifying the alkyl chain length to change the properties of the IL. A study have concluded that density of ionic liquids increases with a decrease in the alkyl chain length on the cation and an increase in the molecular weight of the anion (Yu et al., 2014).
This study focused on screening of ionic liquid as an extraction solvent for phytochemicals, specifically phenolic acid from herbal plant for solvent design purpose. Experimentally, ionic liquid have been used in extraction of many plants substituents. Phytochemical studies using ionic liquid are such as extraction of flavonoids from Bauhinia championii (Benth.) using 2M 1-butyl-3-methylimidazolium bromide (BMIM][Br]) solution with 0.80 M HCl (Xu et al., 2012). In this study, solvent design employed a systematic approach combined with property predictive model to reduce the amount of solvent waste and extraction time, therefore providing an easier option for experimentalists to conduct experiments.

2. Methodology

According to Azmin et al. (2015), solvent design used reverse approach involved two tasks where; first tasks were to define the design targets while the second task is to identify the solvents that match the targets. In this study (Figure 1), first task focused on solvent performance target, collection of database and selection of relevant property models from designed property library. In the second task, suitable models were used to identify a list of solvent candidates that matches the target properties which then further validated experimentally. In this study, screening of ionic liquid were done until verification by case study.

2.1 Stage 1: Problem definition

The needs for extraction solvent will be primarily determine and defined which then translated into target properties. Extraction solvent must promptly dissolve the sample but will not extract any impurities nor react with the sample; other than must be reusable to reduce cost. Constraints were identified to overcome the problems and justified the need of a new solvent for extraction. The requirements and factors were listed and translated into performance criteria to determine the considered properties of a new solvent in the study. The properties were to be validated using model-based approach.

2.2 Stage 2: Database collection & development

A very extensive search was done on the extraction factors and commonly used ionic liquids used for extraction. Data on physicochemical properties of ionic liquid also collected. Review were done by collection of published literature and available database online such as NIST ILThermo. All data obtained were reviewed and stored in two designed databases; database of factors of herb phytochemical extraction and ionic liquid properties. The properties of the herb phytochemicals and the common solvent used for extraction process were reviewed to determine solvent properties. These databases became an input for framework design of ionic liquid as an extraction solvent.

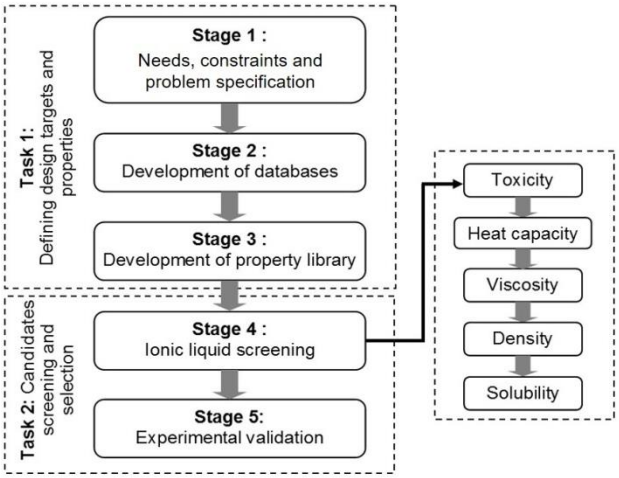

Figure 1: Systematic methodology for ionic liquid solvent design

2.3 Stage 3: Property models library development

The property models library consists of all related equation models of the ionic liquid properties determined in stage 1. Library were designed based on the selected properties of ionic liquid which will be an input data for ionic liquid design framework in stage 4. The properties of target solvent were identified according to the relationship of extraction process and solvent used. As equation models represent each property, an extensive review for applicable models and specific related data (based on the equation models) were done through published literature and books. The equation models were collected went through verification process to determine the accuracy of the equation. This verification process screened through the unsuitable model with a high error and only fit models compiled in the design library. Models for predicting the target properties were selected depending on their suitability and calculated based on available data.

2.4 Stage 4: Ionic liquid screening

Systematic approach was employed in this stage as described in Figure 1. Candidates were reduced over property classification and final solvent candidates were determined. This stage commences with the input of databases created in Stage 2. Related properties and composition with a list of anion and cations were the main ingredient in this task. Based on the related properties, suitable models were selected for framework design to reduce the solvent candidates in the next task. Solvent candidates were screened according to the important properties needed for solvent design. This verification task is to verify the developed algorithm with a base case study. The base case is selected from the published experimental results as the benchmark for the results from the algorithm. The objective of this task is to ensure that the developed algorithm were designed and works correctly. Targeted phytochemicals in this study were gallic acid and caffeic acid. Both phytochemicals and solvent were finally screened down by solubility value to determine the best candidates where both phytochemicals and solvent must have equivalent or approximate value in order to have the best solubility.

3. Case study : Ionic liquid design for extracting phenolic acid from *Labisia pumila*

This case study focused on ionic liquid solvent design to maximise the extraction of phenolic acid from Labisia pumila or known as Kacip Fatimah herb. The main phenolic acid identified were gallic acid and caffeic acid as in previous study of studies of Jaafar et al. (2012). Ionic liquid were designed considering the product of phytochemicals to be consumables and experimental factors by Du et al. (2014). 880 of imidazolium based ionic liquid (from an unpublished IL database of Technical University of Denmark (DTU)) with different cations alkyl chain lengths and anions were used in this designed.

3.1 Stage 1: Problem definition

Different solvent used determined the extracted phytochemicals from the plant. Solvent selection may include the following such as it must readily dissolve the extracted phytochemicals; it should not extract impurities that present in the original mixture; it should not react with the phytochemicals and should be readily separated from the desired phytochemicals after extraction (Curzons et al., 1999); must have a low toxicity, low price and

good solvent appearance. Table 1 describes the solvent needs and criteria. According to the knowledge base, the solvent desired characteristics then were translated into target properties in Stage 3.

Table 1: Ionic liquid solvent design criteria for herbal phytochemical extraction

No	Needs and performance	Properties
1.	Solvent must effectively dissolve the target phytochemicals. Solubility parameter of solvent and phytochemicals must not be too large in difference.	Solubility, δ
2.	Solvent must not be too sticky as it will be recover again at the end of the process	Viscosity, μ
3.	Solvent designed must be safe towards the environment and human as phytochemicals were considered for human consumption	Toxicity, EC50
4.	Solvent must be thermally stable to easily extract the phytochemicals in high temperature.	Heat capacity, Cp
5.	Solvent will be sold by price per weight, thus density will also be considered	Density, ρ

3.2 Stage 2: Database collection & development

In this stage, database of ionic liquid properties and factors that affect phytochemical extraction were developed based on extensive literature search on published experimental and theoretical data. These data were observed to identify solvent property constraints to design the ionic liquid for phytochemical extraction purpose other than as an input for framework designed. Solvent constraints or target values were listed in Table 2.

3.3 Stage 3: Property models library development

Listed ionic liquid properties identified such as toxicity, viscosity, boiling point, heat capacity, density and solubility were explored further for their suitable property models collected in a designed library. These collections of property models were verified for relative error and availability of model parameters. Table 3 listed the references of property models used in this work.

Table 2: Ionic liquid properties target values and property models used

Properties	Unit	Target values	Property models (Ref.)	Ref.
Solubility parameter, δ	$MPa^{1/2}$	Depends on phytochemical target value	$\delta_{IL}^2 = 0.6084(\delta_{cation}\delta_{anion}) - 1958(\delta_{cation}^2) - 0.1958(\delta_{anion}^2)$	Sistla et al., 2012
Viscosity, μ	Pa.s	μ < 0.150	$\ln \eta = \ln A_\eta + \frac{B_\eta}{T - T_{o\eta}}$	Gardas and Coutinho, 2008a
Toxicity, EC50	-	log EC50 < 2.0	log EC50 = 5.33 + 0.549 nCR2	Romero et al., 2008
Heat capacity, Cp	J/K.mol	C > 500	$C_p = 1.951 + 8.33 \times 10^{-4} (T - 298.15)V_m$	Paulechka et al., 2010
Density, ρ	g/cm^3	ρ < 1.5	$\rho = \frac{Mw}{NV_0(A + BT + C_p)}$	Gardas and Coutinho, 2008b

Table 3: Phytochemicals properties

Phenolic acid	Molecular weight (g/mol)	Solubility parameter, δ ($Mpa^{1/2}$)	Boiling point, T_b (K)	Melting point, T_m (K)	Enthalpy of fusion (kJ/mol)
Gallic acid	170.12	28.82	641.52	492.89	89.66
Caffeic acid	180.16	28.34	634.29	443.75	81.05

3.4 Stage 4: Ionic liquid screening

Ionic liquid candidates were screened to reduce feasible candidates according to priority as seen on Figure 2. From 880 ionic liquid candidates, only 280 candidates went through the screening process as the rest of them were not considered due to missing of the physicochemical data. As observed, number of candidates were reduced based on the priority screening from 177 ionic liquid candidates to 16 feasible candidates. Toxicity

were chosen as first priority in order to achieve a green solvent, other than the used of ionic liquid as extraction for phytochemicals which will later considered for human consumption. Finally, the candidates were chosen by the solubility of phytochemicals in the ionic liquid. Table 4 listed all 16 feasible candidates for extraction of phenolic acid from *L. pumila.* These feasible candidates may be allowed to undergo experimental validation process to validate the extraction performance.

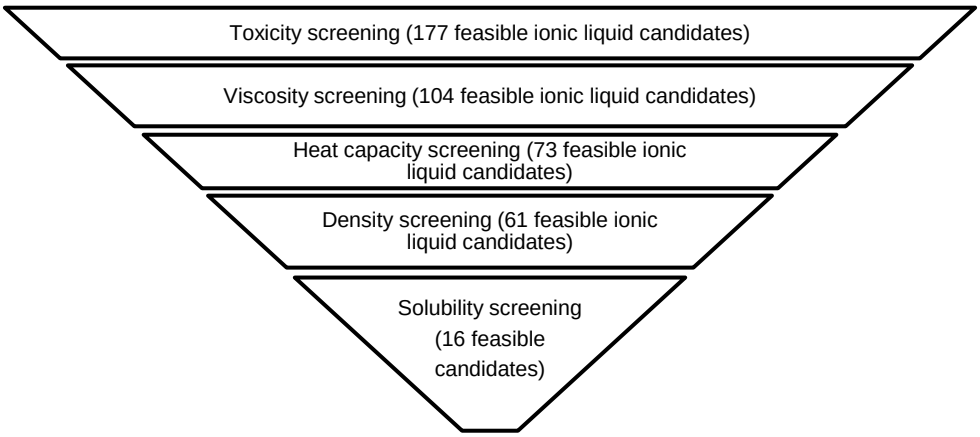

Figure 2: Ionic liquid solvent screening by properties

Table 4: Feasible ionic liquid candidates with their estimated properties

IL Name	δ (Mpa$^{1/2}$)	μ (Pa.s)	ρ (g/cm^3)	C (J/K.mol)	log EC50
1-heptyl-3-methylimidazolium ethylsulfate	28.55	0.1406	1.075	556	1.487
1-ethyl-3-heptylimidazolium tetrafluoroborate	30.31	0.1172	1.098	501	0.389
1-ethyl-3-octylimidazolium tetrafluoroborate	29.99	0.1433	1.081	535	-0.16
1-hexyl-3-propylimidazolium tetrafluoroborate	30.31	0.1172	1.098	501	0.389
1-heptyl-3-propylimidazolium tetrafluoroborate	29.99	0.1433	1.081	535	-0.16
1-butyl-3-pentylimidazolium tetrafluoroborate	30.31	0.1172	1.098	501	0.389
1-butyl-3-hexylimidazolium tetrafluoroborate	29.99	0.1433	1.081	535	-0.16
1,3-dipentylimidazolium tetrafluoroborate	29.99	0.1433	1.081	535	-0.16
1-hexyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide	29.16	0.0390	1.333	676	1.487
1-heptyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide	28.84	0.0477	1.309	709	0.938
1,2-dimethyl-3-octylimidazolium bis(trifluoromethylsulfonyl)imide	28.52	0.0584	1.287	742	0.389
1,2-dimethyl-3-octylimidazolium chloride	27.00	0.0946	0.948	504	0.389
1-hexyl-2,3-dimethylimidazolium trifluoromethanesulfonate	31.02	0.0662	1.206	535	1.487
1-heptyl-2,3-dimethylimidazolium trifluoromethanesulfonate	30.70	0.0810	1.184	568	0.938
1,2-dimethyl-3-octylimidazolium trifluoromethanesulfonate	30.37	0.0991	1.164	601	0.389
1,2-dimethyl-3-octylimidazolium bromide	31.00	0.0946	1.097	514	0.389

4. Conclusion

A systematic methodology for design were used to screen of ionic liquid as extraction solvent for herbal phytochemicals. In this study, the design were verified by the case study of the phenolic acid extraction from L. pumila. According to the case study, the 16 shortlisted ionic liquid needs further verification with experimental study to ensure the extraction efficiency. The methodology applied can be used to design ionic liquid for extracting any other phytochemicals where the scope and size depend on the solvent data base

available and models availability in the property model library. This study can be refined in the future by addition of other properties and new property models into the property library.

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